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A Controlled Study of Visual Symptoms and Eye Strain Factors in Chronic Headache

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SYNOPSIS

In a questionnaire survey we determined the prevalence of visual symptoms and eye strain factors in a group of chronic headache sufferers as compared with age- and sex-matched controls. The visual symptoms studied were those not specific for headache, i.e., sensitivity to light and blurred vision. Sensitivity to light in the absence of headache was reported by 27.8% of controls and 44.7% of headache sufferers ($p<0.05$). The latter figure increased to 71.3% when headache was actually present ($p<0.001$). Blurred vision occurred in 13.5% of controls and 7.4% of headache sufferers (not significant). In the presence of headache, the latter figure increased to 44.7% ($p< 0.01$).

Of the eye strain factors studied, bright light was reported to precipitate headache in 29.3% and to aggravate it in 73.4%. For reading, these figures were 16.0% and 55.3%, respectively; for working at the computer screen, 14.5% and 31.3%; and for watching television, 6.4% and 27.7%. We conclude that visual symptoms are more common in chronic headache and eye strain factors more important than is generally recognized.

(*Headache* 29:523-527, 1989)

INTRODUCTION

The visual symptoms which occur in relation to headache can be divided into specific and non-specific. The specific visual symptoms are those generally looked upon as aura symptoms of migraine. They represent the scintillating scotoma, also known as teichopsia or fortification spectra, as wall as its many variants. Characteristic features of these symptoms are the zigzag pattern, flickering brightness and a particular pattern of development or "march."

The non-specific visual symptoms of headache are sensitivity to light, or photophobia, and blurred vision. These symptoms are neither specific for headache nor for any particular headache condition. The sensitivity to light can range from light being uncomfortable to the eyes, to light actually aggravating or precipitating headache.

In terms of aggravating or precipitating headache, light can also be looked upon as an eye strain factor. In this regard it can be compared with strenuous activities of the eyes such as in reading, working at the computer screen and watching television.

In the present study we determined the prevalence of the non-specific visual symptoms of headache in a group of chronic headache sufferers as compared with age- and sex-matched controls. As sensitivity to light is generally considered in the context of "sensitivity of the sensory organs," we also looked at sensitivity to noise and smell. Finally, we determined the prevalence of light as an eye strain factor and compared it with reading, working at the computer screen and watching television.

METHODS

For the collection of data we developed a questionnaire which included the following items:

1. Age and sex;

2. Headache occurrence, age of onset of headache and present frequency, duration, laterality and intensity of headache;

3. Aggravation of headache by physical activity and whether headaches interfere with or prevent intended activities;

4. Association of headache with nausea, vomiting, sensitivity to light, noise and smell, and the occurrence of the sensitivities when no headache is present;

5. Intensity of headache, nausea and the above mentioned sensitivities expressed on a visual analogue scale with no headache, nausea or sensitivity on one end of the scale and worst headache, nausea and sensitivity possible on the other;[1]

6. Occurrence of blurred vision with and without headache as well as a history of serious visual impairment or eye disease;

7. Precipitation or aggravation of headache by bright light, reading, working at the computer screen and watching television;

8. Occurrence of headache in parents, siblings and children.

The headache-related questions ware based, to as great an extent as possible, on the classification criteria of the International Headache Society.[2]

For data collection, patients attending the John R. Graham Headache Centre at Faulkner Hospital as well as the persons accompanying them and patients attending the Faulkner-Sagoff Centre for Mammography were used. The latter two groups were included in order to establish a control group for which the criterion was either no headaches at all or a frequency of headaches of less than once per month. The questionnaires were filled out under the direct supervision of the first author who was also available for questions, but in answering respondents' questions special care was taken that the answers were not biased.

The answers were entered into a personal computer using the SPSS data-entry module. The SPSS statistical modules were used for analysis of variance (F test), cross tabulations (Chi-Square test) and paired and unpaired comparisons (t-test). For age-and sex-matching and data checking, the EXCEL spreadsheet was employed. A program designed by one of the authors (H.B.M.) was used for the Fisher's Exact test.

In total 260 persons filled out the questionnaire in a way adequate for data entry and analysis. Of these 65 denied having headaches and an additional 30 indicated they had headaches less than once per month. To form the control group these two groups were combined, generating a population consisting of 47 males and 48 females with an average age of 45.3 years. The remaining 165 persons constituted the headache group, consisting of 48 males and 117 females with an average age of 38.0 years.

In matching the two groups by age and sex, we first removed all the 15-year-olds as outliers because there were ten of them at that extreme value in the female headache group. Then random scores were assigned to the remaining cases by multiplying age by a uniform zero-to-one random variable. A random selection with an age bias was achieved by removing cases starting with the lowest scores. This was done incrementally until the age mean for the headache females had been sufficiently increased. At that point, 94 cases remained in that group after which a simple random sample was taken to get 50 cases. The result was a mean age of 41.2 years compared with 48 control females with a mean age of 42.2 years.

The age mean for the control males, initially 48.5 years, was reduced by the same random-score method. The ultimate age mean was 45.3 years for 42 cases to compare with 44 headache males with a mean age of 41.3. Analysis of variance revealed the remaining age and sex differences between the groups not to be significant with the lowest p-value being 0.223.

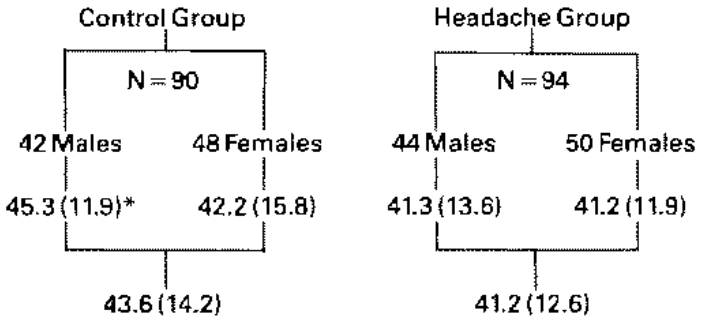
RESULTS

The age and sex distribution of the matched headache and control groups is shown in Table 1. The headache group consisted of 94 cases and the control group of 90 with mean ages of 41.2 and 43.6 years, respectively. Both groups consisted of about half males and half females.

The clinical characteristics of the headache group are shown in Table 2. The mean age at onset of headache was 21.1 years, which indicates an average headache suffering of two decades. The headache frequency was by definition once per month or more in order to be assigned to the headache group. It was once per week or more in 64.9%, including 38.3% with daily headaches. The reported duration of the headaches was less than three hours in 38.3%, between three hours and three days in 39.4%, and longer than 3 days in 22.3%. The headache intensity Was moderate or severe in the majority of cases (87.2%). The location of the headaches was limited to One side of the head in almost two-thirds of cases (61.3%). In more than half, the headaches were

Table 1

The Age and Sex Distribution of the Matched Study Groups



*Means and standard deviations shown.

Table 2
The Clinical Characteristics of the Headache Group (N = 94)

Age at Time of Study	41.2 (12.6)*
Age at Onset of Headache	21.1 (13.7)*
Headache Frequency	
- Once per month to once per week	35.1%
- Once per week to every day	26.6%
- Every day	38.3%
Headache Duration	
- Less than three hours	38.3%
- Three hours to three days	39.4%
- Longer than three days	22.3%
Headache Intensity	
- Mild	12.8%
- Moderate	42.6%
- Severe	44.6%
Headache Laterality	
- Unilateral	61.3%
- Bilateral	38.7%
Gastrointestinal Symptoms	
- Nausea	54.3%
- Vomiting	25.5%
Physical Activity Aggravates Headache	59.8%
Headache Interferes with Activities	85.1%
Headache Prevents Activities	74.5%

*Means and standard deviations shown.

associated with nausea (54.3%) and in one-fourth, with vomiting (25.5%). The headaches were aggravated by physical activity in 59.8% of cases; they interfered with activities in 85.1% and prevented activities in 74.5%.

The prevalences of sensitivity to light, noise and smell in the groups studied are presented in Table 3. For the headache group the figures are given for the sensitivities with and without headache. Without headache, only the sensitivity to light was significantly more common in the headache than in the control group (44.7% versus 27.8%; p=0.026). Under these same circumstances, sensitivity to noise and smell affected about one-fifth of both groups. The sensitivity to smell also remained at that level when headache was present. However, the sensitivities to light and noise significantly increased (p<0.001 in each case) in the presence of headache to 71.3% and 52.1%, respectively.

The intensities of the sensitivity to light, noise and smell, as revealed by the visual analogue scales, are shown in Table 4. No significant differences existed for any of the variables between the headache group while without headache and the control group. In contrast, all three variables were significantly increased (p<0.01) in the headache group when headache was present in comparison to when headache was absent.

In addition to the prevalence of sensitivity to light, Table 5 also shows the prevalence of blurred vision, as another non-specific visual symptom of headache. Blurred vision was less common, although not significantly so, in the headache group without headache as compared with the control group (7.4% versus 13.5%; p=0.273). However, it was significantly increased to 44.7% in the headache group when headache was present (p =0.008). The prevalence of eye disease was almost twice as high in the headache group than in the control group (12.8% versus 6.7%), but the difference was not statistically significant (p = 0.253).

Table 3
The Prevalences of Sensory Sensitivity in the Study Groups

A. Sensitivity without Headache in Control and Headache Groups

	Control Group	Headache Group	X^2-Test
Light Sensitivity	27.8%	44.7%	p = 0.026
Noise Sensitivity	20.0%	19.1%	p = 0.884
Smell Sensitivity	20.0%	22.3%	p = 0.835

B. Sensitivity with and without Headache in Headache Group

	Without Headache	With Headache	X^2-Test
Light Sensitivity	44.7%	71.3%	p = 0.000
Noise Sensitivity	19.1%	52.1%	p = 0.000
Smell Sensitivity	22.3%	20.2%	p = 0.858

Table 4
The Intensities of Sensory Sensitivity in the Study Groups

A. Sensitivity without Headache in Control and Headache Groups

	Control Group			Headache Group			t-Test
	N	Mean	SE	N	Mean	SE	
Light Sensitivity	26	47.1	4.3	41	41.9	3.4	p = 0.341
Noise Sensitivity	16	38.3	5.6	18	39.9	5.1	p = 0.830
Smell Sensitivity	18	38.7	5.2	20	48.0	5.0	p = 0.208

B. Sensitivity with and without Headache in Headache Group

	Without Headache			With Headache			Paired t-Test
	N	Mean	SE	N	Mean	SE	
Light Sensitivity	39	41.6	3.6	39	68.9	4.0	p = 0.000
Noise Sensitivity	14	38.6	6.2	14	70.4	5.3	p = 0.001
Smell Sensitivity	12	46.1	6.5	12	64.1	6.2	p = 0.005

The values are expressed in mm on a scale from 0 to 100; the p-values are for two-tailed tests; SE is standard error of the mean.

Table 5
The Prevalences of Visual Symptoms in the Study Groups

A. Prevalence without Headache in Control and Headache Groups

	Control Group	Headache Group	X^2-Test
Light Sensitivity	27.8%	44.7%	p = 0.026
Blurred Vision	13.5%	7.4%	p = 0.273

B. Prevalence with and without Headache in Headache Group

	Without Headache	With Headache	X^2-Test
Light Sensitivity	44.7%	71.3%	p = 0.000
Blurred Vision	7.4%	44.7%	p = 0.008

Significance levels are based on Chi-Square tests with Yates correction.

The prevalences of the eye strain factors, bright light, reading, working at the computer screen and watching television, in terms of precipitating and aggravating headache, are presented in Table 6. Bright light most commonly precipitated headache (29.3%), followed by reading (16.0%), working at the computer screen (14.5%), and watching television (6.4%). The same order was observed for these factors aggravating headache but the figures were two to four times higher, i.e., for bright light, 73.4%; reading, 55.3%; working at the computer screen, 31.3%; and watching television, 27.7%.

In Table 7, finally, the data with regard to the family occurrence of headache for the two groups are presented. Of headache in parents, siblings and children, only the occurrence of headache in parents was significantly higher in the headache than in the control group (50.5% versus 34.5%; p=0.043). Neither the proportion of siblings or children with

Table 6
The Prevalences of Eye Strain Factors in the Headache Group (N = 94)

	Precipitation of Headache	Aggravation of Headache
Bright Light	29.3%	73.4%
Reading	16.0%	55.3%
Computer Screen	14.5%	31.3%
Watching Television	6.4%	27.7%

Table 7
The Family Occurrence of Headache in the Study Groups

	Control Group N = 90	Headache Group N = 94	X^2-Test
Headache in Parents	34.5%	50.5%	p = 0.043
Headache in Siblings	30.5%	44.4%	p =0.130
Headache in Children	35.6%	41.3%	p = 0.093

The figures presented are the proportion of cases where one or more parents have headaches and the proportion of siblings and children with headaches.

headache was significantly higher in the headache than in the control group.

DISCUSSION

With regard to the visual symptoms of headache, specific attention is generally directed only toward those symptoms looked upon as aura symptoms of migraine, i.e., the scintillating scotoma and its many variants. However, more prevalent than these specific symptoms are the non-specific symptoms which are neither specific for headache nor for any particular headache condition, i.e., sensitivity to light, or photophobia, and blurred vision. The present study shows that sensitivity to light may affect as many as 71% of chronic headache sufferers when headache is present while without headache 45% may be affected, as compared with 28% of a group of age- and sex-matched controls.

Chronic headache sufferers, therefore, seem to be more frequently sensitive to light than controls, although the intensity of the sensitivity to light may only be increased when headache is present, as the present study shows. In contrast, in the absence of headache, chronic headache sufferers do not seem to be more sensitive to noise and smell than controls, judging from the frequency as well as the intensity of these symptoms. However, when headache is present, the intensity of both the sensitivity to noise and smell increases while the sensitivity to noise is also increased in frequency of occurrence.

In a previous study, Drummond[3] determined the sensitivity to light as well as light as a pain inducing factor in headache sufferers as compared with controls. He exposed his subjects to different levels of illumination and asked them to rate the intensity of the glare and pain caused by the light. In moderately bright light, 25% of the control group experienced a sensation of glare which agrees with our finding of 28% of controls reporting sensitivity to light. The corresponding figure for the headache sufferers was 60% to 76% which agrees with our finding of 71% of headache sufferers experiencing sensitivity to light with headache. Light-induced pain was not observed by Drummond in the control group and this was not studied by us. In the headache group, 27% to 71% reported moderately bright light to cause pain while we found bright light to precipitate headache in 29% and to aggravate it in 73%.

Apart from bright light, we also inquired about reading, working at the computer screen and watching television as factors precipitating or aggravating headache. Although these activities were less potent than light in affecting headache, they were still mentioned in considerable frequency. Reading was mentioned by 16% of headache sufferers to precipitate headache and more than half reported aggravation of headache by reading. Working at the computer screen and watching television precipitated headache in about 10% and aggravated headache in more than one-fourth of sufferers.

A visual symptom which, to our knowledge, has so far never been explicitly studied in relation to headache is blurred vision. We found this symptom to be present in about 10% of controls and headache sufferers when headache was absent. In the presence of headache, however, 45% of headache sufferers reported experiencing blurred vision. It is possible that some patients confused "blurred vision" with the experience of a scintillating scotoma or a variant thereof and suffered from "classic migraine" or "migraine with aura." However, the prevalence of classic migraine in the patient population of the John R. Graham Headache Centre was, when a tabulation was made a few years ago, only 12%, which is to no extent close to the 50% that reported blurred vision in the present study.

The frequent occurrence of blurred vision, as we found it, agrees with our clinical impression that many headache patients experience a not-further-delineated sensation of blurring of vision with their headaches, usually affecting both eyes. This is an experience that is generally described as occurring simultaneously with the headache rather than preceding it. However, it needs further study to ascertain the validity of these statements which at this point have to remain conjectural.

The headache group on which the above conclusions are based is a group of chronic headache sufferers as evidenced by the two decades of average headache suffering. It is also a group in which headache frequency is high (once per week or more in 64.9%), headache duration long (three hours or more in 61.7%) and headache intensity moderate or severe (87.2%). In addition, in almost two-thirds the headache was indicated as unilateral and in more than

half associated with nausea. These are important facts related to the possible generality of the results reported herein.

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Book Review

Title: Handbook of Chronic Pain Management
Edited by: C. David Tollison
Williams and Wilkins, 1989

Price: $87.95

This is a well written, extremely comprehensive text book on the management of chronic pain. The comprehensive nature is accomplished by the use of 81 authors connected in various ways to the pain field. The list includes physicians from many different specialties such as Internal Medicine, Neurology, Neurosurgery, Anaesthesia, Physiatry, Psychiatry, Orthopaedics; and many others . . . Dentists, Psychologists, Chiropractors, as well as Physiologists, Pharmacologists and Engineers. Each explains his or her craft and its applicability to pain management. The chapters are in general, well written, and have readily identifiable sub-sections that make the material very readable. Many authors make use of well organized charts and diagrams to complement their text. In general the chapters offer many up-to-date references and the index, like the text itself, is comprehensive.

The chapter on psychopharmacological agents in the treatment of pain syndromes is particularly excellent in its presentation of data and practical aspects.

The first section of the book is titled "Foundations." The chapter on Anatomy here is quite slim, and does not make use of the more current concepts. Diagrams are not used to illustrate the pathways. I felt that this was a weakness. Likewise I felt that a more intense description of biochemical aspects of pain should have been included in the "Foundations" section.

The chapter on headache is very well written. Obviously it would not meet the demands of someone specialized in that field, but would serve as a good introduction to other readers.

A few inconsistencies are noted from chapter to chapter. I believe this is an unavoidable occurrence when 81 authors contribute to one textbook and do not significantly detract from the quality of this work.

Overall, in view of the comprehensive nature of this text and its many excellent chapters, I would highly recommend "The Handbook of Chronic Pain Management" to anyone with an interest in the field.

Warren C. Goldstein, M.D.

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Astigmatism as a Cause of Headache –A Clinical Study

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Astigmatism as a Cause of Headache - A Clinical Study

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ABSTRACT

Objective: The objective of this study is to assess astigmatism prevalence in patients with headache as the only symptom and to evaluate the effect of refractive correction using spectacles on symptomatic relief in headache.
Study Design: Longitudinal analysis.
Methods: It is carried out in the Department of Optometry, Era University, Lucknow for 24 months. In the study a total of 800 patients with headache were found as the main complaint. Patients were diagnosed with astigmatism after vision screening, Objective, Subjective refraction & keratometry, Patients were called for follow up at 4, 8 and 12 weeks to see the headache status.
Results: Uncorrected astigmatism was 49.3 percent of individuals with headache as the main complaint.
The age of patients included in the study ranged from 14 to 35 years with an average age of 22.85 + 6.43 years, but the number of patients < 20 years of age was substantially higher in cases with astigmatism (50.8%) compared to patients without astigmatism (40.9%). Also, the mean age of astigmatic patients was lower (21.72 + 5.53 years) than that of non-astigmatic patients (23.94 + 7.03 years). Patient mainstreams were women (69.8 percent). Statistically, no major gender-astigmatism correlation was found.
Conclusion: The study had shown that among individuals presenting with headache as the single cause, astigmatism is high, and management of uncorrected astigmatism carried out an unexpected improvement in symptoms of headache.

Keywords: Astigmatism, Myopia, Astigmatism, Headache, Refraction.

INTRODUCTION

Astigmatism is a Greek word with two elements, “a”is absence and "stigma" is a point. It is a refractive error (ametropia) that occurs when the parallel light rays coming from infinitive and does not focus on the retina (accommodation is at rest).1 Astigmatism occurs when incident light rays fail toconverge at a single corneal focal point. Nevertheless, in some individuals the cornea is notuniform, and thus the curvature in one meridian (plane) is greater than another, somewhat like a rugbyball, refracted light rays are not brought to focus

on single point, and retinal images from objects both distant and close are distortedand can appear stretched or elongated. The refractive error is known as astigmatism. It is commonly encountered clinically, with prevalence rates of astigmatism was up to 30% or higher depending on the age or ethnic groups. Human infants exhibit origin. It lessens in prevalence and amplitude over the first view years of childhood, with an axis shift from against-the –rule (ATR) to with–the-rule (WTR).

Refractive errors are one of the leading causes of headache and among these Astigmatism is significant.2 In various studies, almost all age groups, association between refractive errors and headache was identified.3,4

Research have shown that refractive errors alone cause headache problems for almost 44 % of the total population, of which

63.6% are astigmated.5While there is a strong public belief that refractive errors have a causative effect on headache, there isno convincing evidence that refractive errors are indeed an reason for chronic headaches.Although international Headache Society (IHS) in its classification system.6 Headache Associated with Refractive Errors (HARE) as a separate category of diagnosis of headache with the following diagnostic criteria:

A. Un-Corrected Refractive Errors.

B. Mild headache in the frontal region and in the eyes themselves.

C. Pain does not present on awakening and worse by prolonged visual tasks at the distance or angle where vision is impaired.

Nevertheless, it stresses that "uncorrected refractive errors can cause headaches, but they are widely overestimated in importance." Despite this debate, however, the evidence indicates a close association between headache, Refractive errors, and astigmatim in general.7-10

A low magnitude of astigmatism is that the commonest refractive explanation for ocular headaches in young individuals. In low grade astigmatism, accommodation attempsplace significant pressure on the eyeball to achievedistinct vision and lead to symptoms of asthenopia,with headache being the most prominent symptom.A symptomatic relief in asthenopia symptoms has been reported following correction of refractive errors, thus lending strength to the relationship between refractive errors and headache. With this background, the present study was planned to study the prevalence of astigmatism among the patients presenting with headache as the only symptom and to evaluate the impact of refractive correction using spectacles on the symptomatic headache. The present research was performed with the intention of making a correlative evaluation of uncorrected astigmatism as the primary cause of headache and quantifying the minimum degree of the astigmatic error that may be responsible for symptomatic and clinical presentation as headache and the use of appropriate spectacle correction for astigmatic error.

METHODS

The present research was performed for a duration of 24 months in the Department of Optometry, Era University, Lucknow in 800 patients with headache complaints presenting for refractive error assessment and fulfilling the inclusion requirements after obtaining informed consent. Demographic data including age and sex were noted. All the patients underwent eye assessment & evaluation consisting of torch light examination, visual acuity measurement, subjective, objective refraction, and keratometry. Astigmatism was defined as a cylindrical refractive error measured after ≥ 0.5 diopter (D) in either eye expressed as a negative cylinder correction.The astigmatism was further graded as: Simple myopic astigmatism, Compound myopic astigmatism, Simple hypermetropic astigmatism, Compound hypermetropic astigmatism, Mixed astigmatism.

All the patients with refractive errors and astigmatism were advised correction by prescribing them glasses. They were advised to use the glasses for their routine activities. All the patients were further invited to participate in the follow-up at 4 weeks, 8 weeks and 12 weeks following intervention. The patients were advised to rate the change in pattern of headache experienced by them in following terms at each follow up: Complete resolution (Relieved), Improvement, No change, worsening.The data was subjected to statistical analysis using Statistical Package for Social Sciences, version 23.0. For, categorical data Chi-square test was used whereas continuous data was analyzed using paired 't'-test

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and student "t"-test. The confidence level of the study was kept at 95% and hence a "p" value < 0.05 indicated a statistically significant association.

RESULTS

The present study was conducted in the Department of Optometry, Era University, Lucknow at on 800 patients having complaints of headache, presenting for refractive error assessment, and fulfilling the inclusion criteria after obtaining an informed consent. The patients were evaluated for presence of astigmatism and those with astigmatism were subjected to correction of astigmatism. Out of 800 patients, a total of 394 (49.3%) were found to have uncorrected astigmatism. These patients comprised the Group I of study while remaining 406 (50.8%) did not have astigmatism and comprised the Group II of study. (Table 1)

Table 1: Distribution of Cases according to Astigmatism Status

S. N	Group	No. of cases	Percentage
1.	Group I - with Astigmatism	394	49.3
2.	Group II - No astigmatism	406	50.8

Table 2: Socio-Demographic Details

S. N	Age group	Group I (n=197)		Group II (n=203)		Total	
		No.	%	No.	%	No.	%
1.	<20 Yes	200	50.8	166	40.9	366	45.8
2.	21-30 Yrs	176	44.7	160	39.4	336	42.0
3.	>30 Yrs	18	4.6	80	19.7	98	12.3
Mean Ages		21.72±5.53 (15-35)		23.94±7.03 (14-35)		22.85±6.43 (14-35)	
χ^2=27.56 (df=2); p<0.001							
SN	Gender	Group I (n=197)		Group II (n=203)		Total	
		No.	%	No.	%	No.	%
1.	Male	120	30.5	122	30.0	242	30.3
2.	Female	2	69.5	284	70.0	558	69.8

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		9 4					
□^{2}=-0.008 (df=1); p=0.929							

S. N	VA	Group I (n=197)		Group II (n=203)		Total	
		No.	%	No	%	No.	%
1.	VA 6/6	294	69.5	326	80.3	600	75.0
2.	VA 6/9	120	30.5	80	19.7	200	25.0
_^{2}=-6.6165 (df=1); p=0.013							

Age of all patients ranged from 14 to 35 years. Maximum number of cases (45.8%) were aged <20 years followed by those aged 21-30 years (42%) and >30 years (12.3%) respectively. On evaluating the data in to groups proportion of those aged <20 years and 21-30 years was found to be higher in Group I (n=200, 50.8% and n=176, 44.7%) as compared to that in Group II (n=166, 40.9% and n=160, 39.4%) whereas proportion of those aged >30 years was higher in Group II (n=80, 19.7%) as compared to that in Group I (n=18, 4.6%). Statistically, this difference was significant (p<0.001). Majority of patients were females (n=558, 69.8%). The proportion of females was slightly higher in Group II (n=284, 70%) as compared to that in Group I (n=274, 69.5%) (p=0.929). Most of patients had visual acuity 6/6 in both the eyes (n=600, 75%). There were (n=200, 25%) patients having visual acuity 6/9 in one or both the eyes. On comparing the visual acuity status between two groups, proportion of those having visual acuity 6/9 was significantly higher in Group I (n=60, 30.5%) as compared to that in Group II (n=40, 19.7%) (p=0.013) (Table 2).

Table 3: Distribution of Cases according to Type of Astigmatism (n=394)

S. N	Type	No. of cases	Percentage
1.	Simple Myopic	340	86.3
2.	Simple Hypermetropic	44	11.2
3.	Compound Hypermetropic	10	2.5
4.	Compound Myopic	0	0
5.	Mixed	0	0

Further, distribution of group I patients into various types of we found that to astigmatism, Simple myopic type was most common (n=340, 86.3%) followed by simple hypermetropic (n=44, 11.2%) and compound hypermetropic (n=10, 2.5%) types. All the 394 patients with astigmatism were invited to participate in an intervention for correction of astigmatism by suitable spectacles. A total of 360 (n=158, 91.4%) consented for participation (Table 3).

All the patients undergoing astigmatism correction were followed up at 4, 8 and 12 weeks. Final follow up was done at 12 weeks. However, finally, 80 out of 360 consenting to participate in the study did not complete follow up. Hence, in final assessment only 280 patients were left. The outcome of intervention is being shown for these 280 patients. At first follow up, a total of (n=74, 26.4%) patients were relieved, (n=110, 39.3%) showed improvement, (n=74, 26.4%) showed no change while (n=30, 7.9%) showed

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worsening in headache. At second follow up, a total of (n=110, 39.3%) patients were relieved, (n=108, 38.6%) showed improvement, (n=44, 15.7%) showed no change while (n=18, 6.4%) showed worsening in headache. At third and final follow up, a total of (n=156, 55.7%)patients were relieved, (n=98, 35%) showed improvement, (n=16, 5.7%) showed no change while (n=10, 3.6%) showed worsening in headache (Table 4).

Table 4: Comparison of Outcome among Different Astigmatism Types

SN	Outcome	Astigmatism Type					
		Simple Myopic		Simple Hypermetropic		Compound Hypermetropic	
At first follow up		n=226		n=44		n=10	
		No	%	No.	%	No.	%
First Follow Up							
1.	No change	62	27.4	8	18.2	4	40.0
2.	Relieved	90	39.8	18	40.9	2	20.0
3.	Improvement	60	26.5	14	31.8	0	0.0
4.	Worsening	14	6.2	4	9.1	4	40.0
$\square^2$=10.033; p=0.123							
Second Follow Up							
1.	No change	88	38.9	14	31.8	8	80.0
2.	Improvement	88	38.9	20	45.5	0	0.0
3.	Relieved	36	15.9	8	18.2	0	0.0
4.	Worsening	14	6.2	2	4.5	2	20.0
$\square^2$=7.066; p=0.315							

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Third Follow Up							
1.	No change	132	58.4	18	40.9	6	60.0
2.	Improvement	72	31.9	24	54.5	2	20.0
3.	Relieved	14	6.2	2	4.5	0	0.0
4.	Worsening	8	3.5	0	0.0	2	20.0
$\square^2$=9.019; p=0.173							

Table 5: Statistical Evaluation of Change Between Different Follow-Up Intervals (Wilcoxon Signed Rank Test)

S.N.	Comparison	Z	'p'
1.	FU 1 vs FU 2	7.54	0.054
2.	FU 1 vs FU 3	35.9	<0.001
3.	FU 2 vs FU 3	11.9	0.008

On evaluating between the follow-up change in status of patients, though proportion of those showing relief and improvement showed a continuous increase by each follow up, however, the difference was significant only between first vs third (p<0.001) and second vs third (p=0.008) follow up intervals. No significant association was observed between Astigmatism type and outcome (Table 5).

DISCUSSION

Refractive errors and headache are the common health problems.[11-12] In several populations the prevalence of refractive errors range from 13 to 80% while incidence of chronic primary headache and sporadic headache are reported to be 15% and 40% respectively.[11] The high prevalence of both problems in general population prompts towards a possible relationship between two. Headache is a recognized symptom associated with refractive errors, especially astigmatism. Experimental studies among computer users have shown that induced astigmatism leads to production of symptoms including headache.[11] The present study was carried out with an aim to make a correlative evaluation of uncorrected astigmatism as the single cause of headache and to assess whether correction of astigmatism has any impact on complaints of headache.

For this purpose, a total of 800 patients presenting with headache as the single complaint visiting our facility for refractive error evaluation were enrolled in the study. The prevalence of astigmatism among these patients was found to be 49.3%. Thus, almost half the patients presenting with complaints of headache had astigmatism. Prevalence of astigmatism among headache cases has been reported to vary substantially in different studies using different sampling frames. In one study, Akinci et al.[7] who conducted a case-control study among patients with headache enrolled as cases and controls without headache found the rate of astigmatism to be 19.7%. In two recent studies from India, the prevalence rates of astigmatism among headache patients were reported to be 41% and 40.8% respectively. The prevalence rates 49.3% as assessed in present study is thus within these ranges and shows that astigmatism remains to be one among the foremost important underlying morbidities among patients presenting with headache.

Patients age ranged from 14 to 35 years with a mean age of 22.85+6.43 years, however, proportion of patients with age ≤20 years was

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significantly higher among astigmatism cases (50.8%) as compared to that of patients without astigmatism (40.9%). Mean age of astigmatism patients was also lower (21.72±5.53 years) as compared to that of those not having astigmatism (23.94±7.03 years). A relationship between type of astigmatism and age has been reported in several previous studies.[11,12] Studies conducted among infants and young children have shown that the prevalence of against-the-rule astigmatism is quite high in infants and toddlers, however, it disappears by the time the children reach school age[11]. Although, the present study did not include too young children, however, the role of age-related disappearance of astigmatism to be the cause behind significantly higher age of patients without astigmatism can be explained to a certain extent on the basis of the phenomenon of disappearance of astigmatism among children with advanced age.

In present study, majority of patients were females (69.8%). Statistically no significant association between gender and astigmatism was seen. The complaints of headache have been reported to be more common in females as evidenced in various epidemiological studies,[11,12] however, the present study failed to find out any association of astigmatism with gender. Impact of correction of refractive error and astigmatism on headache frequency was also evaluated retrospectively in a study by Akinci et al.[7] Who also showed proportion of patients with mis corrected refractive error to be significantly higher in headache cases (16.5%) as compared to controls (2%), thus emphasizing the fact that mis corrected or uncorrected refractive error and astigmatism have a detrimental role on the frequency of headache. Incidentally, there are limited or almost negligible studies on the relationship between headache and astigmatism and evaluation of impact of correction of astigmatism on headache despite a plenty of evidence reporting astigmatism prevalence to be higher in headache patients, especially in young age. The present study is probably the first attempt to systematically study the problem and shows that this relationship exists, and correction of astigmatism can be helpful in relief from headache. Hence, further studies to evaluate this relationship further in detail are recommended.

The findings of the study thus suggested that among cases presenting with headache as the sole cause, prevalence of astigmatism is quite high, and treatment of uncorrected astigmatism brought about a phenomenal improvement in symptoms of headache. The findings of present study thus emphasize the need for evaluation of astigmatism among presents with headache as a sole complaint, especially those in young age. These findings are encouraging however, given a smaller number of studies on the issue require further evaluation. Moreover, considering the subjectivity associated with headache, long-term post-correction follow-up is recommended to confirm whether the treatment effects are lasting.

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Clinical Characteristics of Patients Presenting with Headache at Binocular Vision Clinic: A Hospital Based Study

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Clinical Characteristics of Patients Presenting with Headache at Binocular Vision Clinic: A Hospital Based Study

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ABSTRACT

Purpose: To assess the clinical characteristics of patients presenting with headache at binocular vision clinic.

Place and Duration of Study: Al-Neelain eye hospital, Khartoum, Sudan, from February to October 2018.

Study Design: Descriptive cross-sectional study.

Material and Methods: One hundred fifty patients with history of headache were included in study. Detailed ocular examination was performed. Dissociated heterophoria was measured using Maddox Wing and Maddox Rod. Associated heterophoria was assessed by the Mallett unit fixation disparity and fusional vergence was measured using a prism bar. Data was analysed using SPSS, version 25. The relationship between measures was determined using the chi-squared analysis. For all statistical determinations, significance levels were set at $p < 0.05$.

Results: Mean age was 25 ± 3.5 years. 86.7% patients with headache had visual acuity of 6/6. Females constituted 78% and headache was significantly associated with females (P < 0.0001). Majority of patients (82%) presented with exophoria (mean = 4.74 ± 0.75 Δ Base-In) at near fixation, 10.7% were orthophoric and 7.34percentage were esophoric (mean = 3.24 ± 0.5 Δ Base-Out). The association between near heterophoria and headache was statically significant (χ^2 = 7.426; p = 0.001). Association between distance heterophoria and headache was not statistically significant (χ^2 = 22.172; p = 0.265). The association between headache and positive fusional vergence at near fixation was statically significant (p = 0.03). Leading cause of headache was convergence weakness exophoria (39.3%; p = 0.001), followed by convergence insufficiency (24%; p = 0.02).

Conclusion: Headache was more common in females and was associated with exophoria, convergence insufficiency and inadequate positive fusional vergence at near fixation.

Key Words: Headache, binocular vision, exophoria, convergence insufficiency.

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INTRODUCTION

Headache is one of the commonest health complaints and it affect approximately half of world population. It has significant effect on work productivity and quality of life[1].

The problem may arise from conditions that range from benign to catastrophic. Quick and accurate diagnosis is an important step for successful management of headache[2,3]. A review of studies conducted globally, estimated the prevalence of headache as 58.4% among school-going children and 46% in adult population[2,3,4]. It is commonly believed

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that refractive errors and binocular vision anomalies can lead to headache among young individual[4]. Eye care professional reported that headache is a common patient complaint[5,6,7]. International headache society reported that the diagnostic criteria of headache associated with refractive errors is as follows: a) Uncorrected refractive errors such as hypermetropia, astigmatism, presbyopia, or wearing incorrect glasses, b) Mild headaches in the frontal region and in the eyes, c) pain absent on awakening and worse by prolonged visual tasks at distance or near[8].

In a masked case control study, to assess the relation between headache and binocular vision anomalies it was concluded that people suffering from headache had higher prevalence of heterophoria, associated phoria and reduced stereopsis compared with controls. The study found that there was strong association between exophoria and complaint of headache[9]. Another study has indicated that the positive fusional reserve should be at least twice the magnitude of an exophoria to be compensated (without symptoms)[10].

Binocular visual dysfunctions such as convergence insufficiency (CI) affects young people and is characterised by the inability to accurately converge, or sustain accurate convergence when focusing at near targets. It is associated with symptoms such as headache, blurry vision, eyestrain, and double vision[10]. Headache may also be due to different ocular diseases such as acute glaucoma, optic neuritis, uveitis, and visual anomalies such as uncorrected refractive errors, accommodative and vergence dysfunctions. The most common eye condition leading to headache after refractive errors is binocular vision anomalies[11].

There is a general increase in the number of people suffering from headaches. In addition, headaches have a significant negative impact on the quality of life and productivity. Therefore, the current study was conducted to assess the clinical characteristics of patients suffering from headaches who attended the binocular vision clinic at Al-Neelain eye hospital Khartoum, Sudan.

MATERIAL AND METHODS

One hundred and fifty patients suffering from headache and referred by ophthalmologists to the binocular vision clinic were selected by convenient sampling technique, from February to October 2018. Patients with other ocular or systemic diseases were excluded from the study. All selected patients underwent detailed ocular examinations by trained ophthalmologists. The patients were then referred to the orthoptic clinic for binocular vision assessment. Optometry graduate research assistants with experience in clinical optometry assisted with data collection. The data collectors underwent training in the study protocol procedures. Ethical approval for study was obtained from Al-Neelain University. To facilitate a better understanding of the procedures and conditions of involvement in the study, an information document detailing the nature of the study was provided to all the patients. Participation in the study was voluntary and patients were informed that they could withdraw from the study at any time without giving any reason. All forms and data sheets were shredded as soon as it is entered into database system for analysis.

The demographic information was collected from all the participants followed by measurement of visual acuity at distance using Snellen tumbling E-chart. Amplitude of accommodation and near point of convergence were measured using RAF Rule. Cover test was conducted at 33 cm for near and 6-meter for distance with the patients fixating on one line above the best visual acuity of the poor eye. The subjects underwent motility tests to assess the integrity of the eye muscles. Objective refraction was assessed using retinoscopy (NeitzRX, Japan) while dissociated heterophoria was measured using Maddox Wing and Maddox Rod at near and distance fixation, respectively. Associated heterophoria was assessed by the Mallett unit fixation disparity while the positive and negative fusional vergence were measured using a prism bar at 33 cm and 6 meter for near and distance respectively.

The data was entered in Microsoft Excel spreadsheet and analyzed using SPSS software, version 25 (SPSS, Inc., Chicago, IL). The data were analysed descriptively using standard deviations and percentages. The relationship between measures was determined using the chi-square analysis. Significance levels were set at $p < 0.05$.

RESULTS

A total of 150 patients who attended Al-Neelain eye hospital complaining of headaches were included in this study. The age of the participants ranged between 10 and 35 years with a mean age of 25.0 ± 3.5 years.

Seventy-one percent were between 15-20 years, followed by age groups (21–25) representing 57 (38%). One hundred and seventeen (78%) patients who complained of headache were females. Association of headache with females was statistically significant ($\chi^2 = 149.18$, $p < 0.0001$).

Association of decreased vision with headache was not statistically significant ($\chi^2 = 4.082$, $p = 0.850$), as shown in table 1.

The association between headache and types of refractive errors was not statistically significant ($\chi 2 = 2.05$; $p = 0.562$) as illustrated in table 2.

Majority of the patients (82%) presented with exophoria (mean = 4.74 ± 0.75Δ Base-In) at near. The association between near heterophoria and headache was statistically significant ($\chi^2 = 7.426$; $p = 0.001$) as shown in table 3.

The association between distance heterophoria and headache was not statistically significant ($\chi^2 = 22.172$; $p = 0.265$) as shown in table 3.

Association between near point of convergence and headache was not statistically significant ($\chi 2 = 3.04$; $p = 0.836$). Table 3. 72.7% patients presented without an associated phoria. Association between headache and associated phoria was statistically significant. ($\chi^2 = 13.837$; $p = 0.001$) as shown in table 4.

59.3% patients presented with weak positive fusional vergence at near fixation (2 – 14Δ Base-Out).

The association between headache and weak positive fusional vergence at near fixation was statistically significant $\chi^2 = 10.726$; $p = 0.03$) as illustrated in table 5.

Table 1: *Visual acuity (VA) among patients complaining of headache ($\chi^2 = 4.082$ $p = 0.850$).*

Age of Participants Mean SD (25.0 ±3.5 Years)	VA of Participants 6/6 n %	6/9 n %	≤ 6/12 n %	Total n (%)
10 – 14	11 (7.3)	0 (0.0)	0 (0.0)	11 (7.3)
15 – 20	61 (40.7)	5 (3.3)	5 (3.3)	71 (47.3)
21 – 25	48 (32.0)	3 (2.0)	6 (4.0)	57 (38.0)
26 – 30	8 (5.3)	1 (4.6)	0 (0.0)	9 (6.0)
31 – 35	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)
Total	**130 (86.7)**	**9 (6.0)**	**11 (7.3)**	**150 (100)**

Table 2: *Distribution of refractive error among participants.*

Age of Participants Mean SD (25.0 ±3.5 Years)	Refractive error of participants Emmetropia n (%)	Hypermetropia n (%)	Myopia n (%)	Astigmatism n (%)	Total n (%)
10 – 14	8 (5.3)	0 (0.0)	1 (0.6)	2(1.3)	11 (7.3)
15 – 20	62 (41.3)	1 (0.6)	6 (4.0)	2(1.3)	71 (47.3)
21 – 25	52 (34.7)	0 (0.0)	1 (0.6)	4(2.7)	57 (38.0)
26 – 30	6 (4.0)	1 (0.6)	1 (0.6)	1(0.6)	9 (6.0)
31 – 35	1 (0.6)	1 (0.0)	0 (0.0)	0(0.0)	2 (1.3)
Total	**129 (86.0)**	**3 (2.0)**	**9 (6.0)**	**9(6.0)**	**150 (100)**

($\chi^2 = 2.05$; $p = 0.562$)

Table 3: *Near and distance dissociated heterophoria among the participants.*

Heterophoria		Gender of Participants Male n (%)	Female n (%)	Total n (%)	P-value
Near Dissociated phoria	Orthophoria	5 (3.3)	11 (7.3)	16 (10.7)	
	Exophoria	25 (16.7)	98 (65.3)	123 (82)	0.001
	Esophoria	3 (2.0)	8 (5.3)	11 (7.3)	
Distance Dissociated Phoria	Orthophoria	21 (14.0)	89 (59.3)	110 (73.3)	
	Exophoria	9 (6.0)	25 (16.7)	34 (22.7)	0.265
	Esophoria	3 (2.0)	3 (2.0)	6 (4.0)	
	Total	**33 (22.0)**	**117 (78.0)**	**150 (100)**	

Table 4: *Distribution of associated phoria among the participants.*

Associated Phoria		Gender of Participants Male n (%)	Female n (%)	Total n (%)	P-value
Near Associated Phoria	Orthophoria	19 (12.7)	90 (60.0)	109 (72.7)	
	Base-in	14 (9.3)	17 (11.3)	31 (20.7)	0.001
	Base-out	0 (0.0)	10 (5.3)	11 (6.6)	
	Total	**33 (22.0)**	**117 (78.0)**	**150 (100)**	

($\chi^2 = 13.837$; $p = 0.001$)

Table 5: *Fusional vergence among participants suffering from headache.*

Fusional Vergence		Gender of Participants Male n (%)	Female n (%)	Total n (%)	P-value
Positive Fusional Vergence	Weak (2 – 14 Base-out Δ)	19 (12.7)	70 (46.6)	89 (59.3)	
	Strong (16 – 35 Base-out Δ)	14 (9.4)	47 (31.3)	61 (40.7)	0.03
Negative Fusional Vergence	Weak (2 – 4 Base-in Δ)	8 (5.3)	16 (10.7)	24 (16.0)	
	Strong (6 – 15 Base-in Δ)	25 (16.7)	101 (67.3)	126 (84.0)	0.534
	Total	**33 (22.0)**	**117 (78.0)**	**150 (100)**	

With respects to negative fusional vergence, most of the patients (84%) had strong negative fusional vergence at near fixation (6 – 15Δ Base-in). The association between headache and weak negative fusional vergence at near fixation was not statistically significant ($\chi^2 = 2.139$; p = 0.534) as shown in table 5.

Binocular vision anomalies among patients complaining of headache is shown in table 6. The association between headache and convergence weakness exophoria was statistically significant p = 0.001. The association between headache and convergence insufficiency was also statistically significant P=0.02.

Table 6: *Binocular vision anomalies among patients complaining from headache.*

Binocular Vision Anomalies	Gender of Participants		Total n (%)	P-value
	Male n (%)	Female n(%)		
Convergence Weakness Exophoria	10 (6.7)	49 (32.6)	59 (39.3)	0.001
Convergence Insufficiency	8 (5.3)	28 (18.7)	36 (24)	0.02
Weak Fusional Vergence	4 (2.7)	15 (10.0)	19 (12.7)	0.124
Divergence Excess Exophoria	5 (3.3)	13 (8.7)	18 (12.0)	0.131
Convergence Excess Esophoria	4 (2.7)	7 (4.6)	11 (7.3)	0.423
Divergence weakness esophoria	2 (1.3)	5 (3.4)	7 (4.7)	0.658
Total	**33 (22.0)**	**117 (78.0)**	**150 (100)**	

DISCUSSION

Headache is a common health complaint and is considered a public health problem. It has significant effect on public health as well as personal health. However, diagnosis of headache and its management is not always easy because the list of differential diagnosis of headache is one of longest in all of the diseases. Majority of the patients complaining of headache are referred to eye care professionals, ophthalmologist or optometrist for further diagnosis and management. When headache is a sign of a central nervous system disease, an ophthalmologist can offer valuable information about the nature and localization of the lesion to the neurologists[12]. In the current study, percentage of females presenting with headache was more than males. This was in accordance with a study in which it was reported that headache was three times more prevalent in females than males particularly during the reproductive age[5]. Similar results were published in other studies[13,14,15]. The commonest age group suffering from headaches was 15 – 20 years, representing 47.3%. The reason behind this could be more near tasks like reading and writing, in this age group. Jain et al[12] also reported that headache was more prevalent among young age group and the authors concluded that it could be due to psychological stress caused by educational pressures, emotional factors, and family conflicts.

The current study revealed that the association between headache and near exophoria was statistically significant ($\chi^2 = 12.726$; p = 0.001). This is in agreement with Harle et al[9], who reported that there was a strong association between exophoria and headache. Evans[16] reported that symptoms of exophoria were likely to include headache, which was associated with prolonged use of eyes in near task. This may be due to inadequate positive fusional vergence to compensate the degree of exophoria at near fixation. Another study suggested that the positive relative convergence (positive fusional reserve) should be at least twice the magnitude of an exophoria to be compensated[17]. This is supported by the result of the present study where the majority of patients suffering from headaches presented with weak positive fusional vergence at near fixation. The association between headache and weak positive fusional vergence at near fixation was statistically significant ($\chi^2 = 4.584$; p = 0.03). Gargetal[11] reported that the insufficient positive fusional vergence was more common among patients suffering from headaches. However, in this study there were only 7.3% esophoric patients who complained of headaches. Rabbetts reported that the symptoms of esophoric patients were frontal headaches, which might occur after prolonged use of eyes[18]. The association between near heterophoria and headache was also statistically significant *($\chi^2 = 7.426$; p = 0.001)*. However, the association between distance heterophoria and headache was not statistically significant ($\chi^2 = 22.172$; p = 0.265). This could be due to the fact that, at distance fixation, visual axis need less convergence effort, resulting in less ocular deviation compared to near fixation tasks such as reading and chatting on the smart phone.

Almost 27.4% of patients suffering from headache presented with associated heterophoria (aligning

prism). Several authors[19-23] reported that patients with a fixation disparity (associated heterophoria) on the near Mallett Unit were likely to have symptoms such as headache and eye strain.

With regards to final diagnosis the leading cause of headache among the patients referred to the binocular vision clinic was convergence weakness exophoria which was statistically significant *(χ^2 = 13.426; p = 0.001)*. It was followed by convergence insufficiency *(χ^2 = 6.483; p = 0.02)*. Rouse et al[24] defined convergence insufficiency as a syndrome based on near exophoria, low positive fusional reserves (e.g. failing Sheard's criterion) and near point of convergence more remote than 7.5 cm. In a study to assess the association between binocular vision anomalies and headache, it was revealed that the common binocular vision anomaly found in patients with headache was convergence insufficiency 39.19%.[11] This was supported by the fact that majority of patients in this study had near exophoria and weak positive fusional vergence.

The current study has some limitations. The sample size was small and stereopsis was not assessed in the patients suffering from headache. This was a cross sectional study and the effects of management on headache were also not studied.

CONCLUSION

Headache is more common in females than males, with convergence weakness exophoria and convergence insufficiency being the most common binocular vision anomalies in patients with headache. Weak positive fusional vergence at near fixation and associated phoria was common among patients suffering from headache.

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Ethical Approval

The study was approved by the Institutional review board/Ethical review board.

Conflict of Interest

Authors declared no conflict of interest.

Author's Designation and Contribution

Saif Hassan Alrasheed; Optometrist: *Study design, data collection, and manuscript writing.*

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Current understanding of photophobia, visual networks and headaches

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Abstract

Objective: To review clinical and pre-clinical evidence supporting the role of visual pathways, from the eye to the cortex, in the development of photophobia in headache disorders.

Background: Photophobia is a poorly understood light-induced phenomenon that emerges in a variety of neurological and ophthalmological conditions. Over the years, multiple mechanisms have been proposed to explain its causes; however, scarce research and lack of systematic assessment of photophobia in patients has made the search for answers quite challenging. In the field of headaches, significant progress has been made recently on how specific visual networks contribute to photophobia features such as light-induced intensification of headache, increased perception of brightness and visual discomfort, which are frequently experienced by migraineurs. Such progress improved our understanding of the phenomenon and points to abnormal processing of light by both cone/rod-mediated image-forming and melanopsin-mediated non-image-forming visual pathways, and the consequential transfer of photic signals to multiple brain regions involved in sensory, autonomic and emotional regulation.

Conclusion: Photophobia phenotype is diverse, and the relative contribution of visual, trigeminal and autonomic systems may depend on the disease it emerges from. In migraine, photophobia could result from photic activation of retina-driven pathways involved in the regulation of homeostasis, making its association with headache more complex than previously thought.

Keywords

Migraine; retina; photoreceptors; thalamus; hypothalamus; autonomic

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Introduction

Abundant visual symptomatology in some headaches has driven scientists and clinicians to seek understanding of the intriguing association between the visual system and headache disorders. Historically, the most compelling association between these comes from patients' descriptions of visual hallucinations and scotomas, known today as visual aura (1–3). The phenomenon behind these symptoms is widely accepted to originate in the cortex as a result of altered, genetically-driven ionic imbalances capable of disrupting the dynamic equilibrium between excitatory and inhibitory networks (4). Existing evidence supports the notion that abnormal cortical excitability is not only able to produce such visual or sensory hallucinations through cortical spreading depression (CSD) but also influences the way it processes sensory information from the outside world (5,6). Indeed, one of the hallmarks of migraine is multisensory dysfunction, which expresses itself in the form of increased sensory perception in what is classically referred to as migraine phobias or sensory allodynias. The common notion is that these sensory disturbances originate from abnormal processing in different cortical areas, including the visual cortex, but recent data suggest that pathological processing may occur downstream at lower levels of the visual pathways (7,8).

The pioneering description on the nature of photophobia by Lebensohn emphasizes the duality of the phenomenon by differentiating light sensitivity due to glare from that associated with induction or exacerbation of pain by light, which he called true photophobia. He suggested that painful photophobia depends on the functional integrity of both the optic and trigeminal nerves, and that light-induced pain may originate from iris constriction and vasodilatation driven by sensitized trigeminal axon reflexes. His conclusions were mostly made, however, from patients with ocular conditions, and did not distinguish these from photophobia in migraine (9,10). An effort to differentiate photophobia features in migraine was made by Drummond, who developed a photophobia questionnaire (11) and performed a series of psychophysical studies in headache sufferers. His findings expand on Lebensohn's view and suggest that migraine is associated with a subcortical inability to suppress glare and light-induced pain, and that trigeminal-autonomic reflexes further contribute to pain by promoting vasodilatation in pain-sensitized extra/intracranial vessels (12–14).

Significant progress has been made since then, particularly in the last two decades, towards a better scientific understanding of how specific visual pathways contribute to photophobia. This progress also requires us to reshape the definition of photophobia as a neurological symptom, according to the disease or group of diseases it emerges from. There is, however, a growing body of evidence supporting the notion that neural pathways mediating light-induced intensification of headache in migraine may differ from the pathways mediating increased sensitivity to light or from those mediating ocular discomfort in prechiasmal conditions (8,15,16). For example, photophobia perception in migraine has been recently shown to be influenced by activation of retinal photoreceptors and the photic signals they transmit to multiple brain regions involved in sensory, autonomic and emotional regulation (17,18). Therefore, in migraineurs, light could act as a strong modulator of a vast, multidimensional neuronal network involved in the regulation of homeostasis, making its association with headache more complex than previously thought.

In this review, we will first describe photophobia as a phenomenon, and then discuss clinical and preclinical evidence supporting the role of visual pathways, from the eye to the cortex, in the pathophysiology of migraine photophobia.

Definition of photophobia and mechanistic theories

The current definition of photophobia in medical literature is at best incomplete, as it fails to precisely describe the many forms this light-induced phenomenon can take. The strict meaning of the word – fear (phobia) of light (photo) – distance it from the common use of the term by clinicians and patients (photophobia sufferers) when attempting to describe light-induced neurological symptoms, which usually emerge in the form of (i) increased sensitivity to light or glare, (ii) intensification of headache and (iii) ocular pain or discomfort. Many neurological conditions have been associated with photophobia including migraine, traumatic brain injury, concussion, meningitis, intracranial tumors and subarachnoid hemorrhage. Similarly, a variety of neuro-ophthalmic disorders such as uveitis, iritis, cyclitis, keratitis, retinitis pigmentosa, cone-rod dystrophy, corneal damage and blepharitis present with photophobia as well (19–22). Controversy on the causes of photophobia and its use as a medical term remains, likely due to the scarcity of data and lack of thorough assessment of specific clinical features, particularly in the headache population. The long list of pathologies that are accompanied with photophobia, irrespective of the type, and the complexity of the interaction between visual and trigeminal systems, has made the search for answers quite challenging.

In the past, many theories on the mechanisms of photophobia have been proposed and were focused on whether photophobia depends on the functional integrity of either the optic nerve, the trigeminal nerve, or both. Many of these proposals implied that both systems should interact with each other somewhere along their paths to produce the painful form of photophobia. Altogether, these proposals included abnormal processing of visual stimuli by the visual cortex due to hyperexcitability or reduced habituation (23–29); by the thalamus or its alteration by top-down cortico-thalamic input from the striate cortex (30); due to parenchymal lesions in the occipital lobe, thalamus or anywhere in the central course of the trigeminal nerve leading to non-painful hypersensitivity to light, termed ‘‘central dazzle’’ (31); due to direct activation of pain fibers in the eye (e.g. cornea, iris, uvea) by light, which consequently activate the spinal trigeminal nucleus, midbrain and thalamus in migraine or ocular diseases such as corneal damage (32,33); due to indirect activation of trigeminal pain fibers during parasympathetically-mediated vasodilation of ocular blood vessels (34,35); due to mechanical compression and irritation of the basal meninges by tumors near the optic chiasm (20); and sympathetic dysfunction leading to suboptimal control over the pupil and increased retinal illumination in migraine (12,36) and blepharospasm (37).

Due to the many anatomical structures and medical conditions that are associated with photophobia, efforts to identify the underlying neurobiological mechanisms behind its different forms must continue to focus on the relationship between visual networks, trigeminal pain pathways and autonomic regulation at multiple levels, from the eye to the cerebral cortex, in a pathology-specific manner.

Visual pathways for exacerbation of headache by light

The vast majority of migraineurs with normal eyesight report that exposure to ambient light renders their headache more intense and that lights appear brighter than usual during an attack (11,38,39). These clinical features may also in some cases be accompanied with ocular discomfort or pain, known as photo-oculodynia, especially when exposed to bright lights (15). Migraine patients experiencing these light-induced symptoms of photophobia usually stop performing mundane tasks, wear glasses that diminish the amount of light reaching the eye and, when possible, seek the comfort of darkness. The common notion is that exposure to light that is otherwise comfortable to healthy people exacerbates the intensity of the headache. However, the identity of photophobia in migraine is particularly intriguing because it may express itself as light-induced exacerbation of headache alone, as increased brightness alone, or both, at any given attack, and in some cases with the additional presence of ocular discomfort (15).

Despite the lack of distinction between these photophobia features, the high prevalence in migraine has placed it as one of the main criteria (besides headache characteristics) for the diagnosis of migraine (with and without aura) in the International Classification of Headache Disorders (40), where photophobia is simply defined as ‘‘hypersensitivity to light, usually causing avoidance’’. Although less frequent, photophobia has also been reported in tension-type headache (TTH), headaches associated with traumatic brain injury, unilaterally in cervicogenic and cluster headache and other trigeminal autonomic cephalalgias (TACs) (11,19,39,41). However, there is virtually no research attempting to identify the cause of photophobia in these other headache conditions.

Insight into the role of visual networks for light-induced intensification of headache emerged in a recent translational study with blind migraineurs (42). The authors hypothesized that photic information carried through the optic nerve must be transmitted, at least partially, to retino-recipient brain targets for this phenomenon to occur. Accordingly, intensification of headache was perceived only by blind migraineurs with an intact optic nerve who were able to partially perceive ambient illumination but unable to form images due to degeneration of rod and cone photoreceptors (i.e. patients diagnosed with retinitis pigmentosa, retinal prematurity or cone/rod dystrophy). Conversely, totally blind migraineurs lacking any type of visual perception due to damage of the optic nerve (i.e. those with optic neuropathy, retinal cancer or enucleation), which translates to complete absence of photic information reaching their brain, testified that light does not hurt them during migraine. These optic nerve-compromised subjects also presented fragmented or irregular sleep patterns and deficient pupillary light response. These findings provided evidence that in the absence of visual signaling from rods and cones, light activation of the newly discovered intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing melanopsin photopigment was sufficient to produce photophobia during migraine headaches (43–45). Along with these clinical observations, anatomical and functional data obtained in rats further support this scenario (42). Experiments using in vivo electrophysiological recordings of dura-sensitive (trigeminovascular) neurons in the thalamus showed that shining light into the contralateral eye induces robust and sustained increase in their activity. These light/dura-sensitive neurons, which are located in the lateral posterior (LP) and posterior (Po) nuclei, receive

input from ipRGCs. In addition, the axons of these thalamic trigeminovascular neurons project to multiple cortical areas including somatosensory (S1/S2) and visual (V1/V2) cortices (42,46) (Figure 1). Further evidence supporting the existence of such a pathway in humans comes from imaging studies showing blood oxygen-level dependent (BOLD) responses in the pulvinar (LP/Po area in the posterior thalamus of the rat) of patients undergoing a migraine attack with extra-cephalic allodynia (47), and from diffusion MR tractography showing direct connections from the optic nerve to the pulvinar, and from the pulvinar to several associative cortical brain regions (48). (see ‘‘thalamo-cortical role in photophobia’’ section below).

These studies suggest that the convergence of photic signals from ipRGCs onto the trigeminovascular thalamo-cortical pathway has the potential to explain how light intensifies the perception of headache during migraine. Additional evidence supporting the role of ipRGCs in migraine photophobia comes from a better understanding of their physiological role (49–52), as well as from patients’ testimonies and research reporting that migraineurs are more sensitive to certain wavelengths of visible light (53), and from the significant benefit they obtain when using lenses blocking bands of spectral light (54–56). It is important to note however, that the sensitivity to selective light stimulation of the ipRGCs is not the only responsible for explaining the effects of blocking specific wavelengths, and therefore a single-player conclusion must be tempered by the knowledge that rods and cones provide visual signals to the ipRGCs under dim to moderately bright illumination.

Role of ipRGCs in migraine photophobia

As mentioned above, it is well established that activation of melanopsinergic ipRGCs under conditions when rod and cone visual signaling is compromised allows regulation of biological functions such as circadian photoentrainment, pupillary light reflex (PLR), melatonin release and eye development (44,45,57–60). Comprehensive reviews on the structural and functional properties of these photoreceptors highlight their role as an illumination detector system, optimally-driven by ~480 nm wavelength photons producing blue in the visible spectrum (49,61). In fact, a study with blind individuals who were unable to form images due to the absence of cone-mediated visual signaling and were nominally unaware of light perception, yet with intact ability to photoentrain and regulate melatonin release, showed that they were able to correctly identify the interval period of a 481 nm test light but failed to detect it at other wavelengths. Such perception, described by them as ‘‘brightness’’, led to the conclusion that these photoreceptors might also contribute to some awareness of light (62). This possibility is further supported by anatomical and functional evidence in primates and rodents showing direct ipRGC projections to the lateral geniculate nucleus (LGN), which in turn projects to the V1 cortex (63,64). Also, in neonatal rodents whose rods and cones are not fully developed, light stimulation induces a robust behavioral response of avoidance associated with aversion, which was completely abolished in mice lacking melanopsin photoreceptors (65–67). Altogether, these studies unveiled previously unknown functions for non-image-forming pathways and suggest that the perceptual experience induced by direct activation of ipRGCs likely includes awareness and emotional reactions through continuous sensing of background illumination to regulate functional adaptation of the retina (49,68–71).

In the context of migraine, further support for the role of non-image-forming pathways in photophobia emerged in a proof-of-concept study designed to maximally block blue light (480 nm) using notch filter lenses during 2-week periods in chronic migraineurs (54). Using the headache impact test (HIT-6) and a photophobia questionnaire, the authors found that not only blue but also sham lenses filtering red light (620 nm) were beneficial for the headache and photophobia. The expected benefit of blocking blue and the surprising benefit of blocking red light was interpreted as due to the intrinsic bistable properties of melanopsin photopigment, by which red light could photoswitch melanopsin photopigment to a more sensitive state. Accordingly, under resting state (dark), melanopsin can be maximally activated by short wavelengths of light (~480 nm blue) through photoconversion of 11-*cis* to *all-trans* retinaldehyde isoform, which leads to ipRGC depolarization and transmission of photic information to the brain (49). Direct application of long wavelengths (~620 nm red) was proposed to activate an intrinsic photorecovery mechanism (72,73); however, direct recordings of ipRGCs under red wavelengths failed to show a response (74), thus opposing the bistability hypothesis described above. Nevertheless, despite the mechanisms involved, blocking specific wavelengths of light with tinted glasses has proven effective in decreasing migraine frequency in children and adults (55,56), and photophobia symptoms in blepharospasm (75).

From another therapeutic perspective, normalizing photic neurotransmission along visual pathways remains a potential and attractive target to treat migraine photophobia emerging from visual processes. Along this line, ipRGCs projecting to thalamic, hypothalamic and midbrain nuclei contain glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) as neurotransmitters (76–79), two molecules that have been largely implicated in migraine pathophysiology. For example, PACAP can trigger migraine-like headaches in migraineurs and healthy controls when injected intravenously (80,81), and it has been associated with a variety of functions relevant to migraine biology including stress, feeding, circadian rhythms and pain (82,83). Its receptors are also strategically located in a number of anatomical structures linked to migraine such as cranial vasculature, mast cells, sensory and autonomic neurons in the periphery, and brain areas including ipRGC-projecting targets and brainstem trigeminal nuclei (77,84,85). Although, nitroglycerin-induced photophobic behaviors are greatly attenuated in transgenic mice lacking PACAP (86), the specific role of this peptide in migraine photophobia remains to be determined.

As mentioned above, additional retinal mechanisms are also involved in the type of photophobia experienced by migraineurs with normal eyesight, and although the neural mechanism unraveled by the Burstein's group (42) suggests an association between intensification of headache by light and ipRGCs (especially in blind subjects), activation of ipRGCs is also achieved extrinsically by rods and cones (87) through amacrine and bipolar retinal cells (88,89).

Role of cone/rod-driven retinal pathways in migraine photophobia

The classic image-forming photoreceptor system is at the forefront in color formation and contributes to light intensity processing at all times in activities of our daily life. For migraineurs with normal eyesight, virtually all luminous intensities can trigger

uncomfortable features of photophobia (19). They are hypersensitive to light in plain daylight or while facing a screen, in which S- M- and L-cones are more sensitive to color and high illumination conditions (photopic vision); in low illumination conditions where rods are more sensitive (scotopic vision); or when driving at night using both photoreceptors (mesopic vision) (90,91), which is a serious challenge for photophobic migraineurs. Given that migraine has also been associated with abnormal color vision and color discrimination (92–94), maladaptive dysfunction of cones and/or rods' photoreceptors could play an additional role in migraine photophobia.

In a recent translational study, Noseda et al. (2016) documented classic photoreceptor contribution to migraine photophobia. A psychophysical study was performed in migraineurs with normal eyesight to test the effects of colors in headache intensity and other headache features. White, blue (447 ± 10 nm), green (530 ± 10 nm), amber (590 ± 10 nm) and red (627 ± 10 nm) lights were applied using a full-field Ganzfeld stimulator calibrated to deliver narrow bands of visible light at equal intensity to the human eye for 3 minutes. Surprisingly, green light significantly attenuated the headache intensity, as opposed to the exacerbating effect of white, blue, amber and red lights. Headache features such as throbbing, location and spread were also affected selectively. Mechanistic support was obtained by using color-selective electroretinography (ERG) and visual evoked potentials (VEP) in migraineurs, and electrophysiological recordings of dura/light-sensitive neurons in the rat LP/Po thalamic region. Green light evokes the smallest a-wave signal in the light-adapted flash ERG of migraineurs as compared to white, blue, amber and red. Similarly, neuronal responses of rat dura/light-sensitive neurons were milder under green illumination, and cortical P2 amplitude generated by green in patients interictally was significantly smaller than P2 evoked by other colors. These results suggest that the perception of headache intensity is selectively modulated by spectral light through photoactivation of cone-driven retinal pathways. The unexpected soothing effects of green light observed in the psychophysical study add to the previously known hypersensitivity to blue and red (53,56,75), which is further supported by this study.

In the same cohort of patients, other light-induced non-sensory symptoms were studied under the premise that migraineurs also describe exposure to light as an unpleasant or uncomfortable experience. Psychophysical assessment showed that light, independent of the wavelength, triggered more changes in symptoms associated with autonomic functions during migraine than interictally or in control subjects (18). These symptoms included parasympathetically-mediated lacrimation, salivation, nausea and rhinorrhea, and sympathetically-mediated dry mouth, shortness of breath, chest tightness and palpitations, among other autonomic symptoms. In addition, the association between light and negative emotions such as feeling angry, scared, sad or stressed was stronger in migraineurs, as opposed to the association between light and positive emotions described as relaxing, happy, calming and soothing, which was stronger in control subjects than in migraineurs. Interestingly, green light was the only color able to trigger positive emotions during migraine, and red was most commonly associated to negative emotions. To delineate the neural mechanism behind these observations, a complimentary anatomical study in rats showed RGC axons interacting with hypothalamic neurons that project directly to the brainstem (superior salivatory nucleus, SSN) and spinal cord (intermediolateral nucleus,

IML) nuclei involved in parasympathetic and sympathetic regulation, respectively. Hypothalamic neurons receiving retinal input were also shown to contain dopamine, histamine, orexin, melanin-concentrating hormone, oxytocin, or vasopressin. Altogether, the variety of autonomic symptoms contributing to the unpleasant sensations described by migraineurs could be associated with photic activation of these retinohypothalamic-parasympathetic (RHP) and retinohypothalamic-sympathetic (RHS) pathways (Figure 2). The emotions triggered by colors of light, however, may originate from a more complex interplay between these retino-hypothalamic networks and limbic structures, as well as direct retinal input to the amygdala (64,95,96). In addition, these findings raise the possibility that the hypothalamus is the culprit in abnormal parasympathetic and sympathetic functions during migraine. This possibility is further supported by the pivotal role played by the hypothalamus in migraine pathophysiology (see review on the hypothalamus in this same special issue).

Role of retinal pathways to midbrain and brainstem in migraine photophobia

Independent of the contribution of hypothalamic dysfunction, the role of the autonomic nervous system in photophobia is undisputable. Other potential mechanisms causing dysregulation of autonomic functions in migraine, in addition to the RHP/RHS pathways described above, could be linked to dysfunction of retinal pathways controlling pupillary light reflex (PLR) through autonomically-driven midbrain circuits (12,97–99) (Figure 3). Along this line, further contribution of autonomic dysregulation in migraine photophobia was recently tested in a remarkable study by Brennan's group (100). Quantitative measurement of PLR together with clinical evaluation and psychophysical assessment of photophobia threshold was performed in migraineurs and healthy controls. They showed that abnormal PLR was associated with low photophobia thresholds interictally, and that this abnormality was correlated with migraine severity. Chronic migraineurs and patients experiencing the most severe migraines (i.e. those exhibiting the highest HIT-6 and Migraine Disability Assessment (MIDAS) scores) had the lowest photophobia thresholds and displayed the greatest alteration in constriction latency (parasympathetic) and pupillary re-dilation (sympathetic) measurements. In addition to validating the pupillary function as a biomarker of migraine photophobia, the authors conclude that abnormal PLR is central in origin and reflects autonomic maladaptation to chronic light sensitivity. This is consistent with the notion of altered excitability in CNS structures in migraine pathophysiology (27,101).

Pupillary light reflex involves transfer of photic information by cone/rod-ipRGC photoreceptors to the pretectal area in the midbrain, and from there to preganglionic parasympathetic (E-W) and sympathetic (IML) nuclei controlling iris movement through ciliary and superior cervical ganglia, respectively (102). Interestingly, another mechanism involving retinal input to the pretectal area and autonomic regulation of the ophthalmic region has been proposed to contribute to photophobia. In this case, excess of light may lead to ocular pain or photo-oculodynia, which is another clinical manifestation falling into the definition of photophobia. Accordingly, bright light could induce ocular pain by activation of

a retinal-olivary pretectal (OPN)-SSN pathway that drives vasodilation of choroid blood vessels. Ocular pain may then result from mechanical stimulation of sensitized trigeminal nociceptors innervating dilated eye vasculature (34,35) (Figure 3). Activation of these trigeminal nociceptors can further amplify photophobia through trigeminal-autonomic reflex (12) and hypothalamic facilitation of trigeminal activity (103,104). These complementary mechanisms are thought to play a major role in the type of photophobia associated with inflammation of the uvea (iris, ciliary body and choroid), corneal damage and other prechiasmal pathologies (13,15,32,105).

These ocular structures are richly innervated by trigeminal sensory neurons containing CGRP and, given that CGRP plays a fundamental role in migraine pathophysiology, its contribution to photophobia is beyond doubt (106). Indeed, photophobic behaviors such as increased light aversion or sensitivity to light have been shown in a transgenic mouse model of migraine presenting increased sensitivity to CGRP due to overexpression of the human receptor activity–modifying protein 1 (hRAMP1) (107,108). Behavioral data obtained using this model in combination with selective blockage of CGRP suggest that CGRP may contribute to photophobia through both peripheral and central, yet unknown, mechanisms (109).

Role of thalamo-cortical loop in migraine photophobia

A large body of evidence points to structural and functional abnormalities in the thalamus of migraineurs (47,110,111). How these abnormalities impact the perception of photophobia is unknown, but as described above, thalamic neurons outside the main visual pathway can also process photic and nociceptive trigeminovascular signals and transfer them to the cortex (17,42). This scenario places light as another modulator of nociception at the thalamic level. Indeed, thalamic neurons are subjected to a variety of modulatory inputs from cortical, intrathalamic, hypothalamic and brainstem origin (112,113). In rats, thalamic LP/Po nuclei implicated in photophobia are influenced by a variety of neuropeptides and neurotransmitters from different sources such as GABA from the reticular thalamic nucleus; noradrenaline from the locus coeruleus; serotonin from the raphe nuclei; and histamine, MCH, orexin, acetylcholine and dopamine from a variety of hypothalamic and forebrain nuclei (18,114). Also, besides glutamatergic afferents from ascending trigeminal afferents (115,116), glutamatergic input from ipRGCs to LP but not Po has been shown in mice (64,117), suggesting that activation of thalamic trigeminovascular neurons in these nuclei by light may occur directly through retinal input and indirectly through other structures such as the superior colliculus (95,118–120) and cortex (115). Accordingly, thalamic LP/Po neurons not only send axonal projections to a variety of cortical areas involved in sensory processing (42,46) but also receive massive projections from the cortex (112,121). Indeed, a single Po neuron in the thalamus was shown to integrate sensory ascending information with powerful cortical signals and transfer the integrated activity back to cortical networks (122). In humans and primates, structural and functional homology of the LP/Po area in rodents is found in the pulvinar (123,124), which has been associated with migraine photophobia (48) and projects to several cortical regions including the cingulate, visual association, somatosensory, parietal and prefrontal cortices (47,125–127), suggesting that this region of

the posterior thalamus and its connectivity with the cortex play a wider role in sensory processing.

Observations that migraineurs are also more sensitive to light between attacks (11,39,128) and that lower thresholds for visual detection were measured in migraine with aura (129), led to the hypothesis of altered excitability of cortical areas involved in the processing of photic signals. Indeed, a recent PET imaging study with migraine patients and healthy controls showed that migraineurs have an intensity-dependent increased sensitivity to light correlated with increased activation of the visual cortex (25,130). Therefore, a hyperexcitable visual cortex incapable of habituating to visual stimuli was proposed as the neural substrate of migraine photophobia. Abnormally high neuronal excitability is not limited to the visual cortex; however, it may also include cortical regions involved in the perception of pain, sound, smell and taste, suggesting that other sensory hypersensitivities are mediated by abnormal excitability of cortical regions (23,24,27,131–133), or alternatively, by dysrhythmias in thalamo-cortical networks (134).

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Article highlights

- Photophobia is a poorly defined multi-symptomatic light-induced phenomenon.
- The relative contribution of visual, trigeminal and autonomic mechanisms in photophobia may depend on the condition it emerges from.
- Both cone/rod-mediated image-forming and melanopsin-mediated non-image-forming visual pathways contribute to photophobia in migraineurs with normal eyesight.
- Migraine photophobia emerges from activation of retinal photoreceptors and the photic signals they transmit to multiple brain regions involved in sensory, autonomic and emotional regulation.
- Blocking all colors of light but green may alleviate photophobia symptoms in migraine.
- Photophobia's association with headache appears more complex than previously thought.

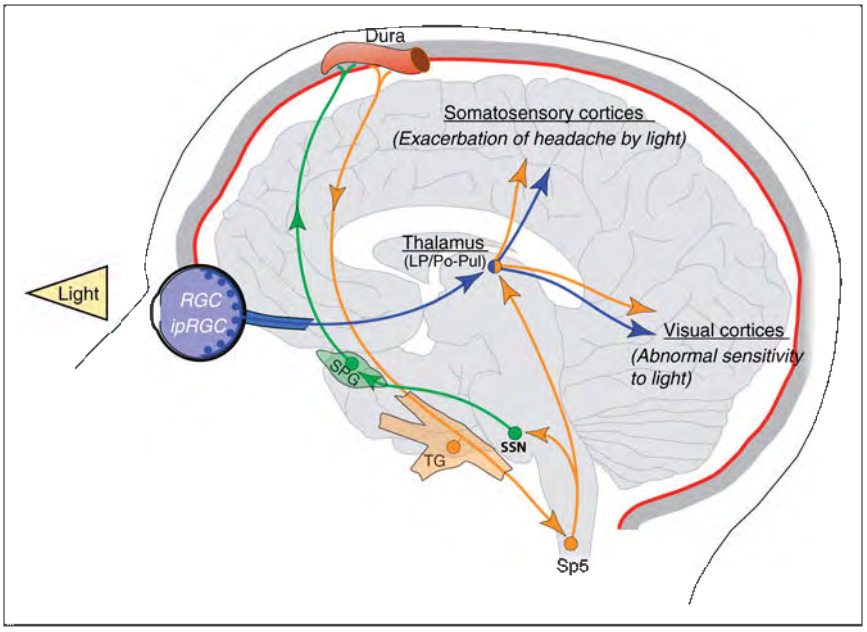

Figure 1.

Schematic representation of the retino-thalamo-cortical pathways proposed to explain the most common light-induced sensory symptoms in migraine when patients are exposed to ambient light during attacks. LP: lateral posterior thalamic; Po: posterior nucleus of the thalamus; Pul: pulvinar; RGC: retinal ganglion cells; ipRGC: intrinsically sensitive retinal ganglion cells; SSN: superior salivatory nucleus; SPG: sphenopalatine ganglion; TG: trigeminal ganglion; Sp5: spinal trigeminal nucleus.

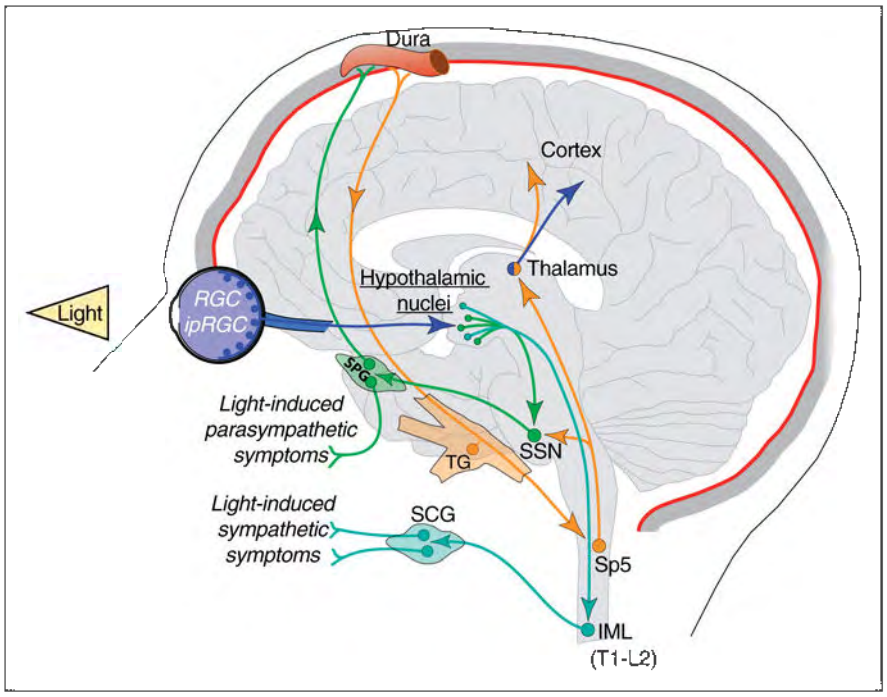

Figure 2.

Schematic representation of the retino-hypothalamo-parasympathetic (SSN) and sympathetic (IML) pathways proposed to explain a host of light-induced autonomic responses during migraine attacks, and to a lesser extent, between attacks. SCG: superior cervical ganglion; IML: intermediolateral nucleus.

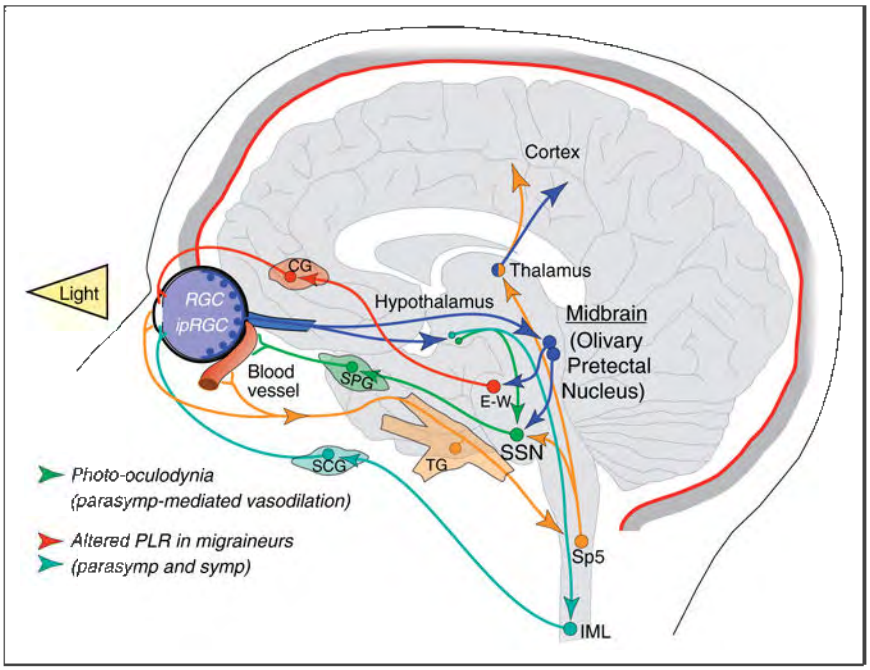

Figure 3.

Schematic representation of the retino-midbrain-parasympathetic (SSN) pathway proposed to explain bright light-induced ocular pain. Pupillary light reflex circuit, which is abnormal in migraine, is also depicted. CG: ciliary ganglion; E-W: Edinger-Westphal nucleus.

Determination of the proportion of refractive errors in patients with primary complaint of headache and the significance of refractive error correction in symptoms relief

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Abstract

Introduction: Headache attributed to refractive errors (HARE) is a common condition caused by myopia, hypermetropia, and astigmatisms. Headache is not necessarily experienced by all individuals with REs. HARE is mainly caused by the strain produced in the ciliary muscles to focus objects more often during near works like reading. This study is an attempt to estimate REs with headache and symptoms relief after correction respectively.

Materials and Methods: 103 cases of both sexes with mean age 19.04±7.27 years referred to the ophthalmology out patient department with complain of haedache were included in the study. Objective refraction was measured with 0.5% cyclopentolate drops and retinoscopy was done with suitable lenses. All cases were followed up for a period of one month.

Results: The frequency of REs in headache patients was found to be (29) 28.15% with hypermetropia 9(31.03%), myopia 6(20.69%), mixed astigmatism 5(17.24%), compound myopic astigmatism 4(13.79%), compound hypermetropic astigmatism 3(10.34%), simple myopic astigmatism 2(6.90%). Asthenopia was found in 62% of cases diagnosed with RE. Symptoms relief was seen in 69% of cases after spectacles prescription. 16 out of 19 patients with asthenopia experienced symptoms relief after one month.

Conclusion: Among the many causes of headache, HARE is a subgroup to be resolved with ophthalmological consultation. The results of this study indicates a positive association of Res in causing headache and the importance of lens correction in symptoms relief. So, all headache cases should have ophthalmological examination since maximum amount of success is possible in HARE management.

Keywords: Asthenopia, Astigmatism, Headache, Hypermetropia, Myopia, Refractive error.

Introduction

Specific eye diseases, such as acute glaucoma, refractive error, heterophoria and heterotropia, ocular inflammatory disorders such as iritis, uveitis, scleritis and optic neuritis[1] are often associated with headache which is an important health complaint and disability worldwide.[2,3] Headache is classified into three types, 1. Primary, 2. Secondary and 3. Painful cranial neuropathies, other facial pains and other headaches by the International Headache Society (IHS). [4] Primary headaches do not have an underlying disorder. Headache attributed to disorders of the eye are classified under secondary headaches.[1]

Refractive errors (REs) affect a large amount of population worldwide, irrespective of age, sex and ethnic group. These refractive errors when diagnosed are corrected with spectacles or other refractive corrections to attain normal vision.[5] The exact role played by refractive errors in the etiology of headache is still inconclusive.[6] Literature evidences significant positive association of refractive errors and headache. On the other hand prevalence of headache is considered as coincidental among the population irrespective of REs.[7,8]

Asthenopia is an ocular discomfort leading to headache and pain in eyes with symptoms like eyestrain, easy fatigability after reading, and heaviness of lids after reading. It is caused by uncorrected refractive errors.[9] Refractive errors that could possibly contribute to headache includes, emmetropia and ammetropia. Emmetropia is defined as the state of refraction wherein the parallel rays of light coming from infinity are focused on the retina, when the accommodation is at rest. The emmetropic eye relies in a relaxed state and focused on an object more than 6 meters or 20 feet away without any effort. Emmetropia is a condition between myopia and hypermetropia in which light rays from the source are too divergent and not focused properly into the retina. Ammetropia is defined as a state of refraction wherein the parallel rays of light from infinity are focused either in front or behind the retina when the accommodation is rest. It includes myopia, hypermetropia, and astigmatism. The strain produced in hypermetropia and astigmatism to focus during near works like reading is more related to headache symptoms.[10]

Diagnostic criteria to confirm that the headache is attributed to refractive error are,

1. Uncorrected or miscorrected refractive error in one or both eyes,
2. Criteria fulfilling at least two of the following:
   i. Headache has developed and/or significantly worsened in temporal relation to the onset or worsening of the refractive error.
   ii. Headache has significantly improved after correction of the refractive error.

iii. Headache is aggravated by prolonged visual tasks at an angle or distance at which vision is impaired.
iv. Headache significantly improves when the visual task is discontinued.[1,4]

This study attempts to find out the proportion of refractive errors in patients attending the outpatient department with complaints of headache and improvement in symptoms after spectacle correction.

Materials and Methods

Study Design: This hospital based cross-sectional study was carried after obtaining approval from the institutional ethics committee in eligible patients who presented to Sri Manakula Vinayagar Medical College and Hospital, Puducherry from September 2013 to January 2015 with headache as a primary complaint for duration of one month or more. The sample size was calculated as 94 with 95% CI using open Epi Software (version 2.3). Considering 10% of subjects as non-response, the final sample is 103.

Inclusion Criteria: Patients in the age group of <40 years including male and female cases attending the ophthalmology outpatient department with primary complaint of headache with duration of one month or more, were included in the study.

Exclusion Criteria: Patients who have already been diagnosed with refractive error, patients with other eye diseases like inflammations (iridocyclitis. scleritis), glaucoma, and other diseases that may be attributed for causing headache as described in the IHS (International Headache Society) criteria were not included in the study.Patients with corneal opacities, optic atrophy and other diseases in which subjective improvement cannot be done were also excluded.

A written informed consent was obtained from all patients who were eligible for the study, based on the inclusion criteria. For the patients below 16 years of age, informed written consent was obtained from the parent.

Each patient was then subjected to a complete workup which included a full medical history and a detailed history regarding the nature of the headache – the location of headache, total duration of headache, duration of each episode, frequency, associated symptoms like aura, asthenopia, photophobia, phonophobia, nausea, vomiting, triggering and relieving factors of headache and history regarding diminution of vision were taken.

All patients underwent a complete ocular examination including visual acuity testing, objective refraction and dilated fundus examination. Objective refraction was measured after assessing the visual acuity, by instillation of 0.5% cyclopentolate drops in the conjunctival cul-de-sac of both the eyes. After 40 minutes retinoscopy was done at 1 meter distance by neutralizing the retinal reflexes using suitable lenses in the two principal meridians. Subjective correction and Post mydriatic test was done after 3 days. Patients with refractive errors were prescribed glasses and followed up after 1 month.

Results

A total of 103 patients, 53 males and 50 females were enrolled in the study. The age group ranged from 6-36 years with a mean of 19.04±7.27 years.

Distribution of refractive errors: Of the 103 patients, 29 (28%) patients were diagnosed with refractive errors. 19 patients of the 103 patients, presented with asthenopic complaints out of which 18 had refractive error while 1 was diagnosed with convergence insufficiency (Table 1). Out of 29 patients with refractive errors, 6 (20.69%) were diagnosed with myopia, 9(31.03%) with hypermetropia, 2(6.90%) with simple myopic astigmatism, 4(13.79%) with compound myopic astigmatism, 3(10.34%) with compound hypermetropic astigmatism and 5(17.24%) with mixed astigmatism. None of our patients had simple hypermetropic astigmatism (Fig. 1).

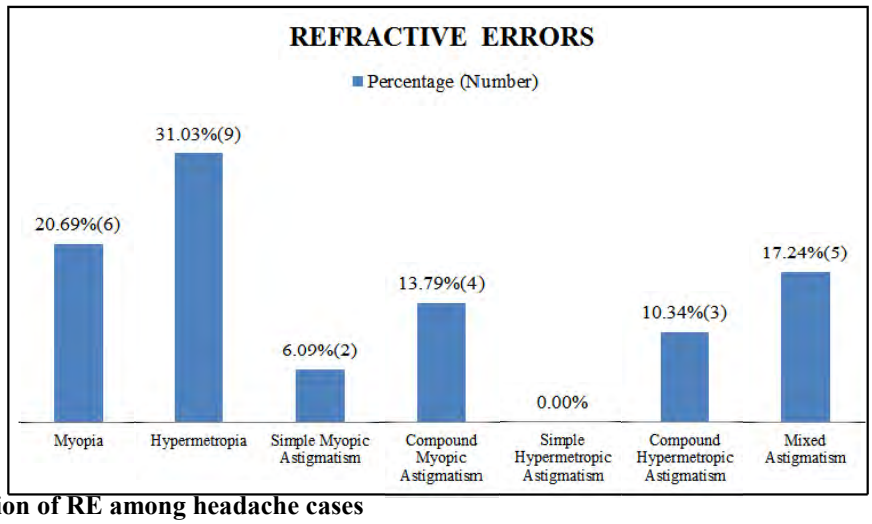

Fig. 1: Distribution of RE among headache cases

Hypermetropia is the most common RE associated with headache followed by myopia.

In myopic patients, the amount of myopia ranged from -0.50 DS to-3.00 DS with a mean of -1.50± -1.00 DS. Hypermetropia ranged from + 0.50 DS to + 2.25 DS with a mean hypermetropia of + 1.50 DS ± +0.75 DS. Myopic Astigmatisms ranged from -0.50 to -1.50D and hypermetropic astigmatisms ranged from +0.50 DC to +1.50 DC.

Distribution of refractive errors in asthenopia: Out of 29 patients who had refractive errors, 18 patients (62%) had complaits of asthenopia, and 11 patients (38%) had no complaints of asthenopia. The 19 patients with asthenopiaform 18.44% of the patients in our study out of which 6 were diagnosed with hypermetropia, 2 with simple myopic astigmatism, 2 with compound myopic astigmatism, 3 with compound hypermetropic astigmatism and 5 with mixed astigmatism (Fig. 2).

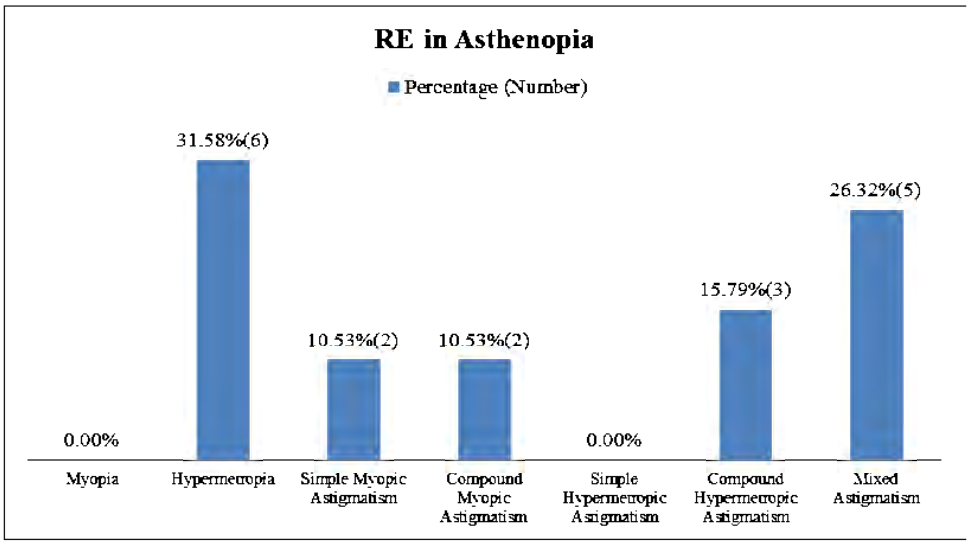

Fig. 2: Distribution of RE among headache cases associated with asthenopia

Hypermetropia is the most common RE found in patients with asthenopic complaints. No incidence of myopia

Symptom relief after RE correction: Out of the 29 patients with refractive errors, 20 patient's symptoms were relieved after refractive error correction by corrective lenses during the follow up at 1 month. 100% relief was seen in simple myopic astigmatism and compound hypermetropic astigmatism followed by hypermetropia (89%), mixed astigmatism (80%) and compound myopic astigmatism (50%). One patient (16%) with myopia experienced relief during the follow up. Among the 19 asthenopia cases, 16 patients were relieved from headache complaints and asthenopia after corrective lenses at 1 month follow up. After the correction of refractive errors, symptomatic relief was seen more in patients with asthenopia (80%) than with patients without asthenopia (Table 2).

Table 1: Study subjects and diagnosis

Proportion of Refractive Errors [N=103]	Proportion of Asthenopia in Refractive Errors [N=29]
Male = 53 (51%) Female = 50 (49%) Total RE = 29(28%)	RE with asthenopia = 18(62%) RE without asthenopia = 11(38%)

103 cases with primary complaint of headache were diagnosed for RE. Abbreviations: RE (Refractive Error)

Table 2: Symptomatic relief after glass prescription

Type of refractive error	Patients (n=29) (100%)	Symptoms relief (n=20) (69%)
Myopia	6 (20.69%)	1(16%)
Hypermetropia	9(31.03%)	8(89%)
Simple Myopic Astigmatism	2(6.90%)	2(100%)
Compound Myopic Astigmatism	4(13.79%)	2(50%)
Compound Hypermetropic Astigmatism	3(10.34%)	3(100%)
Mixed Astigmatism	5(17.24%)	4(80%)

Symptoms relief was seen more in simple myopic astigmatism and compound hypermetropic astigmatism followed by hypermetropia.

Discussion

It has been believed that uncorrected refractive errors may cause eyestrain and headache irrespective of age and sex. This hypothesis is under controversy for a long period of time with researches done in different populations with contradictory conclusions.[11-13] Several studies have been conducted to find out the relationship between headache and refractive error. Even though the International Headache society (IHS) categorized 'headache associated with refractive error' under secondary headaches, the IHS did not cite any evidence in support of its classification.[14]

By analyzing the rate of RE distribution among headache cases, we have observed 28.15% of REs from the 103 patients involved. This rate is similar in trends with most of the studies conducted in different time periods. Gordon et al 1966 examined 100 patients with headache and found that 28% had headache associated REs.[14] By comparing the headache group and normal population, Akinci et al 2008, found a significant association of REs (34.2%) with the headache group.[15] There are also fewer studies that declare no significant difference in the distribution of RE between headache group and the normal population.[16,13]

Among the type of REs distributed over headache, hypermetropia is the most common refractive error diagnosed. Myopia, mixed astigmatism, compound myopic astigmatism, compound hypermetropic astigmatism, simple myopic astigmatism are the next common refractive error in the order of decreasing frequency.

Hypermetropia and astigmatisms are found to be the recurring REs among headache.[17] Akinci et al found that hypermetropia and myopia were distributed equally among the headache group and normal population whereas astigmatism is found more common only in the headache group.[15] In hypermetropia and astigmatisms, the mechanism behind headache is not well explained but it may be due to blur eye and strain.[12]Astigmatic correction of 0.25D could be sufficient to produce relief of many headache complaints.[18] Gil-Gouveia et al 2002, found that hypermetropia appears to be more linked with patients suffering from chronic headache.[1] Eckhardt et al 1943, found that simulated hypermetropia and astigmatism leads to ocular discomfort after a short period of time and simulated myopia did not lead to ocular discomfort. But the experimental method is not described in this study.[19]

After spectacle correction, symptom relief was seen in patients with hypermetropia and astigmatism. In simple myopic astigmatism and compound hypermetropic astigmatism, 100% relief was observed. Among hypermetropia, 89% of cases experienced relief after RE correction which is least effective in myopia (16%) during the follow up. Overall headache relief after RE correction of the present study is 69% in one month which positively correlates the importance of RE determination and correction in headache management. The headache recovery rate of the study is compatible with the previously published data. Turville et al in 1934 analyzed the relation of REs with headache in 123 patients and found 60% of REs were hypermetropia of which 80% symptom relief was seen after spectacle correction.[11] Roth et al 2008, states that improvement in headache relief is irrespective of RE correction in school children.[13] In the same year, Dotan et al 2014, found that 87.5% of children diagnosed with REs experienced complete resolution from headache after RE correction in 1 month to 3years follow up.[12]

Headache is a characteristic of asthenopia accompanied with ocular discomfort, heaviness of eyelids, and brow acheetc. Astheniopia is caused by prolonged near work and strain in accommodation convergence system.[20] By correcting the RE associated with asthenopia, headache and its associated symptoms will be relieved. In our study asthenopia were more common in patients with hypermetropia and astigmatism. Significant improvement was observed (80%) in patients with asthenopia after RE correction.

Conclusion

A significant number of people suffering from headache comes under the category of 'headache attributed to RE (HARE)' and the same should be taken into the consideration of ophthalmologist. The beneficiary effect of RE measurement in headache is the symptomatic relief achieved in majority of the cases after RE correction. Despite of the controversies posing the relationship of REs and headache, the results of our study supports the fact that, 'symptomatic relief is obtained from headache in patients suffering from HARE after RE correction'. Even when the pathogenesis of HARE is not clear, the high recovery rate of hypermetropia and astigmatisms and poor outcome in myopia of the present study states that painful contracture of the ciliary muscle in sustained focusing of near objects could be the reason. A small proportion of people in which symptoms aren't relieved after RE correction, the headache could be related to eye in such a way through ocular diseases and neuro-ophthalmic conditions. We conclude that visual defects could be a risk factor or stimulating factor for headache and ophthalmologic referral is highly recommended.

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MEETING ABSTRACT Open Access

EHMTI-0348. Refractive errors in patients with migraine headache

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Introduction

Migraine is one of the most common debilitating diseases. Despite of intensive research in the pathogenesis and treatment of migraine, its relationship between refractive error have been controversial.

Aims

To evaluate refractive errors in patients with migraine headache and to compare with healthy subjects.

Methods

This prospective case-control study includes patients with migraine and age- and sex- matched healthy subjects. Clinical and demographic characteristics of the patients were noted. Then detailed ophthalmological examination were performed containing spherical refractive error, astigmatic refractive error, spherical equivalent (SE), anisometropia, best corrected visual acuity, intraocular pressure, slit lamp biomicroscopy, fundus examination, axial length, anterior chamber depth, and central corneal thickness. Spectacle use in migraine and control groups was compared. Also, the relationship between refractive components and migraine headache variables were investigated.

Results

Seventy-seven migraine patients with mean age of 33.27 ± 8.84 years and 71 healthy subjects with mean age of 31.15 ± 10.45 years were enrolled (p = 0.18). The migraine patients had higher degrees of astigmatic refractive error, SE, and anisometropia when compared with the control subjects (p = 0.01, p = 0.03, p = 0.02, respectively).

Conclusions

Migraine patients may have higher degrees of astigmatism, SE, and anisometropia. Therefore, they should have ophthalmological examination regularly to ensure that their refractive errors are appropriately corrected.

Seventy-seven migraine patients with mean age of 33.27 ±8.84 years and 71 healthy subjects with mean age of 31.15 ± 10.45 years were enrolled (p = 0.18). The migraine patients had higher degrees of astigmatic refractive error, SE, and anisometropiawhencompared with the control subjects (p = 0.01, p = 0.03, p = 0.02, respectively).

No conflict of interest.

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Enhanced Motion Aftereffects in Migraine Are Related to Contrast Sensitivity: Implications for Models of Differences in Precortical/Cortical Function

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Purpose. Visual tests can be used as noninvasive tools to test models of the pathophysiology underlying neurological conditions, such as migraine. For example, there are reports that the motion aftereffect, which involves neural processing in several cortical areas, is prolonged in migraine. There also are reports of impaired contrast sensitivity in migraine, however, attributed to a precortical dysfunction. This study explored associations between these two tests of visual function. Specifically, it aimed to clarify whether the magnitude of the motion aftereffect is affected by contrast and contrast sensitivity.

Methods. The motion aftereffect was elicited after observers viewed a coherently moving pattern for 45 seconds. The duration of the subsequent aftereffect was measured with three different test display contrasts (high, medium, low). Contrast sensitivity also was assessed.

Results. For each test display contrast, the motion aftereffect was prolonged in migraine compared to the control group. Contrast sensitivity was poorer in the migraine group and was a significant predictor of motion aftereffect duration.

Conclusions. These results suggest an anomaly in early motion processing pathways in migraine that likely is linked with those pathways underlying contrast sensitivity. They provide further evidence for differences in visual processing that begin early, potentially starting at the retina, which have consequences for performance on tasks that putatively examine cortical processing. Differences in precortical and cortical visual pathways are implicated in the pathophysiology underlying migraine.

Keywords: migraine, motion perception, contrast sensitivity, visual processing, cortical processing, motion aftereffect

Migraine is a common neurological condition estimated to affect more than 10% of the world's population at any given time, and women are three times more likely to be affected than men.[1,2] The pathophysiology of migraine still is not entirely understood. Much research has paid attention to visual processing in migraine due to the intense sensitivity to light (photophobia) that patients can experience during a migraine, the visual disturbances that may precede or accompany an attack (the visual aura), and the fact that visual stimuli can trigger attacks.[3–9] The perception of motion has been a particular focus and this study continues in this vein. Psychophysical studies using various visual motion-processing paradigms (e.g., pattern adaptation, threshold discrimination, and threshold detection) have revealed differences in performance between migraine and control groups. Generally, the migraine group's performance is impaired.[10–15] Although different researchers often propose different models of anomaly in the visual system, there is a general consensus that abnormal cortical processing is an underlying factor in the pathophysiology of migraine and underlies these group differences in motion perception.

The experimental paradigm used here is one that has been used recently in migraine research: the motion aftereffect (MAE).[10,13] The MAE can be seen after prolonged exposure to coherent motion in a particular direction. Once the motion stops, any subsequently presented display appears to drift in the opposite direction. The MAE has been used extensively in basic vision research and has contributed significantly to the mapping of motion selective pathways in the visual system. It is a visual illusion that offers a noninvasive and simple opportunity to assess activity attributed to processing in the visual cortex.[10,13,16] One clear indication that the MAE involves cortical activity is its ability to transfer interocularly: that is, if the adapting display is viewed with one eye only, but the test display is presented to the other eye, the illusion still is seen, although it may be at a weaker intensity.[16,17] Binocular cells, which are activated by displays presented to either eye, are found first in abundance in the primary (striate/V1) visual cortex.[18,19]

The MAE is produced by a biased distribution of activity in direction-selective neurons in the visual system.[20] Direction-selective neurons, like any other cortical neurons, produce a steady low-level of spontaneous activity when not engaged by any stimulus. If a visual display contains elements with a certain motion direction and speed that activates particular neurons, their initially rapid firing rate will decline steadily for as long as the stimulus is present, that is, the cells get adapted. When the motion stops, the neurons take a little while to "recover" and regain normal levels of spontaneous activity. During that time, the spontaneous activity of all other neurons sensitive to

different motion directions exceeds that of the suppressed neurons. This produces a biased distribution of spontaneous activity that is similar to activity produced by slow motion in the opposite direction, and that results in the perceived aftereffect.[21,22]

To explore differences in cortical processing between people with and without migraine, Shepherd[10,13] studied the magnitude of the MAE, measured as the duration of the illusory motion, and found that the MAE was more pronounced in migraine, that is, it lasted longer than in the control group. Often, the MAE is examined using drifting sine-wave gratings for adapting displays, and stationary or counter-phasing sine-wave gratings as test displays. Shepherd,[10,13] however, instead used random dot displays for adapting and test displays. Group differences that may arise with gratings are likely to confound differences in motion perception with differences in the perception of gratings, likely since gratings can induce visual discomfort, which is more pronounced in migraine (reviewed previously[7]). The classic motion aftereffect with random dot displays involves stationary test displays, which yields a local motion aftereffect where the test display appears to drift, yet the dots that comprise the display do not appear to change position. When the test display is itself dynamic (which, with random dots, appears like a detuned television), illusory motion is seen again but this time the motion looks like real motion. It is described as a global motion percept. Shepherd[10,13] used stationary and dynamically twinkling random dot test displays that were presented either immediately after the adapting motion stopped, or after a 15-second delay, to compare the phenomenon of storage of the MAE in migraine and control groups. The global MAE stored almost completely over a 15-second delay, whereas the local MAE stored only partially. Because of these differences in appearance and storage, local and global MAEs have been interpreted as showing adaptation at different stages within the visual pathways.

Shepherd,[7,13] therefore, discussed general models or descriptions of the motion aftereffect, as proposed by early researchers, such as Sutherland[21] and Barlow and Hill,[23] in the context of more recent models that have tried to anchor elements of the illusory aftereffect to particular stages of processing within the visual pathways (see prior reports[7,10,13,14]). The conclusion was that multiple sites are involved in adaptation to motion, which can be tapped with careful selection of adapting and test displays.[13] Extrinsic factors (such as context and synaptic efficacy between populations of neurons tuned to various attributes of the adapting and test displays) and intrinsic factors (such as fatigue-like processes/membrane hyperpolarization) can be addressed with particular paradigms.

Shepherd[10,13] proposed that the enhanced MAEs were the result of slow cellular recovery and/or an extended suppression of cortical excitatory synaptic connections between cells that responded to the adapting display. It was concluded, by using the different types of adapting and test displays (stationary or dynamic/twinkling test displays), that cortical processing at early (V1/striate cortex) and later (V5/MT) visual areas sensitive to motion were affected in migraine. Earlier levels of cortical motion processing were assessed with the stationary test displays; early and later levels with the dynamic or twinkling test displays.[10,13,16,17,24,25] No significant differences were found between migraine groups with and without visual aura. Here, the MAE duration was assessed for static displays presented immediately after the adapting motion ceased, thereby involving processes involving changes in synaptic efficacy and cellular recovery.[13]

In this study, the effects of contrast and contrast sensitivity on the MAE in migraine and control groups were explored. Direction-selective cells in early motion processing pathways in the striate cortex (V1) are affected by contrast as well as motion. An early study by Keck et al.[26] investigated the effect of adapting and test display contrasts using drifting sinusoidal gratings as adapting displays, and stationary sinusoidal gratings as test displays. Whether the participants included people with migraine is likely but is not known. Despite this caveat, it is relevant to the present study. They reported that the magnitude of the MAE increased with increasing adaptation contrast or with decreasing test display contrast, that is, it was maximal for high contrast adapting gratings paired with low contrast test displays. As described above, the MAE occurs due to a biased distribution of spontaneous activity in direction-selective cells. Prolonged MAEs for low contrast test displays can occur if the residual firing rate of adapted cells in response to high contrast test displays is stronger than that to the low contrast test displays, while the firing rates of unadapted cells remain higher in both conditions. Thus, the imbalance in activity between adapted and unadapted cells would be greater for low contrast test displays than for high, which results in a longer MAE for the low contrast test displays.

There have been consistent reports of impaired contrast sensitivity in migraine. Such results have been attributed to abnormal precortical processing.[14,27–30] Input to higher order cortical centers relies on the adequate processing of information in precortical pathways. Therefore, contrast sensitivity differences between migraine and nonheadache control groups resulting from precortical abnormalities could result in reduced input to cortical centers. Consequently, differences in early visual processing may have consequences that could be misattributed to differences in cortical processing. Shepherd et al.[14] included contrast and contrast sensitivity in a relative motion, global motion detection, and global motion discrimination study in migraine. They reported their migraine group had significantly poorer contrast sensitivity, that is, they had higher contrast thresholds, than the control group. Contrast sensitivity also correlated significantly with performance on each motion task. As expected from previous work, these correlations showed that poorer contrast sensitivity was associated with fewer correct responses on a motion direction detection task and poorer performance (higher thresholds) on global and relative motion discrimination tasks. When contrast sensitivity was added as a covariate to the analyses, however, the group differences disappeared for the motion direction detection thresholds and relative motion tasks. For their motion discrimination task, the group differences persisted, however, so it was concluded that there are cortical variations in migraine, in addition to impaired contrast sensitivity, and that anomalous processing in low-level (precortical) pathways can confound interpretation of performance on other tasks if not taken into account.

The aim of the current experiment was to assess whether the MAE is affected by contrast and contrast sensitivity in migraine and control groups. As described above, MAEs can be seen in test displays that are either stationary, or that also display temporal modulation. Here, the MAE duration was assessed in stationary test displays as the perceived aftereffect in such displays has been attributed to earlier stages of visual processing and, therefore, may be the more likely to show effects of contrast sensitivity, which also has been attributed to precortical visual processing.[28]

Trials consisted of three different test display contrasts (high, medium, and low). The adaptation contrast was kept constant (medium). The migraine group was predicted to have longer duration MAEs than the control group across all test contrast conditions.[10,13] Larger effects were predicted for low compared to high contrast test displays in both groups.[26]

Poorer contrast sensitivity was predicted in the migraine group.[14,27–30] By including contrast sensitivity in the analyses of the MAE data, this study aimed to determine any contribution of reduced contrast sensitivity to prolonged MAEs or whether any anomaly in early motion processing pathways (e.g.. up to and including V1) is independent of contrast sensitivity. Finally, no distinction was made between migraine participants with and without aura. This was decided due to previous research that has consistently failed to find significant differences between these subgroups in the magnitude of the MAE, nor in other motion tasks.[10,13–15]

Method

Participants

Each participant completed either a migraine or a headache questionnaire that detailed the characteristics of their migraine/headache symptoms, their frequency, and duration. All in the migraine group fulfilled the International Headache Society (IHS) criteria for migraine.[31] None in the control group experienced regular or severe headaches that fulfilled IHS criteria. Of the control participants who reported having headaches, they were tension-type, sinus-related, or due to dehydration. All testing was performed when participants appeared symptom-free and none had experienced a migraine/headache for 48 hours on either side of the test session. None of the participants was on prophylactic medication for any condition, nor had they taken any acute medication within 48 hours of the test session. All participants had a binocular visual acuity of at least 20/25, with or without optometric correction.

We initially recruited 20 migraine participants; however, eight were excluded as they either reported having a migraine within 48 hours of the test session, or they failed to meet the IHS criteria.[31] Thus, 12 migraine participants were tested (11 female, 1 male; age, 32.0 ± 9.9 years; range, 20–54; 6 with visual aura) and they were approximately age-matched to 12 control participants (7 female, 5 male; age, 32.6 ± 6.9 years; range, 20–47). Participants were recruited from advertisements and an existing migraine database at Birkbeck College (London, United Kingdom). They received either course credit or a small honorarium for their participation.

The study received ethical approval from Birkbeck's Department of Psychological Sciences Ethical Committee. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki (1991).

Apparatus/Materials

Motion Aftereffect (MAE). The displays were created using experimental scripts developed in C in conjunction with routines from the Video Toolbox.[32] The stimuli were presented on a 21-inch CRT monitor (LaCie, Paris, France) connected to an Apple Macintosh G4 computer (Apple, Cupertino, CA, USA). The CRT monitor had a spatial and temporal resolution of 1280 × 960 pixels, and 100 Hz, respectively. Trials consisted of an adapting and test display that, together, elicited the MAE.

Adapting Display. A 14° square window displayed random light and mid-grey pixels (average luminance = 30 cdm^{-2}, Michelson contrast = 30%) moving coherently upwards at a speed of 3°/s. The adapting display was presented for 45 seconds. Participants were seated 60 cm from the monitor in an otherwise dark room. During presentation of the adapting displays, participants were asked to look at a fixation point at the center of the screen while paying attention to the whole display. The experiment consisted of 12 trials, divided into the three blocks, one for each of the test display contrasts (the contrast of the adapting display was always the same). Block order was randomized. Thus, the experiment had a mixed quasi-experimental design, with contrast as the within-subjects factor and group as the between. The experiment was preceded by six practice trials (two for each test display contrast).

Test Displays. Immediately after adaptation, participants were presented with a test display. Test displays contained random, stationary, light to dark-grey pixels, which resembled that of a snapshot taken of a detuned television. Three different contrast test displays were used – high (Michelson contrast 78%), medium (30%), and low (0.1%). All test displays had the same mean luminance as the adapting display (30 cdm^{-2}). The presentation of a test display immediately after the adapting display elicited the illusion of slow, downward motion. When the stationary test display appeared, participants were asked to try not to blink and to indicate when the illusory motion stopped by pressing a key on the computer keyboard. The experimental session lasted between 75 and 90 minutes. Participants initiated each trial with a keypress and so could sit quietly between trials, in the darkened room, if they wished to pause or take a break. An experimenter was present throughout the experimental session. As part of the consent, participants were informed they could withdraw at any time without penalty, but none did so.

Contrast Sensitivity. The Cambridge Low Contrast Gratings (CLCG) measure contrast sensitivity at a spatial frequency of 4 cycles per degree, close to the maximum sensitivity of the human visual system. It consists of 10 horizontally oriented square wave gratings viewed at a distance of 6 meters. Each grating is presented together with a blank page that has the same mean reflectance as its grating pair. The participants' task is simply to indicate which page, top or bottom, contains the grating. The gratings decrease in Michelson contrast on subsequent trials through a range of 13% to 0.14%. The test was completed in order of decreasing contrast. Each time an error was made, the sequence was restarted at three plates preceding the error. The plates where errors were made were recorded on three runs through the sequence. Contrast sensitivity was measured before the MAE.

Results

The MAE and CLCG data from each group were normally distributed (Kolmogorov-Smirnov tests, $P > 0.05$), so group differences were assessed with ANOVA, *t*-tests, Pearson's correlation coefficient and analysis of covariance (ANCOVA) using PASW statistics version 20 (SPSS Inc., Chicago, IL, USA). Mauchly's test of sphericity was met for the ANOVA and ANCOVA ($P > 0.15$).

Average MAE durations for each group in each condition are shown in Figure 1A. Several trends are clear. Overall, the MAE lasted longer in the migraine group than in the control group for all three test display contrasts. Second, high contrast test displays produced the shortest MAEs and low contrasts the longest, as expected.[26] This was the same for both groups; however, the trend was more pronounced in the migraine group. A 2 (group) × 3 (test display contrast) mixed ANOVA was first performed on these data. The group *x* contrast interaction was significant ($F[2,44] = 4.9$, $P = 0.01$, $\eta_p^2 = 0.18$, $\omega_p^2 = 0.142$), confirming that the increase in MAE duration with decreasing test display contrast, was greater in the migraine group. Three planned comparisons revealed that the MAE durations for the high and medium contrast test

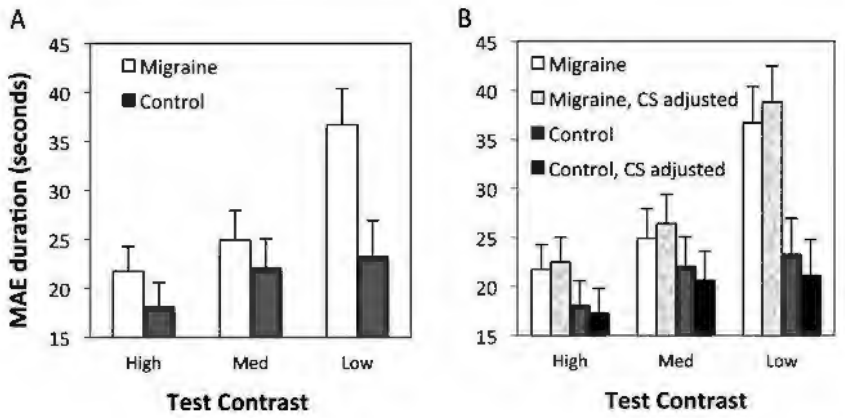

FIGURE 1. Motion aftereffect (MAE) data. (**A**) Means (+1 SE) of the MAE duration for the migraine and control groups for high, medium, and low contrast test displays. (**B**) Same data adjusted for the effect of the covariate, CLCG contrast sensitivity. For each test display contrast, the MAE duration is increased slightly for the migraine group, but decreased for the control group, when adjusted for contrast sensitivity.

displays did not differ significantly between the migraine and control groups ($t[22] = 1.0$, $P = 0.15$; $t[22] = 0.6$, $P = 0.26$; respectively, 1-tailed), but the MAE durations for the low contrast test display did ($t[22] = 2.4$, $P = 0.013$, 1-tailed). This interaction was associated with a significant main effect of contrast, confirming that the MAE duration, for both groups, increased as the test display contrast decreased ($F[2,44] = 14.4$, $P < 0.001$, $\eta_p^2 = 0.40$, $\omega_p^2 = 0.363$). There was no significant main effect of group ($F[1,22] = 2.7$, $P = 0.12$, $\eta_p^2 = 0.11$, $\omega_p^2 = 0.066$).

Scores on the CLCG were converted into Michelson contrast. Higher contrast thresholds equal poorer contrast sensitivity, that is, people needing a higher contrast to identify the gratings. Consistent with previous reports, the migraine group had higher contrast thresholds than the control group (mean ± 1 SE; migraine, 0.38 ± 0.08; control, 0.26 ± 0.03). Nevertheless, the difference was not statistically significant ($t[22] = 1.6$, $P = 0.065$, 1-tailed).

Correlations between each condition on the MAE tests and CLCG produced no significant results in the control group (high contrast test display, $r = -0.15$, $P = 0.64$; medium contrast $r = -0.29$, $P = 0.36$; low contrast $r = -0.17$, $P = 0.60$, Pearson's r, 2-tailed; Fig. 2B). In the migraine group, the MAE and CLCG correlations nearly reached significance for the low contrast test displays only (high contrast, $r = -0.33$, $P = 0.30$; medium contrast, $r = -0.49$, $P = 0.16$; low contrast, $r = -0.51$, $P = 0.088$, 2-tailed; Fig. 2A). Although failing to reach statistical significance, these consistently negative correlations show a trend that poorer contrast sensitivity (i.e., needing a higher contrast to identify the gratings) was associated with shorter MAEs, particularly for the low contrast test displays in the migraine group. The r^2 values indicate that, in the migraine group, between 11% and 26% of the variability in MAE duration was predictable from the variability in contrast sensitivity as assessed by the CLCG, but, in the control group, only between 2% and 9% of the variability in MAE duration was predictable from their variability in contrast sensitivity.

Contrast sensitivity may have had an effect on the MAE in the migraine group despite the nonsignificant group differences and correlations. Therefore, CLCG contrast sensitivity was added as a covariate and the ANOVA repeated as an ANCOVA in a second analysis. Because the analysis included repeated-measures, CLCG contrast sensitivity scores were first mean centered as recommended by Delaney and Maxwell[33]: the mean of all participants was subtracted from individual scores. The relationship between these adjusted contrast scores and MAE duration for each test display contrast did not differ between the groups, indicating that the assumption of homogeneity of regression slopes was met (three univariate ANOVAs, one for each test display contrast, all Fs < 1). The ANCOVA revealed that contrast sensitivity significantly predicted performance on the MAE ($F[1,21] = 5.6$, $P = 0.03$,$\eta_p^2 = 0.21$, see Fig. 1B). Again, the significant group x contrast interaction ($F[2,42] = 6.7$, $P = 0.003$, $\eta_p^2 = 0.24$) reflected that the increase in MAE duration with decreasing test display contrast was greater in the migraine than in the control group (see Fig. 1B). This time this interaction was related to two significant main effects. With contrast sensitivity as a covariate, the main effect of group was significant, indicating that the migraine group had significantly longer MAEs than the control group regardless of test display contrast ($F[1,21] = 6.0$, $P = 0.023$, $\eta_p^2 = 0.22$). As in the previous analysis, the main effect of test display contrast confirmed that the MAE lasted longer for low contrast test displays than for high for both groups ($F[2,42] = 15.5$, $P < 0.001$, $\eta_p^2 = 0.42$). The interaction between contrast sensitivity and test display contrast was not significant ($F[2,42] = 2.6$, $P = 0.09$, $\eta_p^2 = 0.11$).

DISCUSSION

The rationale for the current experiment was based on previous research that has reported longer MAEs in migraine and other research showing impaired contrast sensitivity.[10,13,14,30] In line with the predictions, the MAE in the migraine group lasted longer than in the control group and low contrast test displays produced the longest MAEs in both groups. Significant group and interaction effects confirmed this; however, the significant group difference was only found in the second analysis (ANCOVA) when contrast sensitivity was added as a covariate. Contrary to previous research,[14,27,29,30] and to what had been predicted, there was no statistically significant difference between the control and migraine groups in contrast sensitivity. There was, nevertheless, a trend for the migraine group to have higher contrast thresholds, that is, they needed higher contrasts to be able to see the gratings, and contrast sensitivity significantly predicted MAE duration. This study has, therefore, replicated the trends for group differences in CLCG contrast sensitivity described previously[14] (Michelson contrast thresholds, migraine: 0.3 ± 0.2, control: 0.2 ± 0.1; here, migraine 0.4 ±

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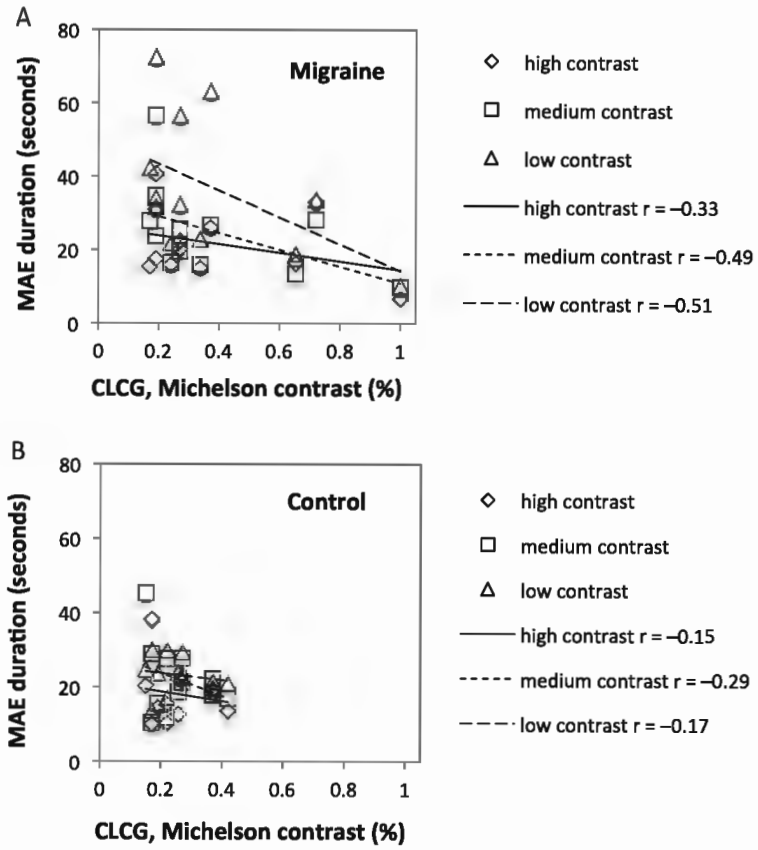

FIGURE 2. Motion aftereffect duration as a function of contrast sensitivity, as measured by the CLCG, for the migraine (**A**) and control (**B**) groups and for high, medium, and low contrast test displays. CLCG contrast sensitivity ranges from 0.14% to 1% (Michelson contrast). Pearson's correlation coefficients (*r*) are included together with regression lines for each condition.

0.3, control 0.3 ± 0.1). As regards the MAE data, Shepherd[13] used the same adaptation and test display contrast conditions (random dot adapting and test displays, Michelson contrast 30%) and reported comparable results for the group differences presented here: longer MAEs in migraine versus control groups. Furthermore, the trend for impaired contrast sensitivity to be associated with poorer performance on relative motion, motion detection, and motion discrimination tasks[14] also is consistent with the data reported here whereby poorer contrast sensitivity, likely arising from processing in early visual pathways (see prior study[34]), is associated with an impoverished/shorter perception of motion in the duration of the MAE.

The current finding of, on average, prolonged MAEs for low compared to high contrast test displays (Fig. 1) is in line with those of Keck et al.[26] As mentioned in the Introduction, adaptation to motion biases the distribution of activity in direction-selective cells throughout the visual pathways from the retina to cortex, but certainly involving the cortex. As soon as the adapting motion stops, however, the adapted cells start to recover and the length of that recovery, together with any residual response to the test patterns, determines the duration of the MAE. Since the direction-selective cortical cells also are responsive to contrast, the adapted cells would have a larger residual response to the high contrast test patterns than the low, resulting in shorter MAEs for the high contrast test patterns.

Impaired contrast sensitivity results in very low contrasts, which may be discernible to others, appearing uniform and, therefore, undetected. This describes the trend for higher CLCG contrast sensitivity thresholds in migraine. The same logic applied to higher contrasts would mean that higher contrast displays appear to have a lower contrast to the migraine than to the control participants. The result should be a longer MAE in the migraine group, which was found across all three contrast test displays. What also was found here, however, was shorter (not longer) MAEs associated with poor contrast sensitivity in the migraine group, although the association, while sizeable, was not statistically significant. It could be speculated that the medium contrast (Michelson contrast = 30%), chosen to be at or above the contrast level where neuronal response to contrast saturates in the early visual pathways,[35] might not have been sufficiently high to leave the adaptation phase unaffected by impaired contrast sensitivity in migraine. If the adaptation display contrast was perceived as lower in some migraine participants, that is, in those with poor contrast sensitivity, the direction-selective cells would have been less strongly suppressed during the adaptation process. This would result in a slight advantage during the recovery process and result in shorter MAEs in migraine participants with poor contrast sensitivity. Future research might usefully include a range of higher adaptation contrasts.

It can be concluded that contrast sensitivity is relevant to the perception of the MAE, as it predicted MAE duration. The current results suggest an anomaly in early motion processing pathways in migraine that is linked with those pathways underlying contrast sensitivity. It provides further evidence for differences in visual processing that begin early, potentially starting at the level of the retina, which have

consequences for performance on other tasks that putatively examine cortical processing (see also prior reports[14,34,36]). Thus, differences in precortical and cortical visual pathways are implicated in the pathophysiology underlying migraine. An extension of this study that varied adapting contrast, as well as test display contrast, would help to clarify the trends reported here.

Conclusions

This study extends earlier work on motion perception in migraine by assessing one aspect of motion perception, the motion aftereffect, together with an assessment of contrast sensitivity (a person's ability to see faint patterns). This study provides additional evidence that contrast sensitivity is associated with differences in motion processing in migraine.[14] This study replicates earlier reports of enhanced visual aftereffects in migraine, showing that this simple visual test is capable of revealing large group differences, and, thus, may be a useful test to include in clinical trials or to track changes during the migraine cycle. The study also confirms the usefulness of recording additional measures when performing visual tests in migraine, if the aim of the research is to provide evidence for or against models of anomalous visual processing in migraine at particular stages within the visual pathways. Tests of precortical visual processing should be included to preclude the possibility of failing to recognize performance differences for nominally cortical tasks have components attributable to the earlier visual pathways that feed into the cortex.

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Original research article

Evaluation of the relationship between Binocular Anomaly and Headache: prospective cross-sectional study

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Abstract

Aim: To evaluate the association of Binocular Anomaly with Headache.

Methods: The prospective cross-sectional study which was carried in the Department of Ophthalmology, Patna Medical College and Hospital, Patna, Bihar, India for 15 months. There were 100 patients with complaints of headache were included in this study. Visual acuity was tested at 6 meters by Snellen's chart and after refraction only the emmetropic patients were included in the study. A slit lamp examination of the anterior segment was done and ocular tension was recorded by applanation tonometer. Fundus fluorescein angiography and OCT for retinal evaluation and Humphrey field charting for glaucoma patients was done if needed.

Results: Majority of patients were young adults in the age group of 20-30yrs (N=48); Females outnumbered males in a ratio of 1.85:1 with 35% males and 65% females. Pain topography showed frontal headache (44%) to be the most common presentation followed by hemicranial type of headache (34%). On orthoptic evaluation, an altered AC/A ratio was found in 73% of individuals complaining of headache, having either low (41%) or high (32%) AC/A ratio ($p < 0.0001$). Out of 100 patients, 40% pts were suffering from convergence insufficiency where as 32% had convergence excess and only 28% had normal convergence range. Direct proportion was seen between Convergence Insufficiency and low AC/A ratio and also between convergence excess and high AC/A ratio (p = 0.000) Accommodation insufficiency was seen in 46% of patients while accommodation excess was present in 36% of patients. Contrary to convergence, accommodation was inversely proportional to AC/ A ratio. Accommodation insufficiency being more common with high AC/A ratio (67.39%)whereas accommodation excess was seen more in patients having low AC/A ratio (83.33%) p=0.0001. Fusional vergence findings showed normal vergence in only 20(20%) patients. Reduced negative fusional vergence was seen in 38% patients and was more commonly associated with high AC/A ratio (39%), while reduced positive fusional vergence was present in 42% patients and was more common with low AC/A ratio 36 (85.71%).

Conclusion: Headache was more common in females and was associated with exophoria, convergence insufficiency and inadequate positive fusional vergence at near fixation.

Keywords: Headache, binocular vision, exophoria, convergence insufficiency.

Introduction

Headache is one of the commonest health complaints and it affect approximately half of world population. It has significant effect on work productivity and quality of life.[1] The problem may arise from conditions that range from benign to catastrophic. Quick and accurate diagnosis is an important step for successful management of headache.[2,3] A review of studies conducted globally, estimated the prevalence of headache as 58.4% among school-

going children and 46% in adult population.[2,3,4] It is commonly believed that refractive errors and binocular vision anomalies can lead to headache among young individual.4 Eye care professional reported that headache is a common patient complaint.[5,6,7] International headache society reported that the diagnostic criteria of headache associated with refractive errors is as follows: a) Uncorrected refractive errors such as hypermetropia, astigmatism, presbyopia, or wearing incorrect glasses, b) Mild headaches in the frontal region and in the eyes, c) pain absent on awakening and worse by prolonged visual tasks at distance or near.[8] In a masked case control study, to assess the relation between headache and binocular vision anomalies it was concluded that people suffering from headache had higher prevalence of heterophoria, associated phoria and reduced stereopsis compared with controls. The study found that there was strong association between exophoria and complaint of headache.[9] Another study has indicated that the positive fusional reserve should be at least twice the magnitude of an exophoria to be compensated (without symptoms).[10] Binocular visual dysfunctions such as convergence insufficiency (CI) affects young people and is characterised by the inability to accurately converge, or sustain accurate convergence when focusing at near targets. It is associated with symptoms such as headache, blurry vision, eyestrain, and double vision.10 Headache may also be due to different ocular diseases such as acute glaucoma, optic neuritis, uveitis, and visual anomalies such as uncorrected refractive errors, accommodative and vergence dysfunctions. The most common eye condition leading to headache after refractive errors is binocular vision anomalies.[11] There is a general increase in the number of people suffering from headaches. In addition, headaches have a significant negative impact on the quality of life and productivity. Therefore, the current study was conducted to assess the clinical characteristics of patients suffering from headaches who attended the binocular vision at department of Ophthalmology, Patna Medical College and Hospital, Patna, Bihar, India.

Material and methods

The prospective cross-sectional study which was carried in the Department of Ophthalmology, Patna Medical College and Hospital, Patna,Bihar India for 15 months, after taking the approval of the protocol review committee and institutional ethics committee.

Inclusion criteria

There were 100 patients with complaints of headache who either had come by their own or were referred from other departments to the department of Ophthalmology. Patients were also referred to other departments to rule out non-ocular cause of headache.

Exclusion criteria

Patients who had non-ocular headache and other causes of ocular headache (hysteria, malingering, neurogenic causes such as intracranial space occupying lesion, benign intracranial hypertension, meningitis, giant cell arteritis; sinusitis, otitis, vascular headaches such as migraine; angle closure glaucoma, uveitis, optic neuropathy, etc; patients on NSAIDs/anticholinergic drugs – psychiatric medicines, cold, dysmenorrhoea etc; or patients using video display terminals for greater than 2 hr/day at a stretch) were excluded from the study.

Methodology

Selected patients were interviewed according to a pre-designed and pre-tested performa. Detailed history of headache pattern, life style pattern and eating habits was taken. Ocular evaluation consisted of detailed refractive check-up, binocular vision assessment and anterior segment and posterior segment examination.

Visual acuity was tested at 6 meters by Snellen's chart and after refraction only the emmetropic patients were included in the study.
A slit lamp examination of the anterior segment was done and ocular tension was recorded by applanation tonometer. Fundus flourescein angiography and OCT for retinal evaluation and Humphrey field charting for glaucoma patients was done if needed.
Detailed orthoptic examination was done and the diagnosis was made as defined below. Convergence insufficiency: (1) Near point of convergence.[12] (NPC)> 6 cm and; (2) Positive fusional convergence.[13,14] (PFC) <15 PD. Accommodative insufficiency[11] (Cacho criteria): Near point of accommodation (NPA) <15-0.25 x Age.
The most common method of determining the AC/A ratio is the gradient method in which the phoria at near is measured after changing the accommodation with a spherical lens (usually +1.00 D or -1.00D) placed in front of the two eyes. It is expressed as
AC/A = (α –α')/ F where α = near phoria and α' is distance phoria: F is power of lens used. (exodeviation is taken as positive and exodeviation as negative).

Statistical analysis
Data entry and statistical analysis was done using Statistical Package for Social Sciences (SPSS software version 20) and inferences drawn. Mantel-Haenszel chi-square test (χ2MH) was used to control any possible confounding variable, wherever necessary. A 'P' value of less than 0.05 was taken as significant.

Results
Total of 100 emmetropic individuals having headache with no other systemic problem were included in the study.
Majority of patients were young adults in the age group of 20-30yrs (N=48); Females outnumbered males in a ratio of 1.85:1 with 35% males and 65% females. (Table 1)
Pain topography showed frontal headache (44%) to be the most common presentation followed by hemicranial type of headache (34%). (Table 2)
On orthoptic evaluation, an altered AC/A ratio was found in 73% of individuals complaining of headache, having either low (41%) or high (32%) AC/A ratio ($p < 0.0001$). Out of 100 patients, 40% pts were suffering from convergence insufficiency where as 32% had convergence excess and only 28% had normal convergence range. Direct proportion was seen between Convergence Insufficiency and low AC/A ratio and also between convergence excess and high AC/A ratio ($p = 0.000$) (Table 3).
Accommodation insufficiency was seen in 46% of patients while accommodation excess was present in 36% of patients. Contrary to convergence, accommodation was inversely proportional to AC/ A ratio. Accomodation insufficiency being more common with high AC/A ratio (67.39%)whereas accommodation excess was seen more in patients having low AC/A ratio (83.33%) p=0.0001. (Table 4).
Fusional vergence findings showed normal vergence in only 20(20%) patients. Reduced negative fusional vergence was seen in 38% patients and was more commonly associated with high AC/A ratio (39%), while reduced positive fusional vergence was present in 42% patients and was more common with low AC/A ratio 36 (85.71%). (p=0.0279) (Table 5).
On correlating the type of headache with AC/A ratio we observed that throbbing type of pain was associated more with low AC/A ratio while piercing type of headache was seen with high AC/A ratio ($p = 0.612$) (Table 6).

Table 1: Headache related with age and sex

	Gender		
Age Group	Male	Female	Total
10-20 Yrs	13 (38.24%)	21 (61.76%)	34
20-30 Yrs	17 (35.42%)	31 (64.58%)	48
30-40 Yrs	3(27.27%)	8 (72.73%)	11
40-50 Yrs	2(40%)	3 (60%)	5
50-60 Yrs	0 (0.00%)	2(100%)	2
TOTAL	35 (35%)	65(65%)	100

Table 2: Distribution of patients according to pain topography in relation to working hours

Working hours	Occipital	Frontal	Hemicranial	Generalised	Total
Upto 4hrs	2 (5%)	21 (52.5%)	13 (32.5%)	4 (10%)	40
5-8hrs	-	13(46.43%)	9 (32.14%)	6 (21.43%)	28
9-12hrs	-	5 (62.5%)	2 (25%)	1 (12.5%)	8
13-16hrs	2 (8.33%)	5 (20.83%)	10 (41.67%)	7 (29.17%)	24
Total	4 (4%)	44 (44%)	34 (34%)	18 (18%)	100

Table 3: AC/A ratio as related with convergence

	Convergence	High	Low	Normal	Total
AC/A ratio	Insufficiency	1 (2.5%)	36 (90%)	3 (7.5%)	40
	Excess	28 (87.5%)	2 (6.25%)	2 (6.25%)	32
	Normal	3 (10.71%)	3 10.71%)	22 (78.58%)	28
	Total	32(32%)	41(41%)	27(27%)	100

Table 4: Accommodation as related with AC/A ratio

	Accommodation	High	Low	Normal	Total
AC/A ratio	Insufficiency	31 (67.39%)	4(8.69%)	11 (23.91%)	46
	Excess	2 (5.56%)	30 (83.33%)	4 (11.11%)	36
	Normal	3 (16.67%)	5 (27.78%)	10 (55.56%)	18
	Total	36 (36%)	39 (39%)	25 (25%)	100

Table 5: Fusional vergence as related with AC/A ratio

Fusional vergence	AC/A ratio			
	High	Low	Normal	Total
Reduced Negative	33 (39%)	2 (3.10%)	3 (7.50%)	38
Reduced Positive	2 (4.76%)	36 (85.71%)	4 (9.52%)	42
Normal	3 (15%)	4 (20%)	13 (65%)	20
Total	38 (38%)	42 (42%)	20 (20%)	100

Table 6: Type of headache as related with AC/A ratio

Type of Headache	AC/A ratio			
	High	Low	Normal	Total
Throbbing	22 (31.43%)	30 (42.86%)	18 (25.71%)	70
Piercing	7 (46.67%)	6 (40%)	2 (13.33%)	15
Dull Aching	3(37.5%)	4 (50%)	1 (12.5%)	8
Gnawing	2 (28.57%)	3 (42.86%)	2 (28.57%)	7
Total	34 (34%)	43 (43%)	23 (23%)	100

Discussion

Headache is experienced by majority of population and has a major impact on public health. The condition has been ranked among the ten most disabling conditions by the world health organisation. Headache is common during childhood and it becomes even more common and more frequent during adolescence.

In our study, the commonest binocular anomaly was accommodation insufficiency was seen in 46% of patients while accommodation excess was present in 36% of patients, while according to Mocii F et al.[15] convergence insufficiency is the most frequent cause of muscular aesthenopia. This prevalence of convergence insufficiency is less than that of Gupta et a[16] (49%), Romania[17] (60.4%) and Patwardhan and Sharma[18] (71.4%), while it is more than that of Sanjay et al[19] (16.25%). These discrepancies might be because of the different working environmentof the patients.

In our study, accomodative insufficiency is associated with low AC/A ratio, which is normally overcome by positive fusional reserve but when this fusional reserve is also insufficient the patient develops the symptom of asthenopia and then actual headache. This fusional reserve become insufficient due to functional causes such as overwork or deficient physiology though there may be other non-functional causes. And this may be the reason for headache in younger age group as they stress their eyes by staying awake at night and watching television or computers and also skipping meals.

In this study, headache was more common in females ($p>0.001$) similar to the observations of Hendricks et al[20] and sanjay et al[19] , with females having more than two fold prevalence over males especially in young adults in the age group of 20-30 years. Headache prevalence in this particular age group might be because of the psychological stress caused by educational pressures for career development and emotional factors. Female preponderance could be because of the culturally set factors and the effects of male dominated society which may lead to psychological stress.[21] In our study, patients in the school age comprised of 34%. Headache in this age group could be because of peer pressure for better performance in the studies and extracurricular activities.

Regarding the site of headache, our study revealed that the frontal (44%) followed by unilateral location (34%) were the commonest sites. According to Unp et al (2005)[22] most of the patients who suffered from headache defined more than one location. More than half of the studied sample (70%) had throbbing type of headache followed by piercing type in 15%. Throbbing headache was commonly associated with low AC/A ratio (42.86%) while piercing type was commonly associated with high AC/A ratio (46.67%). These findings were similar to the studies of Unp et al. 2005[22] and Ayatollahi & khosravi (2006).[23]

Various studies have stated different precipitating factors for headache such as skipping meals, and inadequate or irregular sleep, and stress to be majorly responsible for headache. Isik et al (2006)[24] and El tallawy et al (2006)[25] reported them to be the most common precipitating factors for headache in 69%, 83.6% and 72.6% cases respectively. Hunger or missed meal is shown to be a precipitating factor in 60.06% of children by Blau et al (2004).[26]

Other precipitating factors were staying for long in front of TV or computer, ingestion of cold drink or ice cream and eating chocolate or cheese in a study carried out by Stovner *et al* (2007).[27] These environmental triggers, light, sound and smell are transmitted directly to the central nervous system (CNS) by the special senses and thus cause direct excitation of the neural pathways which then causes headache attack. We could not include them in our study due to limited resources.

Conclusion

The present study conclude that headache was more common in females and was associated with exophoria, convergence insufficiency and inadequate positive fusional vergence at near fixation.

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REVIEW

Exploring the Link Between Dry Eye and Migraine: From Eye to Brain

This article was published in the following Dove Press journal:
Eye and Brain

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Abstract: Dry eye and migraine are common diseases with large societal and economic burdens that have recently been associated in the literature. This review outlines the link between dry eye and migraine, which may have implications for reducing their respective burdens. We highlight possible shared pathophysiology, including peripheral and central sensitization, as the potential link between dry eye and migraine. Finally, therapies targeting similar pathophysiological mechanisms between dry eye and migraine are discussed.

Keywords: dry eye, migraine, brain, sensitization

Introduction

Awareness of dry eye has increased in recent years including its association with specific diseases, such as migraine headaches. However, our understanding of the link between dry eye and migraine is contingent on what is currently known about them as separate diseases. Specificall , dry eye and migraine are both highly prevalent in the population. The prevalence of dry eye ranges from 5% to 50% in the worldwide population, depending on disease definition and population studied, with an overall estimated societal economic burden of $55.4 billion in the United States.[1] As with dry eye, the prevalence of migraine headache is also high. In western countries, the lifetime prevalence of migraine is up to 9.5% in males and 25% in females.[2] The societal economic burden of migraine in the United States is estimated at $36 billion.[3] Thus, migraine headaches and dry eye are important health concerns, and their association warrants further exploration. Understanding shared connections between the two diseases may provide insight into shared pathophysiology and treatments, with a potential decrease in disease morbidity.

To understand the link between dry eye and migraine, we must first define them as separate diseases. Dry eye is defined by the Tear Film and Ocular Surface Society Dry Eye Workshop II as

> a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[4]

The symptoms of dry eye are variable and can include sensations of “dryness”, “grittiness”, “burning” and “stinging”, to name a few.[5] Individuals may also report that these sensations are spontaneous and/or evoked by wind or light.[5] Others complain of visual phenomena, such as blurry or fluctuating vision.[6] Dry eye

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symptoms are commonly assessed in the clinic with specific questionnaires, such as Dry Eye Questionnaire-5 (DEQ-5; range 0–22)[7] and Ocular Surface Disease Index (OSDI; range, 0–100),[8] which incorporate many of the above complaints. The DEQ-5 focuses on intensity and frequency of dryness and discomfort, along with tearing, while the OSDI considers spontaneous and evoked pain, visual complaints, and impact on daily activities. These questionnaires lump responses and generate severity scores, with DEQ-5 scores ≥6 considered indicative of any dry eye symptoms[7] and scores ≥12 considered severe symptoms. OSDI scores are interpreted as normal=0–12, mild=12–32, and severe=33–100.[9] Of note, these severity scales incorporate a number of different aspects of dry eye to reach a final score, including pain, visual complaints, tearing, and activity limitations. Given that specific symptoms may be driven by different contributors, other questionnaires have been developed to specifically assess for ocular pain complaints, including the Ocular Pain Assessment Survey (OPAS), a 28-question survey, that focuses on intensity of eye pain, non-eye related pain, and aggravating factors,[10] and the Neuropathic Pain Symptom Inventory-Eye (NPSI-Eye; range, 0–100), which focuses on neuropathic pain features, inquiring about descriptors such as burning pain and evoked pain to wind and light.[11]

In addition to symptoms, clinical signs are also included under the purview of dry eye. The tear film is composed of 2 layers, a thicker muco-aqueous layer that interacts with the corneal epithelium, and a thinner lipid layer that sits on top of the muco-aqueous layer and inhibits its evaporation.[12] Broadly speaking, dry eye is sub-grouped into categories by dysfunction in these two layers, that is aqueous tear deficient and evaporative dry eye.[13] Signs of aqueous deficiency include decreased tear volume, assessed by examining the tear meniscus under the slit lamp examination or with the Phenol Red Thread (PRT) test, and reduced tear production, assessed with Schirmer strips (strips of paper placed in the corner of the eye and left in place for 5 minutes, mm of wetting recorded). The main sign of evaporative deficiency is a rapid tear break up time (TBUT, measured in seconds until a black spot appears in the tear film), which can occur with a dysfunctional lipid layer. However, any tear abnormality, including aqueous deficienc , can result in a rapid TBUT. Furthermore, the sub-types co-exist and individuals may present with both aqueous and evaporative deficienc . Punctate epithelial erosions, which are small disruptions in the corneal epithelium visualized with vital dyes such as sodium fluorescein, rose bengal, or lissamine green, can be seen in both dry eye sub-types and with other ocular surface abnormalities (eg anatomic abnormalities of the eyelid, conjunctivae, or cornea).

The lipid layer is produced by the Meibomian glands (MG) in the upper and lower eyelids. Eyelid abnormalities such as plugging of the MG orifices, MG atrophy, and production of a thicker than normal lipid product (eg abnormal meibum quality) can accompany signs of tear dysfunction.[14] Point of care tests have also been developed to assess tear composition and inflammation and can specifically evaluate tear osmolarity (TearLab, San Diego)[15] and ocular surface inflammation (matrix metalloproteinase-9, Inflammadr , Quidel Corporation, San Diego)[16] in the clinical setting. Some individuals with clinical tear film abnormalities will have high or unstable tear osmolarity levels and/or detectable inflammation on their ocular surface.

A challenge in evaluating dry eye is that the symptoms and signs of disease are often disparate.[17,18] The presenting symptoms of dry eye can vary even in the same individual and are frequently discordant from the clinical signs and their severity, which can make the diagnosis and management of dry eye difficult. For example, a systematic review of 33 studies assessing associations between dry eye symptoms and signs found that out of 175 individual symptom-sign analyses, only 42 (24%) were significantly correlated with one another. This study also found that the majority (129/148; 87%) of individual analyses reporting correlation coefficients were in the low-to-moderate range (−0.4 to 0.4).[17] In addition, the lack of a single objective test with which to evaluate dry eye signs and the low repeatability of tests (eg Schirmer) contributes to the complexity of the disorder.

One of the reasons it is important to screen for dry eye is that dry eye symptoms have a negative impact on individuals' lives as they decrease the ability to work and carry out activities of daily living.[19] For example, a study recruited 56 individuals with a dry eye diagnosis (International Classification of Diseases, Ninth Revision, ICD-9, codes) for assessment of ophthalmic and quality of life parameters. This study found that individuals with severe dry eye disease (composite score of symptoms [9-level subjective facial expression scale] and signs [Schirmer and corneal surface staining]) had quality of life scores (measured by the time trade-off method) in the range of severe (class III/IV) angina (mean utility

score, range 0 to 1, lower values indicate worse quality of life: 0.72 for severe dry eye disease and 0.71 for class III/IV angina).[20] In addition, dry eye symptoms have a negative impact on mental health and several studies have linked depression and anxiety to dry eye.[21,22] Finally, individuals with dry eye have sleep abnormalities. For example, a meta-analysis of 17 studies found that individuals with dry eye symptoms or disease (diagnosed using varying criteria across studies) or primary Sjogren's syndrome had worse sleep quality scores (using Pittsburgh Sleep Quality Index) compared to controls (weighted mean difference=1.69, 95% confidence interval (CI): 0.82–2.56).[23] Taken together, dry eye is a debilitating disease with profound impacts on social functioning and perception of life quality.

Similar to dry eye, migraine is a prevalent condition in the general population.[2] The International Headache Society (IHS) defines migraine as a "recurrent headache disorder manifesting in attacks lasting 4–72 hours".[24] Migraine headaches are characterized by unilateral location and pulsating quality and can include nausea, photophobia, and/or phonophobia. Migraine attacks are classified into those with or without aura. Migraine with aura involves reversible prodromal symptoms, such as visual, sensory, or other central nervous system disturbance lasting a few minutes.[24] Migraine can also be separated into chronic and episodic. Chronic migraine is characterized as occurring ≥15 days per month for three months, which, on at least eight days per month, has features of migraine, while episodic migraine occurs less than 15 days per month.[24]

As with dry eye, migraine symptoms can be debilitating and decrease quality of life.[25] An observational study of 102 individuals with migraine found disability and health-related quality of life scores were significantly lower than the general population.[26] Similarly, a retrospective cross-sectional survey study of 80,600 European patients found lower health-related quality of life and decreased work productivity among those with ≥4 monthly migraine headaches compared to non-migraine controls.[27] Interestingly, lower quality of life scores among those with migraine closely associate with dry eye symptoms. In a cross-sectional survey-based study of 62 individuals with migraine, visual function (measured via visual functioning questionnaire-25) and overall quality of life (measured via headache impact test-6) correlated with dry eye symptoms (measured via OSDI score).[28] Together, these data show that both dry eye, migraine, and perhaps their interaction, have significant negative impacts on patient quality of life. Thus, in this review, we explore the association between dry eye and migraine with the goal of illuminating overlapping pathophysiology and potential therapies. To do so, we reviewed recent studies that investigated the relationship between dry eye and migraine.

Methods

A PubMed search was conducted using the terms "dry eye" AND "migraine". All published scientific articles were considered including original research, meta-analyses, and systematic reviews. All searches were limited to the English language. Eligible articles were reviewed and summarized.

Clinical Associations Between Dry Eye and Migraine

Epidemiology of Dry Eye, Migraine, and Their Co-Existence

Dry eye and migraine are co-morbid. Using survey data from a Korean population-based cross-sectional study of 14,329 participants, the prevalence of migraine and dry eye diagnosis was found to be similar among participants: 24.2% reported migraine headaches (positive answer to "Do you have, or have you ever experienced migraine [pulsatile pain unilaterally in your head]?"), 22.6% reported a dry eye diagnosis (positive answer to "Have you ever been diagnosed with dry eye by an ophthalmologist?"), and 37.1% reported dry eye symptoms (positive answer to "Do your eyes tend to be dry, with a foreign body sensation including itching and burning or sandy feeling lately?").[29] Furthermore, the frequency of dry eye diagnosis was found to be higher in those with migraine. Of those with migraine, 14.4% reported a dry eye diagnosis compared to 8.2% without migraine, $p<0.0001$. Similarly, of those with migraine, 22% reported dry eye symptoms compared to 15.1% without migraine, $p<0.0001$.[29] While limitations of this study included the use of data assessed via questionnaires, other studies have reported similar results. In a hospital-based case–control study of 72,969 individuals from University of North Carolina-affiliated hospitals, individuals with migraine and dry eye were identified using International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes. The prevalence of a migraine or dry eye diagnosis was 7.3% and 13.2%, respectively. Again, individuals with migraine had a higher frequency of a co-morbid dry eye

diagnosis. Of those with migraine, 19.6% had a dry eye diagnosis compared to 12.7% without migraine.[30]

Looking at the data as odds ratios (OR), in the population-based questionnaire study of 14,329 Korean individuals, after adjusting for confounders, the presence of migraine was found to increase the odds of a dry eye diagnosis 1.58 fold (95% confidence interval (CI) 1.34–1.86) and the odds of dry eye symptoms 1.3 fold (95% CI, 1.15–1.50).[29] In the study of 72,969 individuals from North Carolina, the presence of migraine increased the odds of a dry eye diagnosis 1.42 fold (95% CI, 1.20–1.68). The association was strongest among women ≥65 years old (OR, 2.47; 95% CI, 1.75–3.47).[30]

Other studies have investigated the reverse relationship, that is the odds of migraine in individuals with dry eye. In a large Taiwanese study using ICD-9 codes (n=48,028), the presence of a dry eye diagnosis increased the odds of a migraine diagnosis 1.76 fold (95% CI, 1.57–1.98), after adjusting for co-morbidities.[31] While these studies suggest a reciprocal relationship between dry eye and migraine, they are limited by their retrospective or cross-sectional nature and reliance on ICD coding and questionnaires for migraine and dry eye diagnosis. This is especially relevant as dry eye is a heterogeneous disease and it is unclear which combination of symptoms and/or signs led to the coded diagnosis. Overall, these studies suggest that dry eye and migraine are common conditions and that individuals with migraine are more likely to have dry eye symptoms and carry a dry eye diagnosis compared to those without. However, a limitation of the studies is that they did not look at dry eye signs and as such, it is difficult to understand what component of dry eye is most closely related to migraine.

Dry Eye Characteristics Among Individuals with Migraine

To further explore relationships between dry eye and migraine, several smaller studies investigated associations between migraine and dry eye symptoms and signs. In a cross-sectional study of South Florida veterans seen in a dry eye clinic, 31 individuals with migraine (defined via the American Migraine Study/American Migraine Prevalence and Prevention (AMS/AMPP) migraine diagnostic module)[32] were compared to 219 individuals without migraine. Migraineurs had significantly higher dry eye symptom scores (via OSDI) but similar tear metrics (TBUT, corneal staining, tear production) compared to controls.[33] Interestingly, NSPI-Eye scores, assessing for neuropathic features of eye pain, were also higher among individuals with migraine compared to controls. These data suggest dry eye symptoms, but not dry eye signs, are related to migraine. This conclusion is supported by other studies, as well. One observational study of Turkish individuals seen in a dry eye clinic compared 33 individuals with migraine to 33 controls. Migraine was diagnosed by different neurologists. Dry eye symptoms were assessed using OSDI and dry eye signs using TBUT, corneal staining, and Schirmer test. Migraineurs had significantly higher dry eye symptoms, lower TBUT, and Schirmer scores, and higher corneal staining compared to controls.[34] However, Schirmer scores were within normal limits in both groups (mean >10 mm/5 min) and thus the clinical relevance of the differences in values is unclear. Similar findings were reported in another study of 46 Turkish patients with migraine and 50 controls that were assessed for Sjogren's Syndrome, dry eye symptoms (via OSDI), and dry eye signs (TBUT, Schirmer) in a rheumatology clinic.[35] Migraine was diagnosed by the referring neurologist. In this study, individuals with migraine had significantly higher dry eye symptoms and lower TBUT and Schirmer scores compared to controls, however again, Schirmer results were still within normal limits (mean >10 mm/5 min). Another case–control study performed in a United States ophthalmology clinic assessed dry eye symptoms and signs and corneal nerve parameters in 19 individuals with chronic migraine. This study used 30 controls from a normative dataset for corneal nerve comparisons, but no control data were included for dry eye parameters. Chronic migraine was defined by the International Headache Society guidelines. Dry eye symptoms via measured DEQ-5 were abnormal in all subjects (DEQ-5 >6), but tear parameters were within normal limits among all individuals with chronic migraine (data not reported).[36] Interestingly, corneal nerve fiber density was significantly lower in individuals with migraine compared to controls (48 ± 23 vs 71 ± 15 fibers/m ^{2}). However, given the lack of standard nomograms for corneal nerve fiber density, the interpretation of this finding is uncertain. Together, these studies point to dry eye symptoms being more closely related to migraine than dry eye signs.

Migraine Characteristics Among Individuals with Dry Eye

As above, while some studies evaluated dry eye characteristics in individuals with migraine, other studies evaluated

whether specific migraine characteristics were more closely associated with dry eye. A Turkish study that evaluated 58 individuals with migraine reported that the odds of having dry eye (defined if 2 of 3 criteria met: OSDI >33, TBUT <10 seconds or Schirmer <10 mm/5 min) were 5.03 times higher in those with migraine and aura compared to those without aura (95% CI, 1.42–17.83).[37] These data suggest that migraine with aura is more closely associated with aspects of dry eye than migraine without aura.

In addition to aura, the lifetime duration of migraine has also been explored in its relationship to dry eye. In the above Turkish study, individuals with a dry eye diagnosis had a longer median lifetime duration of migraine compared to those without a diagnosis (10 vs 6 years, p=0.01).[37] Similarly, another Turkish study of 46 individuals with migraine (diagnosed by a neurologist) found that migraine lifetime duration correlated with both dry eye symptom severity (OSDI score) (r=0.3, p=0.01), tear stability (TBUT: r= −0.23, p=0.05), and tear production (Schirmer: r= −0.28, p=0.01). Of note, the negative correlations imply that longer duration of migraine associated with faster break-up time and lower tear production.[35] Taken together, these studies suggest that migraine with aura and longer disease duration are associated with aspects of dry eye. However, it is important to note that definitions of dry eye were not uniform among studies, and migraine criteria were not always clearly outlined.

Photophobia is a Feature of Both Dry Eye and Migraine

Thus far, we have discussed associations between dry eye and migraine. However, the diseases also share a common feature, that is, the presence of photophobia. Although photophobia is variably defined in the literature, in this review, photophobia refers to light-induced neurological symptoms, which usually emerge in the form of (i) increased sensitivity to light or glare, (ii) intensification of headache and (iii) ocular pain or discomfort.[38] With regards to dry eye, our group reported that 75% of 236 veterans with dry eye symptoms (DEQ-5 score ≥6) reported pain sensitivity to light (defined as score ≥1 on a 0–10 numerical rating scale (NRS)).[39] In another study, we found that of 102 South Florida veterans, individuals with persistent dry eye symptoms (DEQ-5 score ≥6 over a 2-year period) were more likely to report photophobia compared to those without persistent symptoms (OR, 15.6; 95% CI, 2.0 to 123, p=0.009).[40] Our data suggest that photophobia is a common feature in individuals with dry eye symptoms, and in fact, presence and severity of photophobia is the first question on the OSDI.

Photophobia is also a common feature in migraine. In a cross-sectional survey of 6045 respondents in the Migraine in America: Symptoms and Treatment Study, 49.1% reported photophobia as the 'most bothersome symptom.[41] In a retrospective cross-sectional study of 117 individuals with chronic migraine (≥15 headache days/month), 80% rated their photophobia (via 0–10 NRS) as severe (a score of ≥7/10; mean 7.91 ± 2.05).[42] Together, the data demonstrate that photophobia is a feature of both dry eye and migraine. The presence of photophobia in both diseases has implications for shared pathophysiology and treatments as discussed later in the review.

Neural Pathways Mediating Photophobia

Studies have explored the neural circuitry underlying photophobia, both in the context of dry eye[43] and migraine.[44] One pathway involves light-evoked signals in rod and cone cells that are transmitted to retinal ganglion cells (RGC) via amacrine and bipolar cells. Some signals in RGCs are transmitted to the olivary pretectal nucleus (OPN), then to the superior salivatory nucleus, and subsequently to the sphenopalatine ganglion, which stimulates parasympathetic-mediated vasodilation of ocular[45] and dural[38] vessels that are innervated by trigeminal afferents. Trigeminal signals subsequently travel to the trigeminal nucleus caudalis, posterior thalamus, and cortical structures (Figure 1).[38] Evidence for this pathway comes from immunocytochemistry experiments in rats that demonstrated light-evoked neuronal activity in the trigeminal brainstem, which was reduced after intravitreal injection of norepinephrine. These data suggest that constriction of ocular blood vessels by norepinephrine plays a role in light-evoked neuronal activity, thus implicating ocular vasculature in the trigeminal brainstem pathway of photophobia.[45] A mouse study similarly found a trend for reduced blue-light aversion behavior (measured by amount of time mice spent in the illuminated portion of a box) after intravitreal injection of norepinephrine, but the reduction did not reach statistical significance [46]

A second neural pathway involves light-sensitive neurons in the posterior thalamus, specifically the lateral

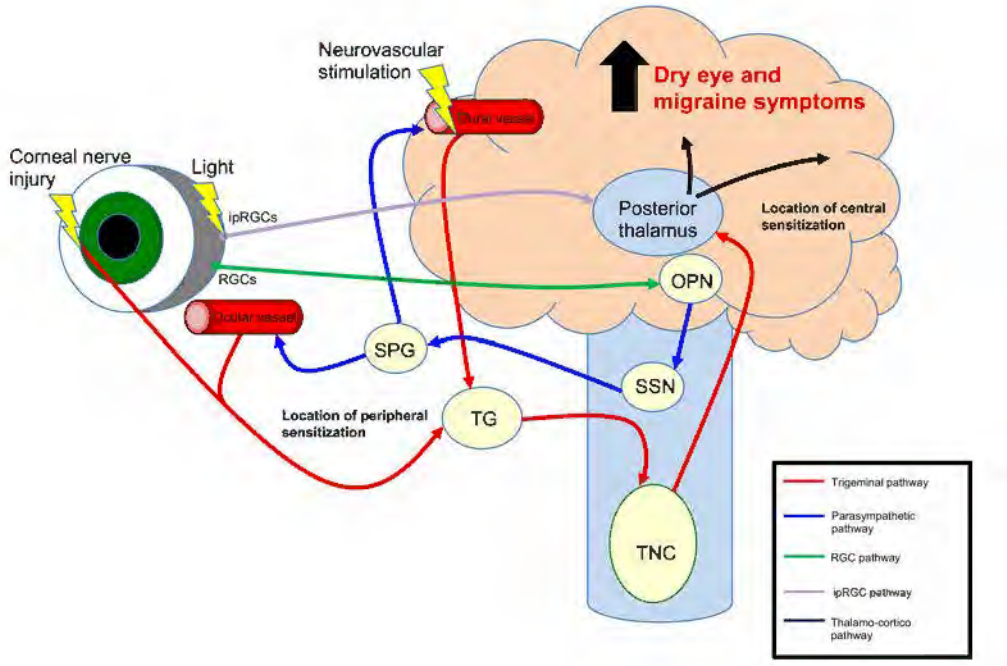

Figure 1 Selected photophobia neural pathways in dry eye and migraine. Light evokes signals from rod and cone cells that are transmitted via amacrine and bipolar cells (not shown) to retinal ganglion cells (RGC), which project to the olivary pretectal nucleus (OPN, green line). Blue line: parasympathetic signals travel from the OPN to the superior salivatory nucleus (SSN), then to the sphenopalatine ganglion (SPG), and ocular and dural vessels to mediate vasodilation. Red line: afferent trigeminal signals from cornea (stimulated by corneal disruptions), ocular vessels, and dural vessels (stimulated by vasodilation) travel to the trigeminal ganglion (TG) then to the trigeminal nucleus caudalis (TNC) and finally the posterior thalamus. Alternatively, light-evoked signals from intrinsically photosensitive RGCs (ipRGC) travel directly to the posterior thalamus (purple line). Black line: signals from the posterior thalamus travel to somatosensory and visual cortices to mediate dry eye and migraine symptoms. Note other pathways of photophobia that involve the hypothalamus and retinal rod and cone cells are not depicted.

posterior (LP) and posterior nuclei (PO),[38] which receives input from both intrinsically photosensitive RGCs (ipRGC) and dural trigeminal afferents, and subsequently send signals to somatosensory and visual cortices (Figure 1).[38,47] Evidence for this pathway comes from a rat study using electrophysiologic and histopathologic techniques which demonstrated that cell bodies and dendrites of dura- and light-sensitive neurons in the posterior thalamus were in close apposition to axons originating from ipRGCs.[48] Other studies have further connected the posterior thalamic nuclei to photophobia. A mouse model found that stimulation of posterior thalamic nuclei (LP and PO nuclei) by optogenetics or injection of calcitonin gene-related peptide (CGRP)[49] triggered light aversive behavior.[50] Beyond these two pathways, other postulated, but less well studied pathways in photophobia involve the hypothalamus, retinal rod and cone cells, and the iris.[47,51,52]

Dry Eye and Migraine Share Underlying Pathophysiology

The clinical overlap between dry eye symptoms and migraine, including the presence of photophobia, suggests pathophysiological links between them. One unifying theory is that dry eye symptoms and migraine involve abnormal peripheral trigeminal nerve activation with subsequent peripheral and central sensitization. Peripheral sensitization is defined as "increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields [53] and below we focus on corneal peripheral nerve abnormalities that have been described in dry eye and migraine. Central sensitization is defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[53] and below we focus on changes in secondary and tertiary nerves that connect corneal afferents to higher cortical areas.

Tests Used to Evaluate Nerve Abnormalities in Dry Eye and Migraine in Animal Models and Humans

In animals, peripheral nerve function is often evaluated via electrophysiological recordings of polymodal (~70%), mechano- (10–15%), and cold thermoreceptors (10–15%) within corneal nerves or via recordings in ciliary nerves.[54–56] Polymodal nociceptors respond to mechanical force, heat, chemical irritants and inflammatory mediators,[57] mechanoreceptors to mechanical forces, and cold thermoreceptors to

temperature drop and changes in tear osmolarity.[58] Electrophysical recordings are also used to evaluate central nerve function along trigeminal pathways, such as in the trigeminal nucleus caudalis.[59] Corneal sensitivity is also tested in animals with von Frey filaments, where increasing force is used to contact the central cornea until a blink-response is elicited.[55]

In humans, electrophysiological recordings of corneal and central nerves are not feasible. As such, clinicians have developed several tests that evaluate corneal nerve pathway function. In the clinic, corneal sensitivity is typically qualitatively checked with a cotton tip or dental floss (rated as 0=absent, 1=reduced, 2=normal, 3, increased). In the research arena, corneal sensitivity can be quantitatively assessed using a Cochet-Bonnet esthesiometer where a nylon monofilament 6 cm in length is used to contact the ocular surface and then retracted in 0.5-cm increments until corneal sensation is felt. For this test, a higher result corresponds to a higher corneal sensitivity.[60] Alternatively, a Belmonte esthesiometer utilizes a non-contact air jet to provide the stimulus, which can either be mechanical (variable airflow), thermal (hot or cold pulses), or chemical (varying CO2 concentrations). In contrast to Cochet-Bonnet, lower values with the Belmonte esthesiometer correspond to increasing sensitivity. The presence of hypo- or hyper-sensitivity suggests abnormalities in the corneal nerve pathway, although it is not possible to determine if the abnormality is in peripheral and/or central nerves. Overall, a wide range of corneal sensitivity values has been found in individuals with and without dry eye.[61] One study of 403 individuals with dry eye symptoms (DEQ5 ≥6) found a mean corneal mechanical detection threshold (using Belmonte esthesiometer) of 87 ± 46 mL/min, with a 10th percentile of 40 mL/min and a 90th percentile of 145 mL/min. Twenty-four percent of individuals had values that fell at or outside this range, 13% (n=51) were hypersensitivity (≤40mL/min) and 11% (n=46) hyposensitive (≥145mL/min).[61]

Peripheral nerve structure can be assessed using in vivo confocal microscopy (IVCM). IVCM images can be used to examine corneal subbasal nerves for density, branching, beading, tortuosity, and abrupt termination with swelling (termed microneuroma).[62] IVCM, however, has limitations in that it lacks built-in software to analyze nerve parameters, there are no normative databases with which to compare values across populations, it provides a small field of view, and it is difficult to scan the exact same location over time.[63]

In humans, certain symptom profiles suggest central abnormalities including the presence of allodynia (pain due to a stimulus that does not normally provoke pain,[53] such as with light), hyperalgesia (increased pain from a stimulus that normally provokes pain,[53] such as with wind) and expansion of the receptive fields (such as pain to light touch of the periocular skin).[43,64] The proparacaine challenge is another clinical test used to detect central abnormalities. Individuals are first asked to rate their ocular pain intensity (typically on a 0–10 scale) immediately prior to placement of topical anesthetic. After one drop is instilled in each eye and 30 seconds to 2 minutes have passed (different investigators use different time periods), ocular pain is reassessed. Elimination of pain suggests nociceptive or peripheral contributors to pain while persistence of pain suggests central or non-ocular contributors. A limitation of this test is that it is not informative if no pain is present at the start of testing. In the research arena, brain functional studies[65] and quantitative sensory testing have been used to identify central abnormalities in trigeminal pathways.[66]

Abnormalities in Peripheral Nerves Have Been Detected in Dry Eye and Migraine

The literature suggests that both dry eye symptoms and migraine pain are driven in part by peripheral sensitization.[67,68] In dry eye, peripheral injury and activation may result from a number of sources including chronic epithelial disruptions, high tear osmolarity, ocular surface inflammation, and/or surgically induced nerve injury (eg refractive surgery).[67] On the other hand, initiators of peripheral nerve injury in migraine remain controversial.[69]

Electrophysiology studies have detected corneal nerve abnormalities in dry eye. In a guinea-pig model of aqueous tear deficiency using lacrimal gland excision, changes in peripheral nerve function were detected in mechanoreceptor spontaneous activity at 1 week post-surgery (0.30 ± 0.22 vs 0.02 ± 0.02 impulses/second, $p<0.05$) and cold-thermoreceptor spontaneous activity at 4 weeks post-surgery (13.22 ± 1.00 vs 10.27 ± 0.78 impulses/second, $p<0.05$) compared to sham controls. Furthermore, a change in cold-thermoreceptor thresholds was observed 4 weeks post-surgery (32.42 ± 0.14 vs 29.87 ± 0.35 °C, respectively, $p<0.05$) compared to controls, indicating increased sensitivity to cooling.[56] In a mouse model, lacrimal gland excision resulted in an

increase in spontaneous ciliary nerve activity compared to sham controls (86.8 ± 7.6 vs 43.4 ± 4.9 impulses/sec, p<0.001). Concomitantly, corneal mechanical thresholds decreased (implying increased sensitivity) compared to sham controls (0.012 ± 0.001 vs 0.028 ± 0.002 g, p<0.0001).[70] Together, the studies demonstrate that the initiation of aqueous tear deficiency causes a change in corneal nerve function, manifesting as hypersensitivity. Unfortunately, corneal nerve electrophysiology studies in migraine animal models are lacking.

Alterations in corneal nerves structure and function have also been reported in various dry eye populations compared to controls. Overall, most studies have reported decreased corneal nerve density and sensitivity in individuals with aqueous tear deficiency and Sjögren's syndrome but not in individuals with evaporative dry eye.[62] For example, an Italian study examined corneal nerves in 39 individuals with symptomatic aqueous tear deficiency (low TBUT, corneal staining, low Schirmer) compared to 30 controls. They found significantly lower corneal nerve fiber density and length, but higher width in the dry eye vs control group (respectively, 20.5 ± 8.7 vs 25 ± 6.7 n/mm^2, p=0.008; 12.6 ± 4.4 vs 14.5 ± 2.9 mm/mm^2, p=0.02; 0.021 ± 0.001 vs 0.019 ± 0.001 mm/mm^2, p<0.001).[71] For corneal sensitivity, an American study of 33 individuals with symptomatic aqueous tear deficiency (OSDI >20, TBUT ≤7 seconds, tear meniscus height <220μM) found decreased sensitivity (measured via Cochet-Bonnet) compared to 10 healthy controls (3.6 ± 1.6 vs 5.5 ± 0.83 cm, p<0.05). Similar to density, individuals with other dry eye sub-types (Meibomian gland dysfunction and conjunctivochalasis) did not have differences in corneal sensitivity compared to controls.[72] Together, the above studies suggest that individuals with aqueous tear deficiency have lower nerve densities and sensitivity than controls, but that these differences are not as robust in other dry eye sub-types.

Corneal nerve alternations have also been documented in migraine. A Chinese study examined corneal nerves in 10 individuals with episodic migraine and 10 controls. Corneal nerve branching and tortuosity were significantly increased in individuals with migraine compared to controls (91 ± 13.8 vs 75 ± 14.2 branches/mm^2, p=0.03 and 2.3 ± 4.6 vs 1.6 ± 0.5, p=0.01, respectively).[73] Photophobia has also been linked to peripheral corneal nerve abnormalities. In a prospective Indian study, individuals with chronic migraine and photophobia (n=36) had significantly lower subbasal nerve parameters, including corneal nerve fiber length (14.8 ± 4.0 vs 18.1 ± 3.3 mm/mm^2, p=0.007), compared to those with migraine but no photophobia (n=24).[74]

Individuals with migraine have also been found to have increased corneal sensitivity compared to controls. One Turkish study compared 58 individuals with chronic migraine to 30 controls. Corneal sensitivity (measured by Cochet-Bonnet) in the nasal region was higher (increased sensitivity) in the migraine vs control group [median (IQR); 5.5 (5.25–6.0) vs 5.37 (5.0–5.75) cm, p=0.02]. Interestingly, in individuals with unilateral migraine, corneal sensitivity was higher in the affected vs unaffected side (median (IQR); 5.4 (5.0–5.7) vs 5.3 (5.0–56.5), p=0.049).[75] The data on sensitivity, however, are limited in that the Cochet-Bonnet can only measure sensitivity up to 6 cm and most healthy individuals can detect the fil - ment when fully extended. No studies have evaluated corneal sensitivity in migraine with Belmonte esthesiometry which has a wider testing range. Overall, while not as robust as for dry eye, studies demonstrate that individuals with migraine have changes in their corneal nerve structure and function compared to controls.

Abnormalities in Central Nerves Have Been Detected in Dry Eye and Migraine

The literature suggests that both dry eye symptoms and migraine pain are driven in part by central sensitization. Given that corneal nerve fibers project to the trigeminal brainstem region, studies have used this region to investigate central nerve changes in dry eye.[70] In a lacrimal gland excision mouse model, an increase in spontaneous firing rate of trigeminal subnucleus interpolaris/caudalis (Vi/Vc) neurons was noted compared to sham controls (6.4 ± 1.9 vs 2.9 ± 1.4 Hz, p<0.05). Additionally, periocular cutaneous receptive field areas of Vi/Vc and Vc/C1 units were significantly enlarged compared to sham controls.[59] These data suggest that aqueous tear deficiency can lead to central nerve abnormalities.

As with dry eye, central nerve abnormalities have been demonstrated in migraine. In a rat model of migraine using dural stimulation with an "inflammatory soup" (i.e histamine, serotonin, bradykinin), electrophysiologic recordings from trigeminovascular neurons in the posterior thalamus showed an increased firing rate and increased magnitude of responses to pressure, pinch, cephalic and extracephalic brush after dural stimulation compared to baseline. In contrast, control animals (dura stimulated

with fluid) showed no change in responsiveness after stimulation compared to baseline.[76]

Central abnormalities have also been noted in humans with dry eye and migraine. With regards to dry eye, a cross-sectional study of 224 South Florida veterans with dry eye symptoms (DEQ-5 ≥6) found that 18 (41%) had persistent ocular pain (0–10 NRS) after topical anesthesia placement. Individuals with persistent ocular pain also had worse dry eye symptoms (DEQ-5, 14.6 ± 3.7 vs 12.7 ± 3.3, p=0.001) and photophobia intensity (5.6 ± 3.1 vs 3.2 ± 3.2, p<0.0005, 0–10 NRS scale) compared to individuals without pain after topical anesthesia.[77] These data highlight multiple clinical features suggestive of central abnormalities in individuals with dry eye symptoms. However, brain imaging studies would provide stronger evidence of central nerve abnormalities. While lacking for aqueous tear deficienc , a case report of functional magnetic resonance imaging (fMRI) in an individual with contact lens overuse (one contributor to dry eye)[78] and photophobia reported activation at the level of the trigeminal ganglion, trigeminal nucleus caudalis, and thalamus when presented with 6-second blocks of light.[65] The strength of this report is that it links corneal epithelial cell disruption to photophobia to activation of central trigeminal pathways. However, more imaging studies in a variety of dry eye sub-types are needed to supplement these fin - ings. Quantitative sensory testing has also been applied to the study of dry eye, with higher dry eye symptoms associated with enhanced temporal summation and the presence of after-sensations, both of which suggest central contributions to symptoms.[66]

Similar to dry eye, central abnormalities have been found in individuals with migraine pain.[79] In a Chinese study of 16 individuals with chronic migraine, 18 with episodic migraine, and 18 controls, individuals with chronic migraine demonstrated increased resting-state functional connectivity between bilateral amygdala and several brain regions compared to those with episodic migraine on fMRI. Compared to controls, those with chronic migraine had decreased functional connectivity between the right amygdala and several brain regions, whereas those with episodic migraine had increased functional connectivity in the left amygdala.[80] In a Korean study, 19 individuals with chronic migraine had increased resting-state functional connectivity between pain processing areas and the dorsal raphe nucleus compared to 45 individuals with episodic migraine on fMRI.[81] Together, these studies demonstrate central abnormities in animal models and humans with migraine, with greater abnormalities noted in individuals with chronic vs episodic migraine.

Inflammation is an important contributor to peripheral and central nerve abnormalities in dry eye and migraine.

Inflammatory mediators likely contribute to the development of peripheral and central sensitization in individuals with dry eye and migraine. For example, CGRP, a neuropeptide involved in neurogenic inflammation, as well as cardiovascular, gastrointestinal and endocrine processes,[43] has been associated with changes in nerve function in dry eye and migraine. In a rat model of corneal abrasion using heptanol, CGRP increased in peripheral corneal nerves at one week (measurement at 24 hours was limited by the abrasion) and in the trigeminal ganglion at 24 hours compared to controls. Concomitantly, rats displayed corneal hyperalgesia (increased eye wipes after corneal application of menthol) at 24 hours compared to controls. Both CGRP levels and hyperalgesia decreased to baseline at 1 week. These results suggest an association between CGRP and peripheral nerve function.[82]

Inflammatory mediators have also been found to increase in the central nervous system in dry eye. In a mouse model of lacrimal gland excision, increased mRNA levels of pro-inflammatory markers were noted in the trigeminal ganglion and brainstem compared to sham controls 21 days post-surgery. Similar to the rat model, these mice also exhibited corneal hypersensitivity after injury. Additionally, increased spontaneous electrical activity in their ciliary nerve was noted compared to controls. Centrally, increased synaptic plasticity in the trigeminal brainstem complex (measured using immunofluorescence of presynaptic zone components) was observed at 21 days.[70] This study demonstrates an association between aqueous tear deficienc , inflammation in central trigeminal pathways, and peripheral and central nerve abnormalities.

Human studies also support the link between infla - mation and corneal nerve abnormalities. A Turkish study of 37 individuals with dry eye symptoms and signs (TBUT<7 seconds, corneal staining, Schirmer<10 mm) measured corneal sensitivity (via Cochet-Bonnet) before and after topical cyclosporine 0.05% (an anti-inflammatory agent). Corneal sensitivity increased post vs pre cyclosporine therapy (58.8 ± 2.1 vs 52.1 ± 5.5 mm, p<0.001).[83] These data suggest that inflammation impacts corneal nerve sensitivity in dry eye.

Inflammation, specifically CGRP, has also been linked to nerve abnormalities in migraine.[49] For example, a rat model

of migraine (recurrent administration of nitroglycerin) found that CGRP-immunoreactive fibers significantly increased in the trigeminal nucleus caudalis compared to controls. This was clinically accompanied by thermal hyperalgesia (withdrawal latency after infrared radiation on hind paw). Furthermore, hyperalgesia was ameliorated by knocking down CGRP with short hairpin RNA.[84] In a rat model of migraine (glass micropipette inserted into the visual cortex), a propagating wave of depolarization was induced with a resultant increase in the firing rate of spinal trigeminal nucleus neurons.[85] The increased firing rate was blocked when rats were pretreated with a CGRP-blocking antibody.[86] These data demonstrate that CGRP impacts nerve sensitivity in migraine.

CGRP has also been linked to migraine in humans. In a placebo-controlled, cross-over study of 13 individuals with migraine, intravenous CGRP induced migraine-like attacks in 10 individuals compared to 0 after placebo (isotonic saline), p=0.002. Median peak headache intensity score (NRS scale 0 to 10) was 5 (5–9) after CGRP compared to 2 (0–4) after placebo (p=0.004).[87] The effectiveness of anti-CGRP antibodies in treating migraine provides further support for the role of CGRP in migraine pathophysiology.[88] Together, the above studies support the interaction between CGRP and nerve function in migraine.

CGRP is Also Related to Light Sensitivity, Independent of Dry Eye and Migraine

CGRP can induce light sensitivity. In wild-type mice, peripheral (intraperitoneal) and central (intracerebroventricular) injection of CGRP induced light-aversive behavior (time spent in illuminated portion of a light/dark box). Furthermore, an anti-CGRP monoclonal antibody attenuated light aversion after the peripheral injection of CGRP.[89] In transgenic mice that overexpressed the CGRP receptor, central, but not peripheral, CGRP administration induced light aversion. In another mouse model, peripheral injection of CGRP produced spontaneous pain (measured by a squint assay) both in complete darkness and in bright light.[90] Together, these studies support the role of CGRP in pain and photophobia via multiple mechanisms.

Light Can Trigger Corneal Inflammation and Nerve Abnormalities

In a mouse model, blue light, but not yellow light, increased corneal sensitivity (via von Frey hair test) 3 hours post vs pre exposure. Exposure to blue light also led to observable changes on in-vivo confocal microscopy including activation of the superficial corneal epithelium (defined as the appearance of hyperreflective nuclei), increased numbers of dendritic (inflammatory) cells in the sub-basal plexus, and increased numbers of keratocytes in the stroma.[91,92] Additionally, blue-light increased inflammation in both the trigeminal ganglia and spinal trigeminal nucleus, as measured by mRNA expression of cFOS and ATF3.[46] These data suggest that the pathophysiology of dry eye and migraine is complex with multiple potential entry points (light, aqueous tear deficienc , corneal epithelial damage, cortical disruptions) that lead to inflammation and nerve abnormalities in multiple compartments (peripheral and central).

Practical Implications for Diagnosing Dry Eye and Migraine

The overlap between dry eye and migraine has potential implications in the evaluation and treatment of individuals with these two diseases as illustrated in Figure 2. First, eye care providers should ask individuals with dry eye about comorbid headache and primary care doctors and neurologists should ask individuals with migraine about symptoms of dry eye. If present, appropriate referrals can be made.

Second, given shared pathophysiology involving nerve dysfunction, eye care providers should think about nerve status when evaluating an individual with dry eye symptoms. This includes assessing for ocular pain via standardized questionnaires (eg NRS, Neuropathic Pain Symptom Inventory-Eye [NPSI-Eye]) and evaluating nerve structure and function clinically. The presence of cutaneous allodynia can be assessed by evaluating for pain to touch around the eyes. In addition, corneal sensitivity can be qualitatively checked with a cotton tip or dental floss (generally rated as 0=absent, 1=reduced, 2=normal, 3, increased). The proparacaine test can help differentiate between nociceptive pain ("pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors")[53] or peripheral neuropathic pain vs centrally mediated or non-ocular pain.[77]

Corneal nerves can be imaged with IVCM and certain nerve findings have been reported to suggest the presence of peripheral neuropathic pain. Specificall , one retrospective study found that in individuals with clinical suspected neuropathic pain, nerves in the subbasal layer abruptly terminated with hyperreflective enlargements.[93] This fin - ing was termed microneuroma based on similar findings in

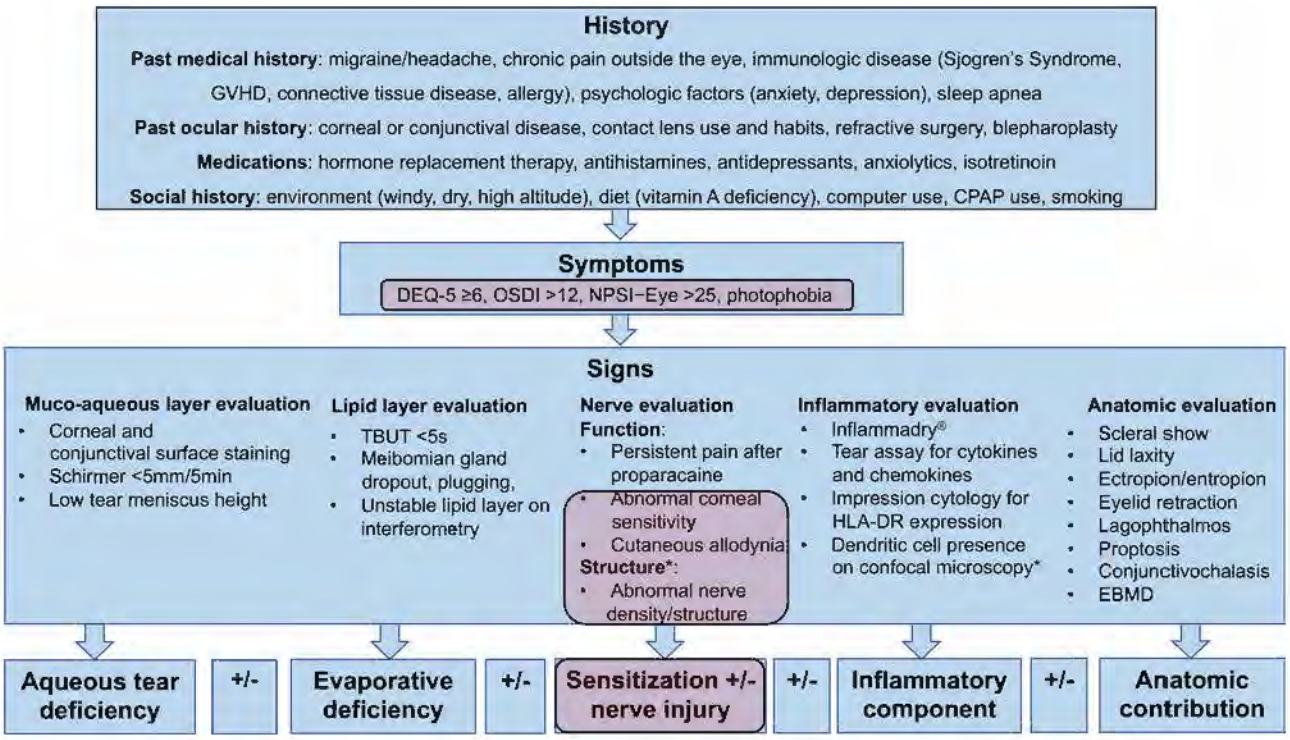

Figure 2 Clinical assessment of patients with dry eye. Purple boxes indicate phenotypes that overlap with migraine. *Nerve structure findings using in-vivo confocal microscopy.

Abbreviations: GVHD, graft versus host disease; DEQ-5, Dry Eye Questionnaire-5; OSDI, Ocular Surface Disease Index; NRS, numerical rating scale; NPSI-Eye, Neuropathic Pain Symptom Inventory-Eye; TBUT, tear break up time; EBMD, epithelial basement membrane dystrophy.

animal models.[94] Microneuromas were observed in all subjects with ocular pain (n=30), but were not present in any subjects without pain (n=30).[93] Other studies, however, failed to replicate these findings in other dry eye populations.[95]

Understanding nerve status in an individual patient may help explain their clinical presentation as different sensitivity profiles have been described in different dry eye populations (eg hyposensitivity in aqueous tear deficienc , hypersensitivity in individual with presumed neuropathic ocular pain[96] and/or migraine).[75] This heterogeneity may explain the disconnect often seen between dry eye symptoms and signs, as nerve function drives sensation, and thus symptomatic interpretation, of dry eye signs (decreased tear volume, rapid tear evaporation). Understanding nerve status can also help tailor an individualized treatment plan.

An Updated Paradigm for the Treatment of Dry Eye Based on Data in Migraine

The current paradigm for managing dry eye is to target tear dysfunction. This new paradigm suggests that when this approach does not sufficiently relieve dry eye symptoms, therapies targeting nerve dysfunction should be considered. Given similarities between dry eye and migraine, therapies that are of benefit in migraine may be beneficial in dry eye.

Anti-Inflammatory Therapy

Anti-inflammatory medications are a first-line treatment in dry eye and migraine.[69,97] Specificall , in dry eye, short-term topical corticosteroids, and long-term cyclosporine and lifitegrast are first-line agents.[67] Decreasing ocular surface inflammation may improve tear composition and dry eye symptoms.[98] However, similar to migraine,[99] not all patients with dry eye respond to anti-inflammatory therapy.[100] Interestingly, baseline nerve status may predict who responds to anti-inflammatory therapy. In an American study, 60 individuals with dry eye (OSDI>22, corneal staining, meibomian gland dysfunction) were grouped by subbasal corneal nerve length (<16.84 (n=9) vs ≥16.84 mm/mm^2, n=11). Symptoms and signs in individuals with higher baseline SNFL improved 4 weeks after starting loteprednol (Symptom Assessment in Dry Eye, SANDE: 60.1 ± 17.4 vs 50.0 ± 22.7, p=0.04 and corneal

staining: 6.7 ± 3.2 vs 4.6 ± 2.9, p=0.01) while those with low baseline nerve length showed no improvement.[100] In patients who fail anti-inflammatory therapies, other therapies need to be considered.

Oral Nerve Modulators

In individuals with features suggestive of centrally mediated pain (peri-ocular allodynia to light touch, photophobia, persistent pain after anesthesia), systemic nerve modulators should be considered. Oral nerve modulators have been effective for migraine prevention including, serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants (TCAs),[25] and for aborting acute migraine attacks, such as triptans.[101] Given similar pathophysiology to migraine, patients with dry eye may also benefit from oral nerve modulators. Indeed, gabapentin and pregabalin, both alpha 2 delta (α2γ) ligands, have been examined in dry eye. These agents are thought to exert their effect by reducing voltage-gated calcium channel currents in the central nervous system leading to decreased excitatory neurotransmission.[102] A case series evaluated the efficacy of α2γ ligands in 8 individuals with ocular pain unresponsive to topical therapies. Gabapentin was escalated to a dose of 600–900 mg three times daily and pregabalin to 150 mg twice in the study. Two individuals reported complete pain relief after adding a α2γ ligand to their multi-modal regimen while 3 individuals reported significant relief.[102] Interestingly, the 2 individuals with complete pain relief were also on concomitant duloxetine. This study demonstrates that α2γ ligands may alleviate ocular pain in dry eye as part of a multi-modal regimen. However, additional studies are needed.

As with migraine, groups have studied the impact of TCAs in nerve-related ocular pain. TCAs inhibit central and peripheral serotonin and norepinephrine reuptake as well as cholinergic, histaminergic, and sodium channels.[98] In a retrospective cohort study of 30 patients who failed other therapies and had persistent pain after anesthesia, nortriptyline (at least 4 weeks of use, started at 10 mg and increased up to 100 mg based on response and tolerability) improved ocular pain in the last 24-hours (measured via NRS) from 5.7 ± 2.1 to 3.6 ± 2.1 after 10.5 ± 9.1 months (p<0.0001) of use. In addition, quality of life score (via an OPAS sub-score) improved from 6.0 ± 2.5 to 4.3 ± 2.4 (p=0.019).[103] Taken together, the above studies suggest that in individuals with dry eye symptoms and clinical features suggestive of central nerve abnormalities, oral nerve modulators may improve ocular pain symptoms. However, in patients with either dry eye or migraine who show no or partial response to oral therapies, adjuvant approaches may be considered.

Adjuvant Approaches

Adjuvant therapies are often employed in migraine and may also be beneficial in the treatment of dry eye. For example, botulinum toxin is an approved medication in migraine[104] and has been explored in dry eye. Botulinum toxin is thought to target pain responses by reducing facial muscle contraction and thus decreasing trigeminal afferent signaling as well as by reducing synaptic release of CGRP.[42] In migraine, a Cochrane meta-analysis of 26 double-blind randomized controlled trials found that botulinum toxin treatment reduced the frequency of migraine (mean difference= −2.39 migraine days/month; 95% CI, −4.02 to −0.76) and migraine severity (measured by NRS 0–10; mean difference= −3.30; 95% CI, −4.16 to −2.45) compared to placebo in those with episodic or chronic migraine.[105] In dry eye, a retrospective study of 117 South Florida veterans with chronic migraine (≥15 headaches or headache days/month) found that botulinum toxin A (mean units injected: 114.4 ± 24.5) improved migraine pain (mean change= −3.43; 95% CI, −3.95 to −2.92; p<0.001), photophobia (mean difference= −2.64; 95% CI, −3.18 to −2.11; p<0.001), and dry eye symptoms (mean difference= −0.716; 95% CI, −1.18 to −0.249; p=0.003) (all measured via NRS 0–10) compared to pre-injection scores.[106] This effect was found to be independent of tear volume,[42] suggesting that mechanisms beyond tear dysfunction drive eye symptoms. In 4 individuals with dry eye symptoms without migraine, a modified botulinum toxin A protocol (35 units in 7 sites) improved photophobia and dry eye symptoms 1 month post vs pre injection.[107] Together, these data suggest that botulinum toxin A may improve photophobia and dry eye symptoms in individuals with and without migraine.

Another adjuvant treatment with success in migraine is device neuromodulation, and this entity has also been studied in dry eye. Specificall , transcutaneous electrical nerve stimulation (TENS) uses pulsed low voltage electrical currents across the intact surface of the skin to stimulate peripheral nerves.[108] TENS has been postulated to improve pain by stimulating deep sensory afferents that secondarily inhibit nociceptive input via gate control theory.[108] As applied to ocular pain, TENS may stimulate deep Aβ fibers in the V1 and V2 distribution and block nociceptive input from unmyelinated C fibers. In terms of migraine, one meta-analysis of four studies using different

TENS devices, Cefaly (company, location), LH202H Han Electrostimulator (company, location), GammaCore® (company, location), HANS-200A machine (company, location), with varying protocols (five times weekly, daily, three times daily) found that TENS significantly reduced monthly headache days (standard mean difference= −0.48; 95% CI, −0.73 to −0.23; p<0.001) and analgesic intake (standard mean difference= −0.78; 95% CI, −1.14 to −0.42; p<0.001) compared to sham TENS (TENS device was applied with far less electrical stimulation or none at all).[108] Similar to migraine, TENS has also shown promise in dry eye. In a retrospective study of 10 individuals with ocular pain, some of which had dry eye signs, an RS4i (RS medical, Vancouver) was used at varying intervals (range 3–21 times weekly) for a median of 6.5 months (range: 3–14 months). Overall, pain scores (one-week recall measured via NRS 0–10) decreased by 27.4% (p=0.02) post- vs pre-treatment.[109] Together, these data suggest that TENS may be incorporated as an adjuvant treatment in individuals with dry eye and migraine.

Another modality less frequently used in migraine is the blockage of peripheral nerve afferents with local anesthetic.[102] In migraine, a meta-analysis of 33 articles showed that blockade of the greater occipital nerve was associated with a significant decrease in the number of headache days (pooled mean difference in headache days= −3.6; 95% CI, −1.39 to −5.81) and headache severity (pooled mean difference in pain scores= −2.2; 95% CI, −1.56 to −2.84).[110] This approach may also benefit patients with ocular pain when applied to trigeminal nerve afferents. A retrospective series of eleven individuals who failed conservative therapy for dry eye and ocular pain reported outcomes after periocular nerve block with 4 mL of 0.5% bupivacaine mixed with 1 mL of 80 mg/mL methylprednisolone acetate targeting the supraorbital, supratrochlear, infratrochlear, and infraorbital nerves. Seven of 11 individuals experienced pain relief after nerve block lasting hours to months and five individuals underwent repeat nerve blocks.[102] Of note, four of the seven individuals who responded to nerve blocks had ocular surgery as the pain trigger, whereas this was the case for one of the four non-responders. The above studies suggest that nerve blocks may benefit some patients with refractory ocular pain. However, these data are limited by their observational nature and limited number of subjects.

In addition to trigeminal afferent blockade, other nerve block sites have shown promise for treatment of migraine and dry eye, such as sphenopalatine ganglion (SPG) blocks.[111,112] In fact, some ocular pain is thought to be mediated by parasympathetic fibers, whose presence has been documented on the cornea.[113] Although biologic plausibility exists, studies are needed to evaluate the effects of SPG blocks in individuals with dry eye symptoms and ocular pain. Overall, the data presented in this section support the use of nerve blocks in appropriate individuals, especially those with surgically induced chronic ocular pain.

Conclusions

To conclude, this review discusses potential links between dry eye and migraine, prompted by an association between the two diseases in the literature. This information can be used to better understand pathophysiological mechanisms and develop targeted treatments by applying therapies successful in reducing migraine pain to dry eye. Neuronal injury leading to peripheral and central sensitization through trigeminal pathways are important mechanisms in some individuals with dry eye symptoms. Clinically, these individuals may manifest as hyperalgesia (evoked pain with wind), photophobia, and expansions of the receptive field (pain to light touch of the skin around the eye). These data highlight the need to test for nerve function in individuals with dry eye and consider the use of therapies that target nerve abnormalities in appropriate individuals.

Disclosure

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Headache and Refractive Errors in Children

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ABSTRACT

Purpose: To investigate the association between uncorrected or miscorrected refractive errors in children and headache, and to determine whether correction of refractive errors contributes to headache resolution.

Methods: Results of ophthalmic examination, including refractive error, were recorded at initial visit for headache. If resolution of headache on subsequent visits was not documented, a telephone call was placed to their caregivers to inquire whether headache had resolved.

Results: Of the 158 patients, 75.3% had normal or unchanged eye examinations, including refractions. Follow-up data were available for 110 patients. Among those, 32 received new or changed spectacle correction and 78 did not require a change in refraction. Headaches improved in 76.4% of all patients, whether with (71.9%) or without (78.2%) a change in refractive correction. The difference between these two groups was not statistically significant ($P = .38$).

Conclusions: Headaches in children usually do not appear to be caused by ophthalmic disease, including refractive error. The prognosis for improvement is favorable, regardless of whether refractive correction is required.

[J Pediatr Ophthalmol Strabismus 2014;51(3):177-179.]

INTRODUCTION

Headache is a common complaint in children. It is estimated to occur at some point in childhood in approximately 50% of the population, with greater than 2% complaining of frequent episodic headache.[1] Among the 196 headache types included in the second edition of the *International Classifications of Headache Disorders* (ICHD-2), 113 are known to occur in children.[2] Among those, acute glaucoma, ocular inflammatory disorders, heterotropia or heterophoria, and refractive error represent potential ophthalmologic bases.[3] Children commonly present to a pediatric ophthalmologist for evaluation of headache because parents and primary care physicians often suspect an underlying ophthalmologic problem.[4-6] Headache can even be a presenting sign of elevated intracranial pressure from a mass or hydrocephalus, which in some cases can be revealed by ophthalmologic examination.

In particular, we have observed that many such patients have presented to our office with headaches suspected to be caused by refractive errors. We have rarely attributed headache to any significant ophthalmologic disorder, including refractive errors,

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in such children. Although other authors have estimated that headaches are uncommonly caused by uncorrected or miscorrected refractive errors,[6-8] no study has compared headache resolution in children receiving versus those not receiving refractive correction. Our goal was to investigate this question among our patients.

PATIENTS AND METHODS

This study conformed to the requirements of the U.S. Health Insurance Portability and Accountability Act. After approval was granted by the Institutional Review Board at Albany Medical Center, we conducted a chart review of pediatric patients seen with a diagnosis of headache (ICD-9 784.0) in our private practice between January 2002 and January 2011. Patients aged 13 years and older were excluded. Every child underwent standard ophthalmologic assessment, including visual acuity, pupils, external or slit-lamp examination, motility, dilated fundus examination, and cycloplegic retinoscopy. On follow-up visits, older children underwent manifest refraction when appropriate. Information was obtained from charts regarding patients' age, gender, headache characteristics, medical and ocular history, family history of migraine, examination findings, prescribed treatment, and future course of headache. If patients did not have a follow-up appointment, or if headache was not mentioned during follow-up visits, their caregivers were contacted by telephone. These telephone calls were made at the time of the study, which ranged from 6 months to 12 years after their initial presentation. If they were unable to be reached initially, a second and then a third attempt were made to contact the caregivers by telephone.

RESULTS

A total of 158 patients were included in this study. Of these, 78 were male and 80 were female. Ages ranged from 3 to 12 years, with a mean of 8.05 years and a median of 8.08 years. A total of 43 patients (27.2%) had a clinically significant refractive error or had previously been prescribed glasses. Forty-eight patients (30.4%) had ophthalmologic history other than refractive error. Among those, 19 (11.9%) had strabismus, including horizontal and vertical deviations, accommodative esotropia, convergence insufficiency, and Duane's syndrome. Other diagnoses encountered included amblyopia, nasolacrimal duct obstruction, functional vision loss, allergic conjunctivitis, retinopathy of prematurity, pseudostrabismus, nystagmus, optic disc anomaly, physiologic anisocoria, and ectopia lentis. A family history of migraine was documented in 28 patients (17.7%).

Temporal association of headaches with visual tasks, including reading, television, computer, or homework, was noted in a total of 22 patients (13.9%). Visual symptoms, specifically blurred vision or diplopia, were noted in 15 patients (9.5%).

Ophthalmologic examination, including refraction, was either unremarkable or not significantly changed from prior examination in 119 patients (75.3%). New or altered spectacle correction was prescribed in 33 patients (20.9%), and prior spectacles were discontinued in 4 patients (2.5%). These decisions were made with reference to consensus guidelines for spectacle correction in children.[9] The remaining two patients (1.3%) were diagnosed as having convergence insufficiency. Otherwise no new ophthalmologic disorders were identified on examination.

We were able to obtain follow-up information from 110 of 158 patients, either through review of subsequent notes or by telephone. A telephone call was required to obtain this information in 62 patients. Overall, resolution or significant improvement was noted in 84 (76.4%) of these. Migraine was later diagnosed by another physician in 5 patients.

Of the 37 children with a change in spectacle correction, follow-up information was available in 32. Of those, 23 (71.9%) noted improvement of headache and 9 (28.1%) did not. Among the remaining 78 patients, 61 (78.2%) noted improvement in headache and 17 (21.8%) did not. Chi-square analysis did not show a statistically significant difference in resolution between those who received a change in spectacle correction when compared to those who did not ($P = .38$). Of the headache characteristics we documented, we were not able to identify any that were predictive of resolution with refractive correction.

DISCUSSION

The International Headache Society published an extensive review of headache categories in 2004. According to these guidelines, headache attributed to refractive error is recognized as recurrent mild frontal headache, noted in temporal relation to prolonged visual tasks and in the presence of an uncorrected or miscorrected refractive error, which resolves with correction of refractive error.[2]

Several authors have previously suggested that the prevalence of headache caused by "eye strain" from uncorrected or miscorrected refractive errors tends to be overestimated by patients and physicians.[6-8] A few studies have shown a slight correlation between headache and refractive errors in children. Akinci et al. demonstrated a higher incidence of headache in children with astigmatism, but failed to show any significant difference in those with hyperopia or myopia.[10] Similarly, Hendricks et al. demonstrated a small but statistically significant correlation between refractive errors and headaches in schoolchildren.[11]

It has been noted that headache, regardless of the cause, tends to improve with optimal correction of refractive error.[7] However, no study to our knowledge has compared headache outcomes of those who received correction of refractive errors and those who did not. We acknowledge that children in both groups likely received concurrent medical treatment for headache. We hypothesize that, in most cases, headaches in children tend to resolve regardless of whether their glasses are changed. Our data support this assertion, suggesting that improvement may occur as part of the natural history of headaches in children, rather than as a benefit from correction of a refractive error.

Our experience indicates that most children with headache did not have any ophthalmologic abnormality, refractive or otherwise. Headaches were no more likely to improve in children receiving new glasses prescriptions. It is reassuring that none of those we reviewed were diagnosed as having any severe sight-threatening or otherwise serious medical conditions.

We acknowledge limitations inherent in a small, single-center retrospective study. Decisions whether to prescribe a change in refractive correction were made with reference to consensus guidelines.[9] It is possible that guidelines for refractive correction should be different for children with headache. Investigating this possibility was beyond the scope of this study. It is difficult to determine to what extent patients were actually wearing their prescribed glasses. We relied on self-reported headache history rather than any formal headache diary. No randomized controls were used; it would be inappropriate to deprive children of appropriate refractive correction. We acknowledge that some patients whose headaches improved following refractive correction may not have improved without this intervention. In 48 cases (approximately one-third), we were unable to contact parents for follow-up. Additionally, some of the headaches occurred up to 10 years previously and it is possible parents were not able to remember details accurately when contacted. On the other hand, significant diagnoses were likely to be remembered.

Ultimately, any child with headache warrants an appropriate and thorough medical evaluation. Primary care physicians may find it more fruitful to investigate more common causes of headache, such as migraine or sinusitis, as well as more serious causes such as brain tumors. On the other hand, a full ophthalmologic evaluation should be available, especially to children with any indication of visual problems.

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Headache and the Eye

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Because of the inextricable link between the eyes and headaches, ophthalmologists are often the first physicians to evaluate patients with headaches, eye pain, and headache-associated visual disturbances. Although ophthalmic causes are sometimes diagnosed, eye pain and visual disturbances are often neurologic in origin. Many primary headache disorders have ophthalmic features, and secondary causes of headache frequently involve the visual system. Both afferent and efferent symptoms and signs are associated with headache disorders. Moreover, the frontal or retro-orbital pain of some primary ophthalmic conditions may be mistaken for a headache disorder, particularly if the ophthalmologic examination is normal. This article reviews common ocular conditions that are associated with head pain, and some secondary causes of headache with neuro-ophthalmic manifestations.

Introduction

A wide differential diagnosis applies when evaluating a patient with neuro-ophthalmic symptoms and headache or periorbital pain. Considerations in the triage of these patients include 1) primary versus secondary headache disorder; 2) ocular or orbital condition versus neurologic disease; 3) extracranial or intracranial process; and 4) the urgency of diagnosis and treatment. Similarly, patients' interpretation of their condition may lead them to seek medical care from a primary care physician, ophthalmologist, neurologist, neurosurgeon, or in the emergency department. Awareness of these various conditions is essential to achieve the correct diagnosis and management.

Primary Headache Disorders with Ophthalmic Manifestations

Migraine

Many of the primary headache disorders have neuro-ophthalmic manifestations. Positive, negative, autonomic, or efferent symptoms and signs are associated with migraine (Table 1). Positive and negative symptoms are part of migraine aura, whereas autonomic and efferent symptoms often occur before or during the headache phase [1–6].

Trigeminal autonomic cephalgias

The trigeminal autonomic cephalgias (TACs) are characterized by unilateral pain in the distribution of the ophthalmic division of the trigeminal nerve and cranial autonomic activation. Cluster headache is the most common TAC; SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) occur infrequently. Autonomic manifestations of TACs referable to the eye are lacrimation, conjunctival injection, Horner syndrome, and eyelid edema.

Cluster headache

Cluster headache is the most common TAC. It generally occurs in men, producing unilateral attacks of severe pain lasting 15 to 180 minutes. The pain is centered around the eye or the temporal region. The attacks may occur more than once daily, often awakening the patient from sleep at the same time each night. Alcohol and nitrites are common triggers. Most patients with cluster headaches become restless or violent during the attacks and prefer to pace or move around while the pain is present. Cluster periods may last from weeks to months and tend to be seasonal and episodic, but occasionally they are chronic, even from the onset.

The autonomic features of cluster headaches affect the ipsilateral eye. During the cluster attack, there is frequently a postganglionic Horner syndrome, with ptosis, miosis, and anisocoria that is greater in dim lighting. In some patients, the Horner syndrome may be permanent; it sometimes predates the onset of cluster headaches by years. Patients may also experience conjunctival injection, eyelid edema, and lacrimation, which may be projectile. Other autonomic symptoms include nasal congestion or rhinorrhea, and forehead/facial diaphoresis.

Table 1. Neuro-ophthalmic features of migraine

Positive visual phenomena
Zig-zag fortification spectra
Scintillating scotoma
Blurred vision
Heat waves
Phosphenes
Kaleidoscope vision
Fragmented vision ("cracked glass")
Visual distortion
Negative visual phenomena
Homonymous hemianopia
Concentric visual field constriction (tunnel vision)
Cortical blindness
Transient monocular visual loss
Cortical visual disturbances
Déjà vu
Jamais vu
Micropsia
Macropsia
Dyschromatopsia
Efferent symptoms
Ptosis
Diplopia
Autonomic symptoms
Horner syndrome
Lacrimation
Conjunctival injection
Benign episodic unilateral pupillary mydriasis
Eyelid edema

Paroxysmal hemicrania

Paroxysmal hemicrania (PH) is often difficult to distinguish from cluster headache because the site and associated autonomic phenomena are very similar. It usually begins in adulthood but may present at any age. Unlike cluster headache, it affects women more often than men. The pain distribution is the same in both conditions, located in the ophthalmic division of the trigeminal nerve. It is described as severe, stabbing, throbbing, or boring, increasing in intensity over a period of 1 to 40 minutes. Individual episodes are side-locked, although the pain may change sides or occasionally be bilateral or occipital. The episodes are generally shorter than cluster headaches, lasting 2 to 120 minutes. The spells tend to be more frequent than cluster headaches, often occurring more than five times daily. Another characteristic distinguishing cluster headache from PH is the patient's response to pain. Most patients with PH lie down, sit quietly, or hold their head during an attack. Attacks may be precipitated by head movement or alcohol and may awaken the patient from sleep. Occasionally PH is associated with aura, migraine headache, or trigeminal nenralgia.

PH may be chronic or episodic. Episodic PH occurs in periods lasting 7 days to 1 year, separated by pain-free intervals of 1 month or more. Chronic PH persists for more than 1 year without remission, or has remissions lasting less than 1 month. Most patients with chronic PH evolve de novo, but there may be a transition from episodic to chronic PH.

Ophthalmic features of PH include an ipsilateral Horner syndrome (ptosis and miosis), as well as the parasympathetic nervous system featnres of lacrimation, conjnnctival injection, and eyelid edema. Nasal congestion and rhinorrhea may occur. Many patients also have migrainous symptoms, snch as photophobia, phonophobia, nausea, or vomiting.

PH is exquisitely sensitive to indomethacin; the effect is so predictable that indomethacin responsiveness is included in the diagnostic criteria for the disorder [5]. Thus, when clnster headache is suspected, a trial of indomethacin is indicated as a "diagnostic test." Oral dosages of 25 to 75 mg three times daily are used during an attack period. Infrequently, patients not responding to indomethacin are successfully treated with aspirin, celecoxib, or acetazolamide. If indomethacin is not effective, cluster headache, migraine, or secondary causes of episodic hemicrania should be considered. Rarely, PH may be mimicked by a tumor in the frontal lobe, cavernous sinus area, or sella. Increased intracranial pressure (ICP) and collagen vascular disease uncommonly produce short-lasting nnilateral headache resembling PH.

SUNCT and SUNA

SUNCT and SUNA are the rarest of the TACs. SUNCT episodes consist of paroxysmal severe, unilateral pain lasting 5 to 250 seconds, with a maximum duration of 2 hours [7]. The attack frequency varies from six to 100 daily, with a mean of 28 attacks per day. The attacks may occur so frequently that the pain seems to be constant. As in PH, individual attacks may be precipitated by neck movement.

The autonomic features of SUNCT are similar to cluster headache and PH, including prominent conjunctival injection, tearing, and eyelid edema. There may be forehead diaphoresis and nasal congestion. SUNA is similar to SUNCT, but the attacks last between 2 seconds and 10 minutes, with an attack frequency of one or more per day.

The differential diagnosis of SUNCT includes posterior fossa abnormalities, such as arteriovenous and other structural malformations, and HIV/AIDS. MRI is warranted to exclude a secondary cause.

Of all the primary trigeminal cephalgias, SUNCT is the most difficult to treat. The best responses are reported with topiramate, lamotrigine, clomiphene citrate, and carbamazepine [8,9]. SUNCT often worsens with prednisone

and verapamil. Surgical treatments, such as retrogasserian glycerol rhizolysis, gamma knife radiosurgery of the trigeminal root exit zone, and microvascular decompression surgery, are not consistently effective, and neural stimulators are being explored.

Other Causes of Headache and Periocular Pain

Table 2 outlines other causes of headache and periocular pain.

Orbital and ocular etiologies

Keratitis sicca (dry eye)

Dry eye a very common disorder, affecting 10% to 15% of adults. It is associated with tear-deficient states, such as Sjögren syndrome and lacrimal disease, as well as excessive tear evaporation. Other common conditions associated with dry eye are thyroid eye disease that affects the lacrimal gland and also produces corneal exposure, and the decreased blink rate of Parkinsonian disorders. Because the cornea is richly innervated by the ophthalmic division of the trigeminal nerve, corneal surface dryness may be painful. Burning, blurred vision, and photophobia commonly occur. Other symptoms of dry eye include monocular diplopia or polyopia, a foreign body sensation in the eye, eye irritation, redness, and tearing. Severe dry eye may cause corneal damage.

Dry eye may simulate headache, and medications used to treat headaches may cause or worsen pre-existing dry eye. Chronic use of medications with anticholinergic side effects, such as tricyclic antidepressants, propranolol, phenothiazines, metoclopramide, and muscle antispasmodics, decreases tear production. Positive airway pressure devices used to treat obstructive sleep apnea also contribute to dry eyes; applying a lubricating ointment at bedtime may be helpful for these patients.

Treatment may include lubricating drops (artificial tears), lubricating ointments at bedtime, reversible or permanent occlusion of the outflow tear ducts, and topical immunosuppressant agents.

Trochlear pain

Trochleitis produces pain in the superomedial part of the orbit that is often exacerbated with eye movement, when the superior oblique tendon apposes the trochlear sling [10]. Some patients experience diplopia and erythema near the superior oblique insertion [11]. The pain is reproduced by palpating the trochlear region. The pain arising from the trochlear area may also trigger the pain of migraine or tension-type headache. It is presumed to be inflammatory in origin and is treated with a local injection of lidocaine or corticosteroids [10].

Angle-closure glaucoma

Angle-closure glaucoma is produced by mechanisms that push the iris forward from behind or pull the iris forward into contact with the trabecular meshwork. Sudden blockage of the trabecular meshwork by the iris prevents drainage of the aqueous humor, producing a rapid increase in intraocular pressure. Acute angle-closure glaucoma is characterized by pain, blurred vision, rainbow-colored halos around lights, nausea, and vomiting. Examinations reveal high intraocular pressure, a mid-dilated and sluggishly reactive pupil, corneal edema ("steamy" cornea), dilated conjunctival blood vessels, a shallow anterior chamber, and mild aqueous inflammatory changes.

Angle-closure glaucoma usually occurs in the setting of shallow anterior angles or a plateau iris (anteriorly positioned ciliary processes), but may occur under certain conditions in patients with normal ocular anatomy. Sulfa derivatives, such as topiramate and acetazolamide, may precipitate angle-closure glaucoma (usually bilateral and simultaneous) as an idiosyncratic reaction. Anticholinergics and antidepressants may produce attacks in predisposed individuals. Prompt treatment is necessary to prevent permanent visual loss and pupillary deformity.

Subacute angle-closure glaucoma may mimic migraine, producing episodes of ocular or periocular pain, halos, and blurred vision [12]. The attacks are often precipitated by rapid miosis, such as when emerging from a dark theater into daylight. Sleep-induced mydriasis relieves the symptoms, which may be mistaken for the sleep-induced pain relief of migraine.

Inflammatory orbital disease

Many conditions produce inflammatory orbital disease, and the differential diagnosis includes systemic disorders, neoplasm, congenital malformations, infectious disease, and trauma [11]. Orbital involvement from idiopathic inflammation may involve any of the orbital structures, including the extraocular muscles (myositis), sclera (scleritis, episcleritis), aqueous or vitreous (uveitis), lacrimal gland (dacryoadenitis), and uncommonly, the retinae or optic nerves. Idiopathic inflammation, also termed inflammatory orbital pseudotumor, produces unilateral or bilateral symptoms of diplopia, pain, proptosis, conjunctival injection, photophobia, and periorbital edema [13•]. The pain may be severe and is exacerbated by manually retropulsing the globe under closed eyelids. The diagnosis is usually made clinically after excluding systemic causes. Corticosteroids are the mainstay of therapy; other immunosuppressive agents and radiotherapy are occasionally used when corticosteroids are ineffective.

Tolosa-Hunt syndrome, characterized by painful ophthalmoplegia, is a form of idiopathic inflammation of the cavernous sinus or superior orbital fissure. It rarely extends into the orbit or affects the lower divisions of the trigeminal nerve. It may occur at any age and responds dramatically to corticosteroids. Tolosa-Hunt syndrome is uncommon and is a diagnosis of exclusion, as lymphoma, metastatic disease, sarcoidosis, Wegener's granulomatosis, vasculitis, and

Table 2. Secondary headache disorders with neuro-ophthalmic features

Condition	Primary eye manifestation	Other eye findings	Headache characteristics	Other features	Diagnosis	Treatment
Carotid dissection	Ipsilateral Horner syndrome	Conjunctival injection, optic nerve ischemia	Ipsilateral neck or head pain	Dysgeusia, contralateral hemiparesis, altered LOC	MRI, MRA, CT angiography, Doppler, catheter angiography	Endovascular, anti-coagulation, and/or antiplatelet
Vertebral dissection	Diplopia	Nystagmus, hom-onymous visual field defect, skew deviation, Horner syndrome	Ipsilateral posterior head, neck, or shoulder pain; rarely frontal	Vertigo, ataxia, syncope, drop attacks, facial numbness, hemiparesis	MRI, CT angio-graphy, ultrasound, catheter angiography	Endovascular, anti-coagulation, and/or antiplatelet
Posterior communicating artery aneurysm	Ipsilateral third nerve palsy		Around ipsilateral eye; if ruptured, thunderclap headache	If ruptured, meningis-mus, photophobia, contralateral hemi-paresis, altered LOC	CT, LP if rupture suspected; MRI, MRA, arteriogram	Endovascular, surgical clipping
Giant cell arteritis	Ischemic optic neuropathy or central retinal artery occlusion	Amaurosis fugax, diplopia	No characteristic features	Scalp tenderness, jaw claudication, scalp necrosis, fever, weight loss, malaise, symp-toms of polymyalgia rheumatica, anemia	ESR, C-reactive protein, CBC with platelet count, temporal artery biopsy	Treat acutely with prednisone, 80–100 mg daily, or intravenous methylprednisolone; arrange temporal artery biopsy
Pituitary apoplexy	Unilateral or bilateral III nerve palsy, proptosis	Conjunctival injection; optic neuropathy; IV, VI nerve palsy	Severe pain, photophobia, meningismus	Hypopituitarism, altered LOC	CT, MRI	Surgery, hormone replacement
Idiopathic intracranial hypertension	Papilledema	Transient visual obscurations, diplopia (abducens palsy), visual loss	Usually frontal pressure	Obesity, back or neck pain, pulsatile tinnitus	MRI, LP	Intracranial pressure–low-ering agents, optic nerve sheath decompression, CSF diversion procedure
Brain tumor	Papilledema, diplopia	Ocular motor palsy, Parinaud syndrome, INO, skew deviation, nystagmus	New or progres-sively worsening headache, aching, worse in the morning or with Valsalva in 1/3	Focal neurologic deficits, ataxia, altered LOC, cognitive dysfunction	MRI	Surgery, CSF diversion procedure, radiation therapy, stereotactic radiosurgery
Tolosa-Hunt syndrome	Ophthalmoplegia	Proptosis, miosis, mydriasis, optic neuropathy	Boring pain behind ipsilateral eye and brow	Upper facial numbness	MRI with contrast (must exclude a noninflammatory cause)	Prednisone

CBC—complete blood count; CNS—central nervous system; CSF—cerebrospinal fluid; ESR—erythrocyte sedimentation rate; INO—internuclear ophthalmoplegia; LOC—level of consciousness; LP—lumbar puncture; MRA—magnetic resonance angiography.

Table 2. Secondary headache disorders with neuro-ophthalmic features *(Continued)*

Condition	Primary eye manifestation	Other eye findings	Headache characteristics	Other features	Diagnosis	Treatment
Inflammatory orbital pseudotumor	Diplopia	Uveitis, myositis, conjunctival injection, chemosis, eyelid erythema, soft tissue swelling, optic neuropathy	Ipsilateral orbit; worse with retropulsion of globe	Fever, leukocytosis	CT, orbital echography, ESR, CBC with differential	Prednisone, other immunosuppressants, orbital radiotherapy
Optic neuritis	Ipsilateral optic neuropathy	Phosphenes	Ipsilateral pain with eye movement, ipsilateral aching head pain	Usually in those < 50 years	Clinical presentation, MRI to look for CNS demyelination	Intravenous methylprednisolone in selected cases

CBC—complete blood count; CNS—central nervous system; CSF—cerebrospinal fluid; ESR—erythrocyte sedimentation rate; INO—internuclear ophthalmoplegia; LOC—level of consciousness; LP—lumbar puncture; MRA—magnetic resonance angiography.

infectious conditions produce an identical phenotype and improve with corticosteroids [14].

Vascular disorders

Cervical arterial dissection

Cervical arterial dissections involving the internal carotid arteries and the vertebral arteries occur at regions where the arteries are mobile and not fixed to other arteries or bony structures. These segments are vulnerable to tearing and are usually unilateral. They begin with a tear in the media that leads to longitudinal intramural dissection proximally and distally. If the intima is torn, partially coagulated blood enters the arterial lumen, expanding the arterial wall, activating the coagulation cascade in the vascular endothelium, and producing an intraluminal thrombus. A dissection originating in the intima produces a flap, creating true and false lumens. An aneurysmal outpouching of the arterial wall dissection plane causes a pseudoaneurysm. Rupture through the adventitia intracranially leads to subarachnoid hemorrhage [15••]. Pain is present in nearly all patients with cervical and intracranial arterial dissections.

Congenital and acquired connective tissue disorders, such as Marfan syndrome, Ehlers-Danlos syndrome, and fibromuscular dysplasia, are predisposing factors. A history of migraine is common among patients with dissection. There may be antecedent trauma or a history of sudden or unusual movements stretching the arteries. Often an underlying cause is not found.

Carotid artery dissection

The most common symptoms of carotid artery dissection are pain in the ipsilateral face, neck, or head; transient monocular visual loss; contralateral weakness or numbness; stroke; Horner syndrome (ipsilateral ptosis and miosis); and pulsatile tinnitus. Lower cranial nerve symptoms include dysphagia, hoarseness, dysgeusia, and sternocleidomastoid weakness. The pain may precede the focal neurologic symptoms by days to weeks. Extracranial dissections usually produce ipsilateral trigeminal pain and a Horner syndrome, which may be indistinguishable from an attack of cluster headache.

CT angiography, MRI, B-mode ultrasound, and magnetic resonance angiography (MRA) are effective for imaging the affected arterial walls and lumen [16]. MRA is more useful in detecting carotid than vertebral dissection. Catheter angiography may be used. There are no evidence-based guidelines for treatment. Endovascular procedures, such as intra-arterial thrombolysis or clot extraction, stenting, and angioplasty, are emerging therapies. Anticoagulation and antiplatelet therapies are also used, although there is no consensus regarding their use [17].

Vertebral artery dissection

The pain of cervical vertebral artery dissection often precedes the neurologic symptoms and is localized to the ipsilateral trapezius, posterior neck, occiput, or cervical nerve roots [15••]. Occasionally, the headache is frontal [18]. There may be transient ischemic attacks, stroke, or no neurologic symptoms. Spinal cord infarction rarely occurs. Intracranial involvement causes infarction or subarachnoid hemorrhage. The most common transient symptoms are dizziness, diplopia, lateropulsion, staggering, and dysarthria. Strokes may produce visual field defects, nystagmus, Horner syndrome, corneal anesthesia, and ptosis [18].

Intracranial aneurysms

Most aneurysms (85%) originate from the internal carotid artery and its branches, whereas the rest are infratentorial. The risk of rupture increases with age, location, size of the aneurysm, and presence of symptoms. Intracavernous, carotid-ophthalmic, and posterior communicating artery aneurysms often cause headache and visual symptoms as initial features [19]. They are diagnosed using CT angiography, MRI and MRA, and catheter angiography. Treatment modalities include neurosurgical and endovascular procedures [20].

Intracavernous aneurysms may not cause symptoms until they are quite large. They are sometimes discovered incidentally when evaluating a patient for another aneurysm. Because they are encased by bone, they rarely rupture, but may present with a spontaneous cavernous-carotid fistula [21]. They generally affect older women, are associated with hypertension, and may be bilateral. The symptoms are produced by compression of surrounding structures, most commonly the abducens nerve. The oculomotor and trochlear nerve may also be affected. Common symptoms are diplopia and pain. Pain, present in approximately 90% of patients, consists of headache, retro-orbital pain, or trigeminal pain. The examination shows one or more ocular motor nerve palsies, Horner syndrome, and corneal anesthesia. Involvement of the distal portion of the intracavernous carotid produces visual loss with the associated features of an optic neuropathy. If treatment is needed, these aneurysms are generally approached endovascularly because of their location.

An aneurysm at the bifurcation of the carotid and posterior communicating arteries may compress the oculomotor nerve as it traverses the subarachnoid space. The pupil is usually involved, and the oculomotor palsy may be otherwise incomplete. The pain associated with an aneurysmal oculomotor palsy is generally localized to the ipsilateral eye area. Prompt diagnosis is needed to prevent rupture. Once rupture occurs, there may be altered level of consciousness, meningismus, photophobia, or manifestations of brain herniation. Posterior communicating artery aneurysms are treated with surgical clipping or endovascular procedures.

Carotid-ophthalmic artery aneurysms arise from the junction of the internal carotid artery and the ophthalmic artery and account for approximately 5% of all intracra-

nial aneurysms. True ophthalmic artery aneurysms are rare. They are more frequent in women, most commonly left-sided, and often associated with other aneurysms. The most common symptom is monocular visual loss, which may be slowly progressive or acnte and painful. An optic neuropathy is the most freqnent sign, although posterior or superior expansion may produce an optic chiasmal or optic tract syndrome. Medial expansion causes bilateral optic neuropathies, often with asymmetric involvement. These aneurysms may enlarge to produce ocular motor palsies and may rupture.

Basilar artery aneurysms usually rupture before they cause focal neurologic deficits. Both ruptured and unruptured basilar artery aneurysms may cause headaches that are generally suboccipital but may be orbital or periorbital. The headaches are often aggravated by head motion. Neuro-ophthalmic signs include abducens paresis, horizontal gaze paresis, nystagmus, oculomotor nerve palsy, dorsal midbrain (Parinaud) syndrome, and internuclear ophthalmoplegia. If the aneurysm is large enough to obstruct the aqneduct, papilledema and visnal loss may occur from ICP. Treatment of basilar artery aneurysms is challenging because of their location and usually approached endovascularly.

Systemic disorders

Giant cell arteritis

Giant cell arteritis (GCA), or temporal arteritis, is a systemic vasculitis with protean manifestations. Thus, patients with GCA may seek care from a primary care physician, dentist, ophthalmologist, neurologist, rheumatologist, dermatologist, or cardiologist, depending on their symptoms. Because it can produce bilateral, irreversible blindness, a high index of suspicion is needed for prompt diagnosis and treatment [22••]. Moreover, there is no single diagnostic test that accurately defines the disorder [23••]. The incidence increases with age, ranging from 1.4 per 100,000 between ages 50 and 59 years to 29.6 per 100,000 between ages 70 and 79 years [24••].

The headache of GCA is not specific; GCA must be considered in any patient age 60 years or older who develops a new headache. The pain may be global, hemicranial, or bifrontal, similar in character to migraine or tension-type headache pain. Other patients experience brief stabbing head pain. There is often accompanying scalp tenderness. Pain and weakness (claudication) of the jaw while chewing is highly suggestive of GCA and is often misdiagnosed as temporomandibular joint dysfunction. Other systemic symptoms include weight loss, fever, myalgias, arthralgias, scalp necrosis, depression, malaise, and fatigue. Polymyalgia rheumatica is present in approximately 50% of cases and may represent a mild form of GCA. Stroke, myocardial infarction, and bowel infarction are infrequent complications.

Unfortunately, approximately one third of patients with GCA evaluated by ophthalmologists and neuro-ophthalmologists present with visual loss in the absence of other systemic symptoms, so-called "occult" GCA. Anterior ischemic optic neuropathy (AION) associated with GCA may produce severe loss of visual acuity and visual field, with pallid swelling of the optic nerve. There may be evidence of retinal ischemia. Rapid progression to involve the fellow eye or bilateral, simultaneous AION commonly occurs with arteritic AION. There is also a nonarteritic form of AION, which is much more common than the arteritic variety and may be difficult to distinguish clinically from GCA. Fluorescein angiography may be helpful in this circumstance, showing delayed choroidal filling time in arteritic AION. Some patients with GCA experience amanrosis fugax or transient diplopia prior to developing permanent visual loss. Central retinal artery occlusion is responsible for about 10% of GCA-associated visual loss.

The diagnosis of GCA is supported by several laboratory tests, including an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein, thrombocytosis, anemia of chronic disease, and increased fibrinogen levels. However, all of these tests may be normal in GCA, and none is specific for GCA. The sensitivity of an elevated ESR is 84.9%, an elevated C-reactive protein is 97.5% sensitive, and the sensitivity increases to 99.2% when both tests are abnormal [25]. First-pass contrast-enhanced 3T MRI may successfully image small superficial cranial arteries, but the sensitivity and specificity of this technique in GCA is unproven [26].

The "gold standard" for diagnosis is a temporal artery biopsy, showing narrowing or thrombosis of the arterial lumen, inflammation with or without giant cells, and disruption of the internal elastic lamina. A 2-cm–long specimen with 1-mm serial-sectioned histology preparations is recommended, as skip lesions occur. The overall sensitivity of a temporal artery biopsy is 87.1% [25], and bilateral biopsies do not increase the yield significantly. Many physicians dismiss the biopsy as unnecessary and make a diagnosis solely on clinical grounds. I disagree with this approach, as the diagnosis may be questioned later after the patient experiences complications from corticosteroids. Moreover, GCA requires daily corticosteroid treatment for upwards of a year; one should be as certain of the diagnosis as possible before committing a patient to the treatment.

The philosophy of suspected GCA, particularly if there is visual loss, optic disc edema, or amaurosis, is to "treat first and ask questions later." The generally accepted window for performing a temporal artery biopsy after starting treatment is 10 days, although evidence of inflammation may persist after longer time periods. There are no evidence-based dosing guidelines, but high-dose corticosteroids (80–100 mg of prednisone) should be started expeditiously. In the setting of acute, unilateral, arteritic AION, one may elect to administer intravenous corticosteroids to prevent visual loss in

the other eye, although progression may occur despite intravenous therapy. Corticosteroids are the mainstay of treatment; other immunosuppressant agents have not been proven effective for corticosteroid substitution, and their role as steroid-sparing agents is limited. Neuro-ophthalmologists tend to taper the steroids more slowly and use a high maintenance dose of prednisone (20 mg daily vs 10–15 mg daily), compared with rheumatologists. I suspect that this reflects differences in patient populations between specialties; patients with visual loss tend to have more severe disease. The systemic symptoms remit quickly with prednisone treatment, but the visual prognosis is quite poor in arteritic AION.

Idiopathic intracranial hypertension and increased ICP

Headaches associated with bilateral optic disc edema indicate increased ICP, which may be caused by tumors, infarction, inflammation, and congenital anomalies. Idiopathic intracranial hypertension (IIH) is characterized by increased ICP without a mass, ventriculomegaly, or other identifiable cause. It most commonly affects obese women of childbearing age, although it may occur in children and men. The most common symptom is headache, present in over 90% of patients. The headache is nonspecific and may be retro-orbital, bifrontal, unilateral, or posteriorly located. The pain may be throbbing or steady, constant or intermittent, and is generally severe. There may be accompanying photophobia, phonophobia, nausea, and vomiting. Some patients, particularly children, have more prominent neck and back pain than headache [27••]. Brief episodes of complete or partial visual loss, termed transient visual obscurations, are often precipitated by postural change and reflect papilledema. Other symptoms include visual loss, pulsatile tinnitus, diplopia, radicular pain, and ataxia. The diagnostic hallmark of IIH is papilledema, although it is not universally present and may be asymmetrical.

IIH is diagnosed by excluding a mass lesion or venous sinus thrombosis, and demonstrating an increased cerebrospinal fluid (CSF) pressure with otherwise normal CSF contents. Thus, MRI, magnetic resonance venography, and a diagnostic lumbar puncture should be performed on all patients. Detailed documentation of the visual status is necessary, including perimetry. One must also exclude a secondary cause [28••].

The goal of treatment is to preserve vision. With minimal or mild visual impairment, medication is usually an appropriate first-line treatment. Medical therapy includes decreasing salt intake, acetazolamide, and headache therapy. If acetazolamide cannot be tolerated, furosemide or other diuretics are used. Retrospective studies suggest that modest weight loss (5% to 6% of body weight) may hasten the resolution of papilledema. Preventive headache therapy is often required, and medication overuse is possible in these patients; topiramate has the advantages of mild carbonic anhydrase activity and possible weight loss.

When vision is impaired or if the visual status rapidly deteriorates, surgical options include optic nerve sheath fenestration and CSF diversion procedures (shunting). The role of venous sinus stenting for IIH is controversial [29,30].

Conclusions

The diagnosis and management of conditions producing headache with ocular or neuro-ophthalmologic manifestations is challenging. Many of these conditions require a multidisciplinary approach. Recognizing ocular conditions and secondary disorders, and obtaining appropriate referral and testing, results in prompt intervention that may preserve vision or save the patient's life.

Disclosure

No potential conflict of interest relevant to this article was reported.

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Headache Attributable to Disorders of the Eye

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Headache Attributable to Disorders of the Eye

Deborah I. Friedman · Lynn K. Gordon · Peter A. Quiros

Abstract Sensory innervation to the eye and periocular area arises from the ophthalmic branch of the trigeminal nerve. Thus, ocular, orbital, and systemic disorders may produce head pain with ocular signs and symptoms. Whereas some of these entities have characteristic diagnostic features, others mimic primary headache disorders such as migraine and cluster headache. This article reviews common ocular and neuro-ophthalmic conditions that are accompanied by pain in or near the eye.

Keywords Ocular pain · Trochleitis · Oculomotor nerve · Orbit · Inflammation

Introduction

Patients with head or eye pain may be challenging to evaluate, as both primary and secondary headache disorders may produce symptoms referable to the trigeminal system, eye, and orbit. Signs of orbital disease, such as eyelid edema, eyelid erythema, and orbital congestion, are also features of the trigeminal autonomic cephalalgias. Relatively benign conditions, such as dry eyes, often produce disabling pain and discomfort; monocular diplopia from keratitis sicca may erroneously suggest a neurological condition. The overlap between the signs and symptoms of primary and secondary disorders affecting the afferent and efferent visual systems leads to bidirectional confusion, as patients with ophthalmic disease are misdiagnosed with headache disorders, and vice versa. Awareness of these conditions is essential to arrive at the correct diagnosis and management strategy.

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Ocular Disorders

Ocular Surface Disease

Pain is a common symptom of dry eye and keratitis. Pain may result from a primary tear film deficiency or abnormality, corneal epithelial disease, contact lens use, and exposure to topical medication, or may be secondary to systemic inflammatory diseases, including rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosis, and psoriasis. Dry eye affects at least 2% of individuals with rheumatoid arthritis; a large study of almost 10,000 patients documented persistent oral or ocular dryness in more than 11% of patients, and the prevalence of dryness positively corresponded to disease activity [1]. Dry eye and pain or redness was the source of dissatisfaction following laser in situ keratomileusis (LASIK) in almost 28% of patients [2]. Other common causes of ocular pain are a corneal foreign body, abrasion,

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or infectious keratitis. Dry eye also occurs with conditions that interfere with normal blinking, such as thyroid eye disease, Parkinson's disease, progressive supranuclear palsy, and facial paresis. An underlying cause is not identified in many cases.

Symptoms of ocular surface disease or dry eye may range from a mild discomfort to severe, debilitating symptoms that interfere with activities of daily life. Patients may experience ocular pain, a burning or foreign body sensation, pruritus, redness, reflex tearing, blurred vision, monocular diplopia, or visual distortion. The symptoms often fluctuate and characteristically worsen during activities requiring visual concentration, such as reading, driving, using the computer, or watching television.

Examination of the eye and ocular adnexa using fluorescein dye with a blue light and magnification will identify corneal foreign bodies, abrasions, or keratitis. Abnormalities in the Schirmer sterile test strip evaluation of tear production, vital staining of the corneal surface, and the tear break-up time are helpful in making the diagnosis of dry eye. Therapy for dry eye symptoms includes topical lubricants, anti-inflammatory medications, and punctal occlusion to prolong ocular tear contact. Infectious keratitis is an ophthalmic emergency that must be evaluated immediately by an ophthalmologist in order for prompt initiation of definitive antimicrobial or antifungal therapy.

Intraocular Inflammation

Severe pain is a common symptom of patients with acute anterior uveitis and is often associated with extreme light sensitivity and redness of the eye [3]. The pain is variable, and the absence of pain does not preclude a severe uveitis. For example, pain is not a typical characteristic of juvenile idiopathic uveitis despite potentially sight-threatening sequelae [4, 5]. Anterior uveitis, the most common form of uveitis, may be idiopathic or secondary to infectious or noninfectious etiologies. Systemic inflammatory diseases may present with uveitis, including many spondyloarthropathies, sarcoidosis, inflammatory bowel diseases, and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitides. In particular, headache and uveitis are frequent symptoms and signs of patients with Behçet disease or Vogt-Koyanagi-Harada syndrome [6, 7].

The diagnosis of uveitis requires an ophthalmologic examination of the anterior chamber and posterior segment, as well as a dilated evaluation of the peripheral retina. Once intraocular inflammation is identified, then the differing etiologies must be considered, and targeted laboratory and diagnostic evaluations are performed. Therapy for noninfectious etiologies may include local or systemic immunosuppressive agents.

Angle Closure Glaucoma

Acute angle closure glaucoma occurs when intraocular pressure rapidly rises as a result of closure or blockage of the drainage angle of the eye, the site of aqueous outflow. It may occur in any situation associated with pupillary dilation, which causes the iris to move anteriorly (eg, emerging from a darkened movie theater). Risk factors include advancing age, a strong family history of glaucoma, a history of ocular trauma, Asian ethnicity, hyperopia (farsightedness), and pseudoexfoliation [8]. Systemic medications, such as topiramate, are associated with angle closure glaucoma [9•].

Typical symptoms are ocular pain, headache, nausea, and vomiting. The attack is often accompanied by blurry vision, and patients often complain of seeing halos around lights. Therefore, these attacks may be mistaken for migraine. However, unlike migraine patients, patients with acute angle closure will typically demonstrate the following ocular signs [10]:

- Elevated intraocular pressures (typically>30 mm Hg): When tonometry is unavailable, the affected eye may be palpated under closed lids using the thumb pad. A hard, unyielding globe indicates an elevated pressure.
- Conjunctival injection: The eye is typically red, and there is often a ring of vascular congestion surrounding the corneal-scleral junction.
- Shallow anterior chamber: The iris is commonly rotated forward toward the back side of the cornea, making the anterior chamber shallower.
- Mid-dilated pupil: The pupil is usually dilated, and either fixed or sluggishly reactive (Fig. 1). The combination of pain and dilated pupil in angle closure may be mistaken for a third cranial nerve palsy, but the elevated pressure and the lack of ptosis or ocular motor palsy exclude that diagnosis.

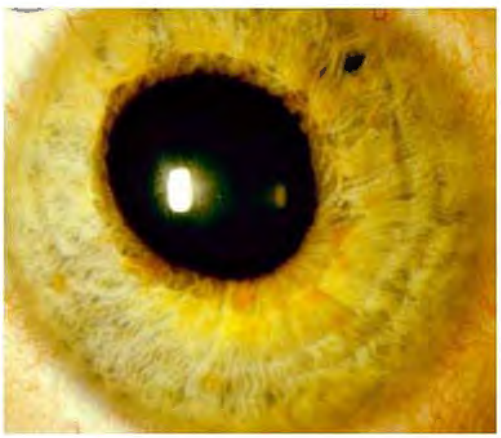

Fig. 1 Angle closure glaucoma. The pupil is fixed and mid-dilated, bowing the iris forward and creating a shallow anterior chamber

- Corneal edema: The cornea may appear edematous or cloudy.

Whereas the pain associated with angle closure may improve with the use of analgesics, it quickly subsides once the intraocular pressure is controlled. Intraocular pressure control is usually achieved using cholinergic agents such as pilocarpine to constrict the pupil and open the angle. When the intraocular pressure is very elevated (> 45 mm Hg), topical medications, such as β-blockers and α-2-adrenergic agonists, as well as intravenous mannitol and carbonic-anhydrase inhibitors, may be needed. Laser peripheral iridotomy is a definitive therapy in nearly all cases.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) is a reactivation of the varicella-zoster virus after a period of dormancy in the dorsal root ganglion. The primary infection may have occurred years to decades prior. HZO affects the dermatomal distribution of the first branch of the trigeminal nerve (V1). It is characterized by a vesicular eruption on the skin accompanied by severe pain [11] (Fig. 2). Intraocular inflammation (iritis) may accompany involvement of the globe [12].

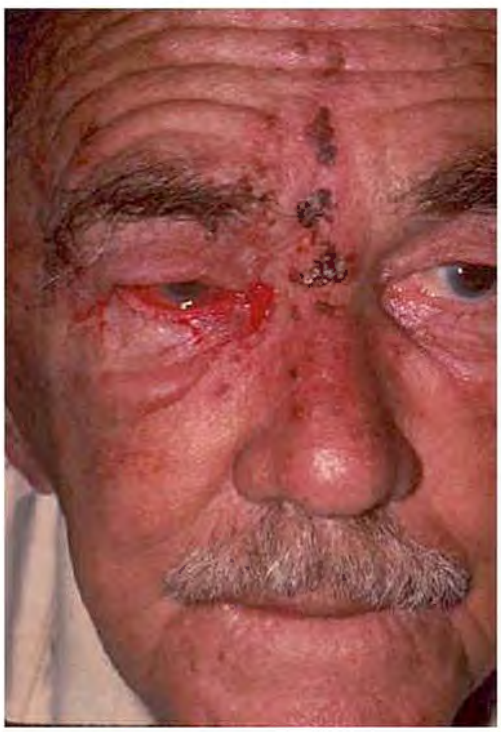

Fig. 2 Herpes zoster ophthalmicus. There is a vesicular eruption at medial canthus, with crusting of older vesicles on bridge of nose

The pain of HZO is described as burning, aching, stabbing, shooting, or throbbing. Stimulus-evoked mechanical allodynia may be present. The pain may precede the skin eruption by days and persist for more than 120 days as postherpetic neuralgia; rarely, there is pain without the rash [12]. Postherpetic neuralgia may be difficult to treat but often responds to gabapentin, carbamazepine, or topical anesthetics. The percentage of patients developing postherpetic neuralgia may be as high as 50%, although there is some evidence that acute treatment of HZO with antiviral therapy may reduce the incidence of postherpetic neuralgia [13].

"Eye Strain" (Asthenopia)

It is a popular misconception that "eye strain" is a common cause of headaches. Although eye strain is annoying, it is seldom serious and usually improves with rest. Patients experience sore, tired eyes, burning and tearing, blurred vision, and light sensitivity. Patients who read or use the computer for prolonged periods of time may complain of trouble shifting focus. Eye strain may at times be the presenting sign of a more serious underlying eye condition, such as intermittent angle closure, ocular inflammation, or orbital inflammation. Eye strain is frequently relieved by limiting prolonged reading and near work, as well as using reading glasses. Most complaints of eye strain result from dry eye, and treatment with artificial tears may help further alleviate the discomfort. Patients in whom eye strain persists despite ophthalmic lubricant treatments should be referred to an ophthalmologist for a complete eye examination.

Orbital Conditions

Idiopathic Orbital Inflammation

Idiopathic orbital inflammatory disease (OID) may occur at any age, presenting with acute, chronic, or recurrent symptoms and signs. Patients with diffuse inflammatory disease typically demonstrate exophthalmos, external swelling, and conjunctival hyperemia, whereas individuals with specific involvement of the extraocular muscles may present with diplopia and limitation of eye movements [14•, 15]. OID must be differentiated from infectious orbital cellulitis, neoplasms with inflammatory signs, and vascular lesions, which may have similar findings. OID may be idiopathic or a component of a systemic inflammatory disease such as sarcoidosis, ANCA-associated vasculitides, inflammatory bowel disease, or systemic lupus erythematosus [16].

Orbital pain is a variable symptom, occurring in at least half of affected individuals, and is typically associated with other signs and symptoms depending on the involved orbital structures [17, 18]. The pain is often severe and may worsen with eye movement or retropulsion of the globe. Headache or severe eye pain may be present without external inflammatory signs. Orbital ultrasonography is useful to demonstrate involvement of the posterior sclera, a less common but important form of OID. Diagnosis requires ocular and orbital evaluation followed by targeted laboratory studies and radiologic imaging. As lymphoma and other malignancies may have similar manifestations, a biopsy may be required to rule out neoplasia. Treatment includes systemic corticosteroids and other immunosuppressant agents.

Orbital Masses and Vascular Malformations

Rapidly expanding orbital masses are often painful. They are usually accompanied by proptosis, edema, decreased vision, and elevated intraocular pressure. Vascular lesions of the orbit include capillary hemangiomas, venous vascular malformations, venous lymphatic malformations, arterial and arteriovenous malformations (AVMs), and neoplasms such as melanoma, hemangiopericytoma, and hemangiomas [19]. Orbital AVMs produce engorged corkscrew vessels on the conjunctiva and generate pain from expansion of the vascular mass, an increase in intraocular pressure, or both.

Dural shunts arise from low-flow intracranial arteriovenous connections and often involve intracerebral vessels originating from the external carotid artery. They are most common in middle-aged women, and are usually less painful than traumatic high-flow fistulas or orbital malformations. There may be a subjective bruit associated with conjunctival injection (Fig. 3) and modest elevations in intraocular pressure, edema, and proptosis [20]. This entity is frequently misdiagnosed as chronic conjunctivitis. Orbital imaging reveals a dilated superior ophthalmic vein. The diagnosis is confirmed by angiography, and the fistula may close during or following the procedure without requiring additional intervention.

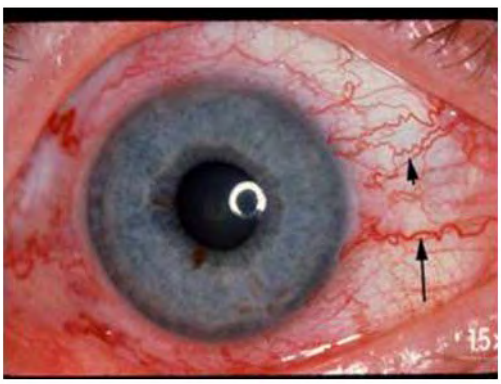

Fig. 3 Dural fistula. The conjunctival vessels are dilated with a radial corkscrew appearance

MR angiography, CT angiography, and cerebral angiography are the best means of fistula detection, the latter being the most sensitive. If cerebral angiography is performed by an interventional neuro-radiologist, embolization can be undertaken at the same time, precluding the need for an additional procedure [21].

Abscess and Cellulitis

Infections involving the orbit typically present similarly to nonspecific OID with orbital pain and concomitant inflammatory signs, including periorbital and eyelid edema and erythema [22]. It is critically important to differentiate preseptal cellulitis involving the superficial periorbital tissue from orbital cellulitis, a serious and potentially life-threatening soft tissue infection of the deep orbit [23, 24]. Preseptal cellulitis produces eyelid edema, erythema, and inflammation. Orbital cellulitis will often produce exophthalmos and partial or total restriction of extraocular movements, pain on eye movement, chemosis, a relative afferent pupillary defect, and reduced visual function.

Contiguous sinusitis accounts for 90% of cases of orbital cellulitis. Other causes of orbital cellulitis include endogenous infections, dental disease, and trauma. Although bacterial etiologies are most common, various fungi may also cause orbital cellulitis in both immune-compromised and immunocompetent hosts. Orbital cellulitis from mucormycosis or other fungi may include a severe ischemic orbitopathy and present with minimal inflammatory signs or symptoms [23, 25].

The diagnosis is made by clinical examination and orbital imaging studies. Broad-spectrum antimicrobial coverage must be initiated immediately. Emergence of antimicrobial resistant organisms such as the community-acquired methicillin-resistant *Staphylococcus aureus* must also be considered as a potential causative organism in orbital cellulitis.

Orbital abscesses are diagnosed with radiologic imaging modalities, including CT or MRI with special orbital evaluation. Clinical signs include nonaxial exophthalmos or distortion of the contour of the globe, appreciated on indirect ophthalmoscopy or ultrasonography. Surgical drainage may be necessary. Medical management with close observation is often successful in younger patients with small abscesses without visual loss or extraorbital extension.

Thyroid Eye Disease

Thyroid eye disease (TED), or Graves' orbitopathy, is part of an autoimmune disease constellation of hyperthyroidism,

orbitopathy, pretibial myxedema, and acropachy [26]. Symptoms and signs of TED arise from inflammation of the orbital connective tissue, inflammation and fibrosis of the extraocular muscles, and adipogenesis. TED is the most common cause of unilateral proptosis in adults and may precede abnormalities in thyroid function. Radioactive iodine treatment is a predisposing factor for developing or reactivating TED, particularly in smokers [27, 28]. Ophthalmic manifestations include eyelid retraction, proptosis, chemosis, periorbital edema, and ocular motility abnormalities, leading to corneal exposure, diplopia, and compressive optic neuropathy [29•] (Fig. 4). Pain and ocular discomfort are common symptoms of TED, and are often present early in the disease process. The pain most often originates from dry eyes and corneal exposure, a result of lacrimal gland dysfunction, proptosis, and eyelid retraction that prevents complete eyelid closure.

TED is diagnosed by clinical examination. Orbital imaging (CT, MRI) shows enlargement of the extraocular muscles, sparing the tendons. The inferior and medial recti are generally affected first. Imaging studies often reveal lacrimal gland enlargement and proptosis. Many treatment modalities are available to address the multiple morbidities of TED such as dry eyes, disfigurement, optic neuropathy, and diplopia. Frequent ocular lubrication, employing lubricating ointments at bedtime, may ease the discomfort from ocular surface dryness. Strabismus surgery and procedures to reposition the eyelids may be employed once the disease runs its course of about 18 months. Orbital decompression surgery is used urgently for compressive optic neuropathy and after the active phase of disease to reposition a proptotic globe. Nonsurgical treatments include corticosteroids, orbital radiotherapy, and other systemic immunosuppressant agents [29•].

Optic Neuritis

Demyelinating optic neuritis presents with unilateral subacute vision loss and eye pain in patients between ages 15 years and 45 years. The vision loss may progress over 1–10 days, and the nadir is within 2 weeks of onset. Any type of visual field defect may occur, and the asymptomatic fellow eye may also have subtle visual field defects [30, 31]. The eye pain is often a deep, aching sensation that worsens with eye movement and may precede the visual symptoms [32]. Vision is often characterized as gray, foggy, cloudy, or like looking through a veil or screen. Some patients also describe positive visual phenomena, such as sparkles, bright spots, or colors in their vision. Patients should be queried about symptoms consistent with prior episodes of demyelinating disease.

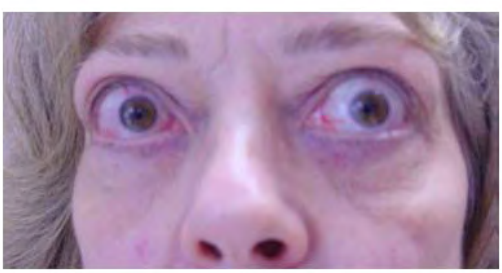

Fig. 4 Common features of thyroid eye disease include lid retraction with scleral show superiorly and inferiorly, exophthalmos, and conjunctival injection

Examination reveals decreased visual acuity, abnormal optic nerve functions (color perception, brightness sense), a relative afferent pupillary defect, and a visual field defect. The external and orbital evaluations are normal. The optic nerve head is generally normal, although disc swelling occurs in up to a third of cases. Intraocular inflammation of the posterior segment with vascular sheathing and peripheral "snowbanks" may be observed.

Recovery of vision usually starts within 4 weeks of symptom onset. Corticosteroid treatment (intravenous methylprednisolone, 1 g daily for 3 days, followed by a 7-day prednisone taper) hastens the recovery within the first 2 weeks and often relieves the pain but does not influence the visual outcome [33]. Although recovery may be dramatic, patients often realize that their vision does not completely normalize.

The differential diagnosis for demyelinating optic neuritis includes anterior ischemic optic neuropathy, sarcoidosis, lymphoma, vasculitis, cat scratch disease, and syphilis. Anterior ischemic optic neuropathy usually affects individuals over the age of 50 years and is typically painless, although the presence of mild to moderate pain does not preclude the diagnosis of anterior ischemic optic neuropathy [33]. The diagnosis of optic neuritis is based on the clinical presentation and examination. Laboratory testing is important in atypical cases to rule out alternative diagnoses. MRI is critical to both assess the prognosis for developing multiple sclerosis (MS) and prior to consideration of disease-modifying therapy for MS [34].

Trochleitis and Primary Trochlear Headache

The superior oblique tendon and its surrounding fibrovascular sheath pass though the trochlea, a ring-like cartilaginous structure that is innervated by the ophthalmic nerve [35]. Inflammation of the superior oblique tendon within the trochlea, or trochleitis, is characterized by local pain, swelling, and tenderness, which worsen with upward gaze in abduction (Fig. 5). Palpation of the superomedial angle of the orbit provokes exquisite tenderness, and localized swelling may be felt. The etiology is most often primary, although trochleitis may accompany rheumatoid arthritis, systemic lupus erythematosis, sarcoidosis, and other

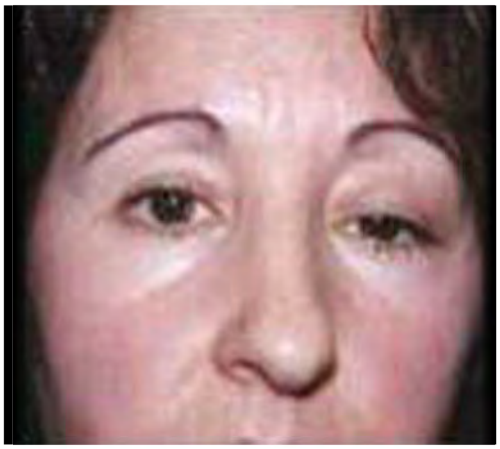

Fig. 5 This patient with trochleitis exhibits left upper lid ptosis and edema without conjunctival injection

inflammatory disorders. Most often, it is akin to a tendonitis and has been called "tennis elbow of the eye."

Primary trochlear headache is distinguished from trochleitis by the absence of inflammation and its common association with other headache disorders, particularly migraine [35]. It affects women 90% of the time, producing pressure-like or dull pain in the trochlear and temporoparietal regions that worsens with supraduction of the affected eye. There may be nocturnal awakening, but autonomic features are absent [35].

The treatment of both conditions is a single injection of corticosteroids (3 mg of betamethasone acetate or 0.5 mL of methylprednisolone 80 mg/mL, which may be given in combination with 0.3–0.5 mL of 2% lidocaine). Relief occurs rapidly, and the patient may be rendered pain-free for months or years. The injection may also provide relief of associated migraine pain [36].

Intracranial Processes

Microvascular Ocular Motor Cranial Mononeuropathies

Microvascular disease affecting one of the ocular motor nerves is a common cause of diplopia in adults over the age of 50 years. Either the oculomotor (III), trochlear (IV), or abducens (VI) nerve may be affected; rarely, more than one nerve may be involved simultaneously. By definition, no other neurological symptoms or signs are present, and other disorders (eg, giant cell arteritis) are excluded. Most affected patients have a history of type 2 diabetes, hypertension, hypercholesterolemia, arteriosclerosis, or other vascular risk factors.

The condition is painful in approximately 40% of cases, and the pain is localized around the eye and in the ipsilateral ophthalmic nerve distribution. The pain may be severe and is attributed to innervation of the affected nerve by trigeminal sensory fibers within the cavernous sinus. The pain may precede, accompany, or follow the onset of diplopia or ptosis. Although the diplopia is noticed suddenly, the degree of eye movement limitation or ptosis often progresses over a period of up to 10 days, and involvement may ultimately be complete or incomplete. Ischemic ocular motor palsies generally resolve within 3–16 weeks. Resolution is generally complete.

The major diagnostic challenge arises in patients with an isolated painful oculomotor (III) nerve paresis, as an expanding cerebral aneurysm (usually at the junction of the internal carotid artery and posterior communicating artery) may have a similar presentation, particularly if the aneurysm has not ruptured. A pupil-sparing third nerve palsy is more typical of microvascular disease, whereas a pupil-involving third nerve palsy suggests a compressive lesion. A pupil-sparing but otherwise complete third nerve palsy is almost always vasculopathic, but many patients present with incomplete involvement [37]. The anisocoria associated with a microvascular etiology is generally less than 1 mm [38]. Approximately 20% of aneurysms and compressive lesions spare the pupil; an aneurysmal third nerve palsy will typically involve the pupil within days of symptom onset. However, the presence of pain, degree of ophthalmoparesis, and involvement of the pupil do not necessarily distinguish vascular from compressive oculomotor palsies [39]. If there is any question about a possible aneurysm, MR angiography or CT angiography will reveal an aneurysm large enough to impinge on the oculomotor nerve. Neuroimaging is always indicated in adults under the age of 50 years with a new isolated cranial ocular motor palsy, regardless of concurrent medical conditions.

Pituitary Tumor Apoplexy

Pituitary tumor apoplexy is a medical and neurosurgical emergency, and should be suspected in patients with headache, ophthalmoparesis, and an alteration in consciousness. It generally occurs with hemorrhage or infarction of a preexisting pituitary tumor but may be caused by infection of the pituitary gland, or postpartum infarction and hemorrhage in a normal gland (Sheehan syndrome). The apoplectic event is the first indication of a pituitary tumor in most patients. Most occurrences are spontaneous, although anticoagulation, trauma, hypotension, dopamine agonist therapy, dynamic pituitary testing, history of irradiation, and cardiac surgery may be predisposing factors [40••].

The presenting features of pituitary apoplexy vary depending on the location and extent of the hemorrhage [41]. Headache is present in more than 90% of patients and is often accompanied by nausea, vomiting, and other symptoms of meningeal irritation from subarachnoid

hemorrhage. Bilateral visual symptoms and signs are common, and include paresis of the ocular motor nerves from lateral extension into the cavernous sinus, as well as loss of visual acuity and visual field defects from optic neuropathies and chiasmal compression. Other symptoms include epistaxis, seizures, and meningismus. Superior extension of hemorrhage into the hypothalamus produces an alteration in consciousness. Hypopituitarism and adrenal insufficiency occur when the sudden increase in intrasellar pressure compromises the blood supply to the pituitary gland.

Pituitary tumor apoplexy is often misdiagnosed as meningitis or aneurysmal subarachnoid hemorrhage. Although a plain CT scan may reveal a sellar mass and hyperdense acute hemorrhage, MRI is the preferred imaging modality because of its higher resolution and ability to demonstrate the changes of subacute hemorrhage and infarction (Fig. 6). Pituitary hormone levels should be obtained. Urgent medical stabilization of fluids and electrolytes, glucocorticoid administration (hydrocortisone, 50 mg intravenously, every 6 h), and continuous monitoring are required until neurosurgical intervention is possible. The ophthalmic manifestations often improve shortly after surgery. Surgery may restore some pituitary function, but long-term hormone replacement is needed in most instances.

Carotid Artery Dissection

Carotid artery dissection produces pain in the ipsilateral head, neck, face, or jaw. The pain is frequently located in the forehead or periocular region. The pain may precede the neurological symptoms by hours, days or, rarely, weeks.

Neurological symptoms and signs include an ipsilateral Horner syndrome, transient monocular visual loss, contralateral limb numbness or weakness, or stroke [42••]. Compromise of the nerves emerging from the jugular and hypoglossal foramina produces sternocleidomastoid weakness, hoarseness, dysgeusia, and hemilingual paralysis.

Many patients can identify a preceding event of minor direct trauma or a twisting injury to the neck. Abnormalities of the arterial media and elastic tissue, such as Ehlers-Danlos syndrome and fibromuscular dysplasia, may predispose to dissection but are seldom found.

The major confounding diagnosis of patients with carotid artery dissection is cluster headache, as both conditions may present with a unilateral headache and Horner syndrome. A patient with the new onset of cluster headache symptoms lasting longer than the typical duration

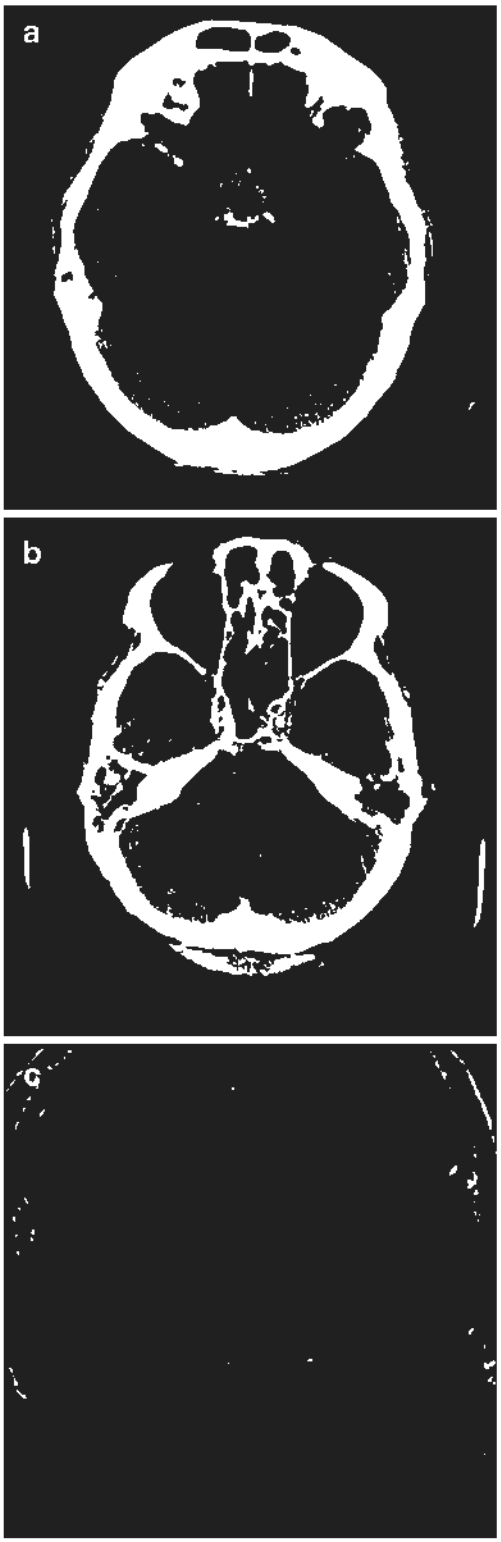

Fig. 6 Pituitary apoplexy. A 83-year-old man experienced worsening in his vision for a few days followed by bilateral visual loss, severe headache, and altered ental status. CT scan without contrast shows a hyperdense suprasellar mass, indicating hemorrhage into the pituitary tumor (**a**). There was extension of hemorrhage into the cavernous sinuses (*arrows*) bilaterally (**b**). Coronal T1-weighted MRI with contrast demonstrates a pituitary tumor compressing the optic chiasm with heterogeneous signal characteristics and partial contrast-enhancement (**c**)

of cluster headache (2 h) should be evaluated for a carotid dissection. Preferred imaging techniques are CT angiography, MR angiography, and axial MRI scans with fat saturation, which demonstrates the lack of flow void, intramural blood, and mural expansion of the dissection. Doppler imaging may also be helpful.

Various treatments are utilized, although no controlled trials of medical or surgical therapy have been performed. Anticoagulants, antiplatelet treatment, and thrombolytic agents have been employed. Stenting is rarely indicated.

Cerebral Aneurysm

Most aneurysms producing pain and neuro-ophthalmic manifestations are saccular aneurysms. They are usually sporadic; familial aneurysms tend to affect women much more frequently than men, rupture at an early age, and involve the middle cerebral artery. Aneurysms may originate from any intracranial artery, although 85% arise from the internal carotid artery (ICA) or one of its branches. About 25% to 40% of all intracranial aneurysms arise from the trunk of the ICA, usually at the origin of the posterior communicating artery. Aneurysms less than 3 mm in diameter are usually asymptomatic unless they rupture, and are much less likely to rupture than larger aneurysms. More than one aneurysm is found in at least 15% of patients with one aneurysm; hypertension, atherosclerosis, and smoking increase the risk of harboring multiple aneurysms.

Aneurysms produce symptoms from mass effect (and tend to enlarge over time), hemodynamic effects, or rupture. Rupture is the most common mechanism, although many patients develop "warning signs" days to months prior to experiencing a subarachnoid hemorrhage. The most common sentinel experience is headache that is often very severe and associated with nausea, vomiting, photophobia, phonophobia, or neck pain. Facial pain, eye pain, diplopia, lethargy, or dizziness may occur. As many of the symptoms are nonspecific, they are often dismissed as being insignificant.

Visual symptoms resulting from aneurysms may arise from the afferent or efferent visual pathways. Ruptured anterior communicating artery, carotid-ophthalmic, or anterior cerebral artery aneurysms may affect the optic nerves, producing central visual loss, or involve the optic chiasm or optic tracts, leading to visual field defects. Aneurysms located more posteriorly may produce homonymous visual field defects or diplopia. Subarachnoid hemorrhage often leads to intracranial hypertension with abducens paresis, papilledema, and retinal hemorrhages.

An aneurysm at the junction of the ICA and posterior communicating artery is a feared cause of a painful oculomotor nerve palsy. As mentioned in the section on microvascular ocular motor neuropathies, the oculomotor palsy from aneurysmal compression frequently involves the pupil. One should suspect an aneurysm as the etiology of this syndrome in patients under the age of 60 years, or at any age if no vascular risk factors are present. Patients with hypertension and diabetes may also have an aneurysm; therefore, neuroimaging (eg, CT angiography or MRI angiography) is warranted in these cases. The prognosis improves considerably if aneurysms are discovered and treated prior to rupture. Treatment includes interventional techniques (eg, coiling, particles, glue) and surgery. Despite recent advances in treatment, the morbidity and mortality of a ruptured aneurysm remain quite high.

Intracavernous aneurysms may affect any of the ocular motor nerves, the oculosympathetic fibers, and trigeminal nerve producing pain or facial numbness. The abducens nerve is frequently affected. They generally do not rupture, as they are encased in bone, but may expand into the nasopharynx, sphenoid sinus, or petrous portion of the temporal bone and rupture secondarily. Erosion through the superior orbital fissure leads to proptosis, optic neuropathy, and orbital congestion.

Ophthalmic artery-internal carotid artery aneurysms are uncommon and are intradural in 90% of patients. They generally cause symptoms by direct compression of the optic nerve, producing either gradual or abrupt monocular visual loss, often associated with ocular or periocular pain simulating acute optic neuritis. Less commonly, they expand posteriorly or superiorly to produce a chiasmal or optic tract syndrome. If they rupture, their intradural location leads to subarachnoid hemorrhage.

MR angiography and CT angiography are good screening tests for aneurysms. Catheter angiography remains the gold standard for diagnosis, particularly for small aneurysms. Treatments include endovascular procedures and neurosurgical intervention. Randomized trials comparing endovascular and surgical treatment for ruptured aneurysms suggest that the morbidity, mortality, and risk of rebleeding may be lessened with endovascular treatment for aneurysms suitable for either treatment modality [43].

Pseudotumor Cerebri

Pseudotumor cerebri (PTC) is a syndrome of increased intracranial pressure without hydrocephalus, mass, or meningeal process [44••]. When there is no identifiable cause, it is termed *idiopathic intracranial hypertension* (IIH). IIH typically affects obese women of childbearing age, although the incidence in men is rising commensurate with the increasing rates of obesity. Frequent secondary causes include tetracyclines, hypervitaminosis A, human growth hormone, corticosteroid withdrawal, venous sinus thrombosis, and obstructive sleep apnea. Numerous other

associations exist, but the underlying pathogenesis remains unknown.

Headache is the most common symptom of IIH, affecting more than 90% of patients. The headache characteristics are nonspecific, and it may resemble new daily persistent headache, migraine, or tension-type headache. It is generally bilateral and often frontal. The headache is commonly severe and debilitating. Patients with a prior history of headache may describe a change in their headache characteristics or frequency. Ophthalmic manifestations include brief episodes of visual loss or visual blurring (transient visual obscurations), diplopia, and persistent visual loss. Pulsatile tinnitus is common; other symptoms include neck, back, or radicular pain [45].

Physical examination nearly always reveals papilledema, which may be asymmetrical. Visual acuity loss, visual field defects, or a unilateral or bilateral abducens palsy may be present. Neuroimaging studies show no tumor or meningeal enhancement; there may be an acquired Chiari malformation, an empty sella, flattening of the posterior sclerae, distended optic nerve sheaths, protrusion of the optic nerve papillae into the globe, or transverse venous sinus stenosis [46]. A lumbar puncture confirms the presence of intracranial hypertension with normal cerebrospinal fluid contents.

Treatment options include medical management (weight loss, acetazolamide, furosemide, headache treatments) and surgical treatment (optic nerve sheath decompression, shunting). Permanent visual loss is the most serious sequela of PTC. This disorder is best managed by a neuro-ophthalmologist, or a neurologist working closely with an ophthalmologist.

Systemic Disease

Giant Cell Arteritis

Giant cell arteritis (GCA) is a systemic vasculitis with many manifestations (Table 1). Thus, patients with GCA may seek medical attention from a variety of providers, including internists, rheumatologists, dentists, neurologists, dermatologists, and ophthalmologists. It must always be considered in the differential diagnosis of headaches developing in individuals over the age of 50 years, and rarely occurs in younger persons. The prevalence of GCA rises with age, ranging from 20/100,000 in the 6th decade to 1110/100,000 in the 9th decade of life [47••]. It is more common among Caucasians than in other racial or ethnic populations. The greatest risk factor is age, the most common presenting symptom is headache, and the most significant consequence is blindness.

The headache of GCA is nonspecific. It may be unilateral or bilateral, aching or throbbing, and is often severe enough to interfere with sleep. The headache features may suggest new daily persistent headache, migraine without aura, tension-type headache, or hemicrania continua. Visual symptoms include amaurosis fugax, visual loss, diplopia, and eye pain, with findings of ocular ischemic lesions such as anterior ischemic optic neuropathy, central retinal artery occlusion, cilioretinal artery occlusion, ocular ischemic syndrome, and posterior ischemic optic neuropathy. Approximately one third of patients have "occult" GCA, experiencing only the visual complications with no systemic symptoms.

The presence of jaw claudication is highly specific for diagnosing GCA. Other symptoms include malaise, fever, weight loss, scalp tenderness, myalgias, arthralgias, depression, necrotic lesions of the skin or tongue, transient ischemic attack, stroke, and cardiac involvement [48].

The diagnosis may be difficult to prove, as no test is 100% sensitive. A markedly elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein, anemia of chronic disease, thrombocytosis, and elevated fibrinogen levels support the diagnosis. However, patients with GCA may have a normal ESR, particularly if they are not anemic. Temporal artery biopsy, the gold standard for diagnosis, is abnormal approximately 95% of the time. Patients with initial negative biopsies who were later diagnosed with GCA accounted for 19% of all negative biopsies in one

Table 1 Symptoms and signs of giant cell arteritis

Relative sensitivity for diagnosis	%
Symptom	
Headache	74.5
Myalgia	46.7
Fever	41.5
Weight loss	37.7
Any visual symptom	33.4
Arthralgia	33.0
Scalp tenderness	32.5
Jaw claudication	31.9
Polymyalgia rheumatica	30.2
Anorexia	30.1
Diplopia	9.0
Sign	
ESR>50 mm/hr	80.4
Clinically abnormal temporal artery on palpation	63.0
Temporal artery tenderness	59.6
Thrombocytosis	46.3
ESR>100 mm/hr	36.1
Anemia	37.6
Normal ESR	10.9

(*Adapted from* Niederkohr and Levin [50])

ESR erythrocyte sedimentation rate

series; older age, headache, and thrombocytosis were more common in that group [49].

High-dose corticosteroid treatment (intravenous methylprednisolone or oral prednisone, 100 mg daily) must be initiated immediately, especially if the patient has amaurosis fugax or evidence of visual loss [50]. The eyes are often involved sequentially, and prompt treatment usually prevents second eye involvement. The biopsy should be performed within a week to increase the likelihood of finding the typical pathological changes of GCA. The systemic features generally respond quickly to prednisone treatment, although vision loss may not improve. Treatment with prednisone is continued for at least a year, with close monitoring of laboratory parameters and clinical symptoms. As the treatment itself may create significant morbidity (eg, diabetes, osteoporosis, weight gain, fracture), pathologic confirmation of the disease is recommended.

Conclusions

The patient's history and examination will often help to distinguish a painful ophthalmic condition from a primary headache disorder. A team approach between the primary care physician, neurologist/headache specialist, and ophthalmologist is often required to arrive at the correct diagnosis.

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Headaches Associated With Refractive Errors: Myth or Reality?

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Introduction.—Headache and refractive errors are very common conditions in the general population, and those with headache often attribute their pain to a visual problem. The International Headache Society (IHS) criteria for the classification of headache includes an entity of headache associated with refractive errors (HARE), but indicates that its importance is widely overestimated.

Objectives.—To compare overall headache frequency and HARE frequency in healthy subjects with uncorrected or miscorrected refractive errors and a control group.

Methods.—We interviewed 105 individuals with uncorrected refractive errors and a control group of 71 subjects (with properly corrected or without refractive errors) regarding their headache history. We compared the occurrence of headache and its diagnosis in both groups and assessed its relation to their habits of visual effort and type of refractive errors.

Results.—Headache frequency was similar in both subjects and controls. Headache associated with refractive errors was the only headache type significantly more common in subjects with refractive errors than in controls (6.7% versus 0%). It was associated with hyperopia and was unrelated to visual effort or to the severity of visual error. With adequate correction, 72.5% of the subjects with headache and refractive error reported improvement in their headaches, and 38% had complete remission of headache. Regardless of the type of headache present, headache frequency was significantly reduced in these subjects ($t = 2.34$, $P = .02$).

Conclusions.—Headache associated with refractive errors was rarely identified in individuals with refractive errors. In those with chronic headache, proper correction of refractive errors significantly improved headache complaints and did so primarily by decreasing the frequency of headache episodes.

Key words: refractive errors, headache, visual effort

Abbreviations: HARE headache associated with refractive errors

(*Headache.* 2002;42:256-262)

Specific eye diseases, such as acute glaucoma or optic neuritis, can cause ocular pain or headache and certain primary headaches often are accompanied by ocular or visual symptoms that range from the oculosympathetic signs of cluster headache to the complex visual phenomena characteristic of migraine aura.[1-5] Although there is a strong popular belief of such a causative effect, there is no definite evidence that refractive errors can be a cause of chronic headaches. Despite this, an ophthalmologist is the specialist third most often consulted for headaches of recent onset.[6]

Headache associated with refractive errors (HARE) is described in the International Headache Society's (IHS) classification system (11.3.2).[7] The diagnostic criteria for HARE are:

A. Uncorrected [or miscorrected] refractive errors (e.g. hypermetropia, astigmatism, presbyopia, wearing of incorrect glasses).
B. Mild headaches in the frontal region and in the eyes themselves.

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C. Pain absent on awakening, and aggravated by prolonged visual tasks at the distance or angle where vision is impaired.

It is stressed that "uncorrected refractive errors... may cause headaches but their importance is widely overestimated."[7]

Compelled by their personal or clinical experience, some authors nevertheless stress the existence and importance of this entity, but others contend that the diagnosis may be misinterpreted or overestimated simply reflecting the high prevalences of both conditions in the general population.[2,3,5,8-11] One can argue that the existence of refractive errors and headache in a given individual can be explained simply by their coincidental association, without the implication of a cause-effect relationship.

The purpose of this study was to determine the overall frequency of headache and HARE in a sample of otherwise healthy subjects with refractive errors, to compare them with a control group possessing no eye disorders, and to assess what impact proper ocular correction might have on headache severity.

SUBJECTS AND METHODS

Subjects.—A cluster sample was recruited from an outpatient clinic specializing in the treatment of refractive errors and from a clinic where occupational health checkups were performed. The individuals observed in the outpatient clinic were self-referred; most complained of difficulties in seeing and some complained of headache associated with visual effort. The individuals observed in the checkup clinic were presenting for an annual occupational health examination, and most had no presenting complaints. One of the authors (G.G.) visited the clinics on a random day, once a week, for consecutive weeks, and all individuals who gave informed consent were included in the study. All individuals who presented with heterophoria, heterotropia (latent/manifest squint), glaucoma, or other eye disorders recognized by the IHS as a cause of headache were excluded from this study.

Questionnaire.—The first part of the evaluation consisted of a structured interview conducted by one of the authors (G.G.) and utilizing a headache questionnaire which surveyed demographic data (eg, sex, age, and occupation) and headache occurrence and characteristics and assisted in the determination and quantification of headache types.[12] The first question was "Do you usually suffer from headaches?" If the answer was no, the individual was classified as "without headache;" if the answer was affirmative, the individual was classified as "with headache," and the headache was characterized by type. The questionnaire went on to survey age of headache onset, episodic versus continuous pain, number of days per month with headache (frequency of attacks), average duration of an attack (in hours), and timetable (categorized into morning, afternoon, dinnertime, during the night, or none). There were questions regarding pain topography and quality and intensity of pain; the latter was categorized as "mild" (no interference with daily activities) or "moderate/severe" (activities inhibited or prohibited). The presence or absence of accompanying symptoms (nausea, vomiting, photophobia, phonophobia) and visual aura were assayed, as were treatment patterns (nonpharmacological measures or medication), the presence or absence of aggravating factors (including physical or visual effort), and family history of headache. Questions were designed in accordance with current IHS diagnostic criteria, allowing the investigators to classify such subjects' headaches as follows: migraine (IHS code 1), tension-type headache (IHS code 2), HARE (IHS code 11.3.2), and other (any headache not included in any of the previous categories). To confirm interobserver reliability, the structured interview described was followed by a clinical evaluation in an outpatient clinic devoted to patients with headache, and after the consultation, the respective diagnoses were compared. Interobserver agreement (Cohen's kappa) in 30 consecutive patients was 76%.[13]

Each subject was asked the average number of hours spent daily in visually straining tasks (eg, reading, watching television, working with a computer) and whether headaches accompanied those tasks. Any use of glasses or contact lenses, age of onset of eye disorders, any significant past medical history, and regular use of medication were also recorded.

Ophthalmologic Evaluation.—The ophthalmologic reevaluation was subsequently performed by an investigator unaware of the results of the intake survey.

No information was exchanged between investigators. To estimate the refractive error, automated refraction was used and refined by subjective refraction. Individuals whose previous correction matched exactly the results of the present evaluation were considered to have "adequate correction" of their refractive errors. Individuals whose present evaluation was normal were considered "without refractive errors." All individuals whose previous correction was considered inadequate or who had not received previous correction were considered to have "miscorrected or uncorrected refractive errors" and were prescribed adequate corrective lenses.

All participants were grouped in accordance with the results of their ophthalmologic evaluations. As such, the study group included all individuals with refractive errors (miscorrected or uncorrected refractive errors) and the control group included individuals without refractive errors (adequate correction or without refractive errors). Subjects within the study group who complained of headache were reevaluated 10 months after proper correction. The reevaluation was made by telephone and via structured interview similar to that performed at study entry.

Statistical Analysis.—Statistical analysis was performed using Statistix, version 4.0 statistical software.[14] The statistical tests used were chi-square test of association and comparison of mean values (Student *t* test). A *P* value at or below .05 was considered statistically significant.

RESULTS

The study group (with refractive errors) and the control group (without refractive errors) were similar in regards to age, gender ratio, and presence of associated diseases (Table 1).

Comparative Analysis.—The overall frequency of headache was similar in both groups (44.7% in the

Table 1.—Comparison of Groups*

	Study Group (n = 105)	Control Group (n = 71)	Statistical Analysis
Ratio of men to women	53:52	33:38	$\chi^2 = 0.27$, P = NS
Age, mean, y	37.6	34.8	$t = -1.17$, P = NS
Associated diseases	26	16	$\chi^2 = 0.12$, P = NS
Headache (total)	47	36	$\chi^2 = 0.92$, P = NS
Migraine	3	3	$\chi^2 = 0.24$, P = NS
Tension-type	19	15	$\chi^2 = 0.25$, P = NS
HARE	7	0	$\chi^2 = 4.93$, $P = .02$
Other	26	29	$\chi^2 = 0.25$, P = NS
Frequency, mean ± SD, days/month	4.8 ± 9.1	2.8 ± 6	$t = -1.76$, P = NS
Duration, h			$\chi^2 = 0.12$, P = NS
<6	33 (70)	24 (66)	
>6	14 (30)	12 (33)	
Intensity			$\chi^2 = 1.25$, P = NS
Mild	27 (57)	25 (69)	
Moderate/severe	20 (43)	11 (31)	
Photophobia			$\chi^2 = 2.93$, $P = .08$ NS
Yes	31 (66)	17 (47)	
No	16 (34)	19 (53)	
Visual effort aggravation			$\chi^2 = 2.85$, $P = .09$ NS
Yes	23 (49)	11 (31)	
No	24 (51)	25 (69)	
Relief by closing eyes			$\chi^2 = 4.07$, $P = .04$
Yes	12 (26)	3 (8)	
No	35 (74)	33 (92)	

*Values are number (percentage) unless otherwise indicated. HARE indicates headache associated with refractive errors.

study group versus 52.1% in the control group), and there were no differences in the relative frequencies of migraine, tension-type, or other primary headache disorders. Headache associated with refractive errors was found in 6.6% of study group subjects. Using only criteria B and C from the IHS definition of HARE (11.3.2), we found no HARE-type headache in the control group. Analyzing headache characteristics regardless of diagnosis, we found no differences in pain duration, pain intensity, frequency of photophobia, or aggravation of pain by visual effort. Study group subjects had more days of headache per month than controls, but the difference was not statistically significant. Subjects in the study group were significantly more likely to report relief of pain by closing their eyes (Table 1).

Study Group Analysis.—Analysis of the subgroup with both refractive errors and headache did not reveal any correlation between headache frequency and the type of refractive error presented (Table 2). When we compared each type of refractive error with each headache diagnosis, however, we found a significant association between hyperopia and HARE ($\chi^2 = 4.4$, $P = .03$) but not with other refractive errors. Severity of refractive error did not correlate with the occurrence of headaches generally or with any specific headache diagnosis. Visual strain habits had no significant influence on headache frequency (Table 2). Headache associated with refractive errors was diagnosed in 7 individuals (3 men and 4 women with an average age of 28 years). Of these, 3 also had tension-type headache, 1 had "other" headache, and 3 had no other headache diagnosis (Table 3).

Study Group Reevaluation.—Forty-seven individuals from the study group were scheduled for reevaluation and 7 subsequently were lost to follow-up (Table 4). Of the remaining 40, 36 used their eye correction exactly as prescribed, and 4 did not. Two individuals changed their ocular prescriptions subsequent to the initial evaluation, and another 2 reported that they were not seeing properly with the prescription from the first evaluation.

Twenty-nine individuals (72.5%) reported that their headache syndromes had improved, and the re-

Table 2.—Headache Occurrence and Refractive Errors/Visual Effort*

	With Headache	Without Headache	Statistical Analysis
Refractive error			$\chi^2 = 2.82$, $P = $ NS
Mild	44	48	
Severe	3	10	
Myopia ± Presbyopia	9	9	
Hyperopia ± Presbyopia	2	1	
Astigmatism ± Presbyopia	11	19	$\chi^2 = 3.31$, $P = $ NS
Myopia + Astigmatism ± Presbyopia	12	16	
Hyperopia + Astigmatism ± Presbyopia	8	5	
Presbyopia	5	8	
Reading, h			$\chi^2 = 1.56$, $P = $ NS
<6	23	121	
>6	7	20	
Watching television, h			$\chi^2 = 0.87$, $P = $ NS
<6	14	86	
>6	1	2	
Computer work, h			$\chi^2 = 0.22$, $P = $ NS
<6	14	28	
>6	6	9	
Other, h			$\chi^2 = 0.07$, $P = $ NS
<6	6	23	
>6	2	6	

*Values are number of subjects.

Table 3.—Characteristics of Subjects With Headache Associated With Refractive Errors (HARE)*

Feature	Subject 1	2	3	4	5	6	7
Sex	M	M	F	F	M	F	F
Age, y	16	20	20	27	28	30	55
Type of headache	HARE + TTH	HARE + TTH	HARE + TTH	HARE + other	HARE	HARE	HARE
Frequency, days/mo	3	4	4.5	15	8	2.5	30
Refractive error	Hyperopia	Astigmatism + hyperopia	Astigmatism + myopia	Astigmatism	Astigmatism + myopia	Myopia	Astigmatism + hyperopia
Error severity	Mild	Mild	Mild	Mild	Severe	Mild	Mild
Use of corrective lenses	No	Yes	Yes	Yes	Yes	Yes	Yes
Following evaluation							
Type of headache	Nil	Nil	HARE	HARE	Other	Other	Nil
Frequency, days/mo	0	0	12	9	1.5	2.5	0

*TTH indicates tension-type headache; other, other type of headache.

maining 11 individuals (27.5%) reported that their headaches were unchanged. None reported worsening of headache. Fifteen subjects (37.5%) with initially uncorrected or miscorrected refractive errors had ceased to suffer from headache within the 10 months following proper correction. Those subjects who continued to have headaches experienced no change in headache duration or intensity, but did report a significant reduction in the number of days with headache per month.

The 7 subjects with HARE were analyzed in detail. Three ceased having headaches, 2 continued to suffer from HARE, and 2 (28.6%) had other headache diagnoses. One did not use the glasses prescribed and yet had no headache complaints.

COMMENTS

From our results, we conclude that HARE, as defined by IHS criteria, can occur in individuals with refractive errors but is rare. Its occurrence does not appear to increase significantly the prevalence of chronic headache in individuals with refractive errors relative to a population lacking such errors. Headache associated with refractive errors appears to be linked with hyperopia more so than any other refractive error.

Although the severity of refractive errors and visual strain habits did not influence the headache frequency initially reported by our patients, our results suggest that individuals with headache and uncorrected or miscorrected refractive errors often will experience an improvement in their headaches following correction. Thus, one need not have HARE per se to benefit from corrective refraction.

Our results indicate that a small proportion of individuals with uncorrected or miscorrected refractive errors do suffer from mild frontal or ocular headache that is aggravated by visual effort; ie, HARE. Of the few epidemiological studies that previously have addressed this topic, none has been conclusive, and the pathogenesis of HARE remains unclear.[9,10] Some authors relate HARE to painful contracture of the ciliary muscle evoked by the sustained accommodative effort involved in attempting to compensate for visual impairment at near distance (as with hyperopia or astigmatism).[3,15] Presbyopia, in which the aging lens loses its accommodative capacity and cannot compensate for variations in focal distance, also results in visual impairment at near distance but usually occurs with no other symptoms.[9,15] Conversely, individuals with myopia (nearsightedness) use the pinhole effect to sharpen

Table 4.—Study Group Reevaluation*

	First Evaluation	Reevaluation	Lost to Follow-up	Statistical Analysis
Subjects	47	40	7 (15)	
Men	16	11	5 (31)	
Women	31	29	2 (6)	
Headaches				
Yes	47	25 (62.5)		$\chi^2 = 18.8$, $P < .00$†
No	0	15 (37.5)		
Improvement				
Better	—	29 (72.5)		
Same	—	11 (27.5)		
Worse	—	0		
Frequency, mean ± SD, days/mo	10.6 ± 11.1	5.7 ± 6.7		$t = 2.34$, $P = .02$
Duration, h				$\chi^2 = 0.03$, $P =$ NS
<6	28	18		
>6	12	7		
Intensity				$\chi^2 = 0.01$, $P =$ NS
Mild	22	14		
Severe	18	11		

*Values are number (percentage) unless otherwise indicated.
†Yates corrected.

distance vision,[16] achieving this by squinting and narrowing the palpebral fissures, with prolonged and repetitive contraction of the periorbital muscles and potential production of a tension-typelike headache.

We did not find any increase in headache frequency or of tension-type headaches specifically in individuals with myopia, but we did find an association of HARE and hyperopia. We therefore conclude that the exaggerated effort required to compensate for hyperopia can, in fact, provoke HARE, either alone or accompanied by symptoms of tiredness or soreness or straining of the eyes.

Those with chronic headache are reported to have a higher frequency of nonspecific visual symptoms than the general population.[17,18] In those individuals, stimulation by light or routine visual tasks (reading, watching television, working on the computer) may trigger or aggravate their headaches.[19] We found an increased frequency of nonspecific visual symptoms in individuals with refractive errors, but no associated increase in headache frequency. In addition, none of the visual activities surveyed had any correlation with headache frequency. It, thus, remains unclear whether those with chronic headache with refractive errors have a higher predisposition to the occurence of nonspecific visual symptoms during their headache crises. Individuals with headache with refractive errors have more crises per month than those without refractive errors. The use of proper eye correction significantly decreases the frequency of headache episodes (days with headache per month) in all headache types studied, including HARE, although a placebo effect cannot be excluded since there was no other treatment group. We therefore conclude that visual difficulties can be a causative or trigger factor of headache crises.

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REVIEW
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Imaging the Visual Network in the Migraine Spectrum

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The involvement of the visual network in migraine pathophysiology has been well-known for more than a century. Not only is the aura phenomenon linked to cortical alterations primarily localized in the visual cortex; but also migraine without aura has shown distinct dysfunction of visual processing in several studies in the past. Further, the study of photophobia, a hallmark migraine symptom, has allowed unraveling of distinct connections that link retinal pathways to the trigeminovascular system. Finally, visual snow, a recently recognized neurological disorder characterized by a continuous visual disturbance, is highly comorbid with migraine and possibly shares with it some common pathophysiological mechanisms. Here, we review the most relevant neuroimaging literature to date, considering studies that have either attempted to investigate the visual network or have indirectly shown visual processing dysfunctions in migraine. We do this by taking into account the broader spectrum of migrainous biology, thus analyzing migraine both with and without aura, focusing on light sensitivity as the most relevant visual symptom in migraine, and finally analyzing the visual snow syndrome. We also present possible hypotheses on the underlying pathophysiology of visual snow, for which very little is currently known.

Keywords: migraine, migraine spectrum, neuroimaging, visual snow, visual network, aura, photophobia

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KEY CONCEPTS

- A key feature of migraine, during and between attacks, is represented by altered visual cortex excitability. Multiple functional and structural neuroimaging studies have shown alterations in several areas of the visual network in migraine both with and without aura compared to controls, particularly of the motion processing network.
- Visual symptoms are the most common clinical manifestation of the aura phenomenon. The neurophysiological correlate of visual aura is likely represented by cortical spreading depression, starting in the extrastriate area V3A. Neuroimaging has shown in various forms that migraine with aura is characterized by lower and higher visual processing impairment, both ictally and interictally.
- Photophobia is an important aspect of migraine biology, present during, before and after the headache attacks. Migrainous photophobia is most likely linked to abnormal sensory processing in thalamic structures, particularly the pulvinar.

- Visual snow is a neurological disorder, commonly comorbid with migraine, characterized by a continuous visual disturbance that takes the form of uncountable tiny flickering dots covering the entire visual field. Its underlying pathophysiology is possibly characterized by a combination of peripheral, subcortical, and cortical dysfunctions causing an increased perception of normally subthreshold visual stimuli.

INTRODUCTION

In the last decades, imaging has gained considerable interest in the field of neuroscience and has allowed researchers to begin to unravel important mechanisms in the biology of complex neurological disorders. Several conventional and more advanced neuroimaging techniques have been implemented over the years and have proven to be important tools in the understanding of normal and pathological brain biology.

In the field of primary headaches, and migraine in particular, a growing body of neuroimaging work has served the purpose of dissecting important structural and functional alterations that characterize the disorder. One of the main aspects that has emerged from these studies is the confirmation, previously shown through animal models, that migraine does not represent a primary vascular disorder, rather a complex brain dysfunction involving several cortical and subcortical networks (1, 2).

The visual network has been one of the most studied systems in the migraine brain for several reasons. The most obvious explanation is certainly linked to the intriguing phenomenon of aura, a fully reversible neurological dysfunction which occurs in about a third of migraine cases and is represented chiefly by positive or negative visual symptoms (3, 4).

Another reason for the rising interest in studying visual function has been photophobia, a clinical hallmark of migraine both during attacks and in the interictal phase (5, 6). Recent evidence has led to better insight on the link between light inputs and pain, through the discovery of a pathway where photic signals from the retina converge on thalamic trigeminovascular neurons (7).

Finally, the notion that visual function is abnormal in migraineurs even in between attacks has lead researchers in the past to carry out extensive neurophysiological investigation of the visual network in migraine (8, 9). This uncovered important pathophysiological mechanisms now known to be typical of the migrainous brain, such as lack of habituation (10, 11). This particular form of altered excitability has been found interictally (12), although it typically fluctuates through the migraine cycle and can revert with disease chronification (13).

The visual brain is an extremely complex system consisting of multiple, hierarchical nodes which specialize in different functions at different times. These separate systems—which are incredibly uniform at a cytoarchitectonic level within the human cortex—work in parallel synchrony and autonomously from each other, resulting in the final conscious percept of vision (14). The complex integration between different areas of the visual network is made possible by existing connections between different cortical and subcortical areas specializing in different aspects of vision, and also between other cortical sensory, attentional, and cognitive processing networks (15, 16). The visual motion network is a perfect example of such integration and hierarchical sub-specialization, and it is particularly relevant in migraine biology, as this review will highlight. The motion network is composed chiefly of visual area V5, which specifically responds to motion stimuli, of sub-compartments within V1/V2, of area V3/V3A in the cuneus and finally of Brodmann area (BA) 7 in the precuneus (17).

In this review, we focus on neuroimaging findings that have shown direct involvement of the visual network in migraine. We will review studies broadly considered as being in the "migraine spectrum," thus focusing on migraine both with and without aura, photophobia, and finally visual snow.

Visual snow (VS) is a common comorbidity of migraine, with which it may share some pathophysiological mechanisms (18, 19). In addition to describing the limited neuroimaging literature available for VS, we will proceed to present distinct hypotheses for putative pathophysiological mechanisms underlying visual snow, hoping to elucidate the neurobiology of the disorder and provide insight for future studies attempting its investigation.

METHODS

For the purpose of this narrative review, we performed a literature search using PubMed database in April 2019, with the following key words: "migraine," "aura," "migraine with aura," "migraine without aura," "visual snow," "prolonged aura," "visual," "visual network" combined with "imaging," "neuroimaging," "BOLD," "functional MRI," "fMRI," "VBM," "PET," "spectroscopy." Articles were chosen based on their relevance to the topic. The reference lists of most publications and any other relevant papers known to the authors were further reviewed.

THE VISUAL NETWORK IN MIGRAINE BIOLOGY

In the last decades, we have learnt much about migraine pathophysiology by studying the visual system of migraineurs, particularly in, but not limited to, the context of aura and light hypersensitivity. Both structural and functional neuroimaging techniques have been used for this purpose. The majority of studies have focused on the interictal migraine phase, as this is generally more practical, however, an increasing number of recent studies have also successfully investigated the ictal phase. This has been achieved either by imaging attacks of spontaneous onset (20) or by triggering headache through different forms of pharmacological provocation (21).

Functional imaging approaches are particularly suitable for a disorder characterized by pathological network dysfunction such as migraine. Positron emission tomography (PET) - using different radiotracers to investigate brain metabolism— and functional magnetic resonance imaging (fMRI), either with visual stimuli to capture the blood-oxygen-level-dependent (BOLD) responses or scanning during the resting state to study brain connectivity, are commonly used techniques in this context. These powerful approaches have uncovered important

information regarding brain function and network configuration between attacks and at their initiation.

Structural techniques, such as voxel and surface-based morphometry (SBM) or DTI, on the other hand, provide insights on the morphological characteristics of key gray and white matter structures that are implicated in the biology of the migrainous brain.

Finally, magnetic resonance spectroscopy (MRS) allows to investigate brain metabolism directly.

Functional Neuroimaging in Migraine

Several functional neuroimaging studies have shown a dysfunction of the visual network in migraine, both with (MwA) and without aura (MwoA). A summary of these is provided in **Table 1**.

Visual stimulation is capable of triggering migraine attacks, and this has shown to involve brainstem structures, in particular the red nucleus and substantia nigra (23). Furthermore, MwoA and MwA have been repeatedly associated with increased BOLD response in the primary visual cortex and higher-order visual areas, both during the interictal period (24, 25) and during visually triggered attacks (23).

Migraineurs, both with and without aura, show a more extensive photoresponsive area in the visual cortex in response to light (26) as well as a general increased response to visual stimuli (28). These patients also display a lack of interictal habituation for repetitive visual stimulation (29) in event-related fMRI studies in between attacks.

Spontaneous migraine attacks have also been associated with increased activity in the visual cortex with $H_2^{15}O$ PET (27) in response to increasing intensities of light stimulation used to induce photophobia.

In an fMRI study investigating the same MwoA patient daily over the course of 30 days, a bilateral visual cortex activation (specifically Brodmann areas 17 and 18) was found in the 24 hours prior to attack onset, as well as in response to trigeminal nociceptive stimulation during the postictal phase. Interestingly, the same area showed significant deactivation during attacks compared with the interictal phase. These results indicate either an increased visual and nociceptive integration in the build-up of the migraine attack, which in turn reverts during the actual attack, or an increased activation of the visual cortex at baseline in migraineurs, whom therefore lack a normal occipital response during pain (45).

Functional connectivity (fc) is also altered within the visual network in MwoA. In a resting-state fMRI study using PACAP38 to induce attacks, decreased fc was found between the sensorimotor network and the left visual cortex, while conversely, increased connectivity was found between the default mode network (DMN) and the visual cortices bilaterally (36). It is possible that part of these BOLD signal changes were due to PACAP38 itself, given that it is a potent vasodilator, however, its effect on intracerebral arteries seems limited (46).

Another study found interictal fc reduction between the DMN and the visuo-spatial system in episodic migraineurs without aura in-between spontaneous attacks (37), whereas a more recent connectivity analysis in migraineurs without aura showed increased functional anti-correlation between the right temporo-parietal junction and the bilateral visual cortex (42).

Finally, a combined visual evoked potentials (VEPs) and [^{18}F]-FDG PET study in interictal migraineurs without aura showed significantly reduced glucose uptake in the left BAs 19, 18, and 7, in patients. This results was present when regressing for the VEP area under the curve, thus suggesting an activity-induced rupture of cerebral metabolic homeostasis in migraine (41).

Structural Alterations of the Visual Network

Several imaging studies have shown changes in cerebral gray matter (GM) and white matter (WM) volume in patients with migraine (**Table 2**).

A cortical thickness and DTI study in 12 MwA and an equal number of MwoA patients showed an increase in the thickness of motion-processing areas V5 and V3A area in migraineurs respect to controls, accompanied by reduced fractional anisotropy in the WM subjacent to V3A as well as the lateral geniculate nucleus (LGN) (47). Another DTI study showed tractography alterations in the optic radiations of seven migraineurs with visual auras compared to healthy controls and migraineurs without visual aura (48).

Zhang et al. combined voxel-based morphometry (VBM), SBM, and DTI to investigate structural alterations in 32 MwoA patients compared to healthy controls. They found that migraineurs had increased GM volume in an area encompassing the lingual, fusiform, and parahippocampal gyri. Further, cortical thickness in the lateral occipital cortex and gyrification index in the right lateral occipital cortex were significantly increased in migraineurs. No changes in white matter microstructure using DTI were found in this study (49).

Slightly contradicting these results, Coppola et al. analyzed 20 patients with chronic MwoA and found decreased GM volume in the left primary occipital cortex and visual association areas (corresponding to Brodmann areas 17 and 18) with respect to healthy volunteers. It should be noted that these results only survived cluster-wise multiple comparisons correction at a more lenient cluster-forming threshold than normally adopted (50).

A larger study on 84 migraineurs both with ($n = 52$) and without ($n = 32$) aura showed a decrease in GM volume of visual areas V3 and V5 (Brodmann area 19) in patients, compared to controls. A *post-hoc* analysis showed that changes in V5 were more pronounced in migraineurs with an "active" disease (51).

In an elegant study comparing females with MwA to their unaffected twins and unrelated controls, Gaist et al. assessed the cortical thickness of V1, V2, V3A, and V5 areas, finding an increased thickness of areas V2 and V3A in the patient group (52). This alteration was not associated with clinical parameters such as disease activity or aura attack frequency, leading the authors to hypothesize that the morphometric changes represented an inherent trait of migraine with visual aura.

A recent study combining VBM and VEP by Lisicki et al. found no global differences in gray matter volume of migraine patients respect to controls. There was, however, a significant correlation in migraineurs between VEP amplitude and GM volume within the visual cortex, among other regions (53).

TABLE 1 | Main functional neuroimaging studies investigating the visual network in migraine with (MwA) and without aura (MwoA).

References	Patient cohort	Migraine phase and attack type	Methodology	Main results
Hadjikhani et al. (22)	2 MwA	Ictal and during aura; 2 spontaneous and 3 induced attacks with physical exercise	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 16 s)	Focal increase followed by a decrease in BOLD signal, starting in area V3A of extrastriate cortex (lingual gyrus), and progressing congruently with retinotopic representation of visual aura percept
Cao et al. (23)	10 MwA 2 MwoA	Ictal and during aura (in 4 MwA patients); induced attacks with visual stimulation	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 14 s)	Visual stimulus can trigger migraine attacks (with and without aura) through the activation of brainstem structures (red nucleus and substantia nigra)
Vincent et al. (24)	5 MwA	Interictal	Event-related fMRI with visual stimulus (alternating lines simulating zigzags of aura)	Increased activation of extrastriate cortex respect to controls
Boulloche et al. (6)	4 MwA, 3 MwoA, episodic	Interictal	$H_2^{15}O$ PET with visual stimulus (luminous stimulation at three intensities) with and without noxious trigeminal heat stimulation	Light stimulation caused increased striate and extrastriate visual cortex activation (cuneus, lingual gyrus, and posterior cingulate cortex) in migraineurs respect to controls
Antal et al. (25)	12 MwA 12 MwoA	Interictal	Event-related fMRI with visual motion stimulus (moving dots alternated with static dots)	Decreased activation of inferior-posterior V5 complex (middle temporal area) and increased activation of superior-anterior V5 complex in migraineurs respect to controls, showing that higher-order visual areas are affected in migraine
Martin et al. (26)	7 MwA 12 MwoA	Interictal	Event-related fMRI with visual stimulus (luminous stimulations at four intensities)	Wider photoresponsive area in the visual cortex in response to light, as well as hyperexcitability of the visual cortex respect to controls
Denuelle et al. (27)	8 MwoA, episodic	Ictal, post-ictal, and post treatment; spontaneous attacks	$H_2^{15}O$ PET with visual stimulus (luminous stimulations at increasing intensities to induce photophobia)	Increased activation in the visual cortex of migraineurs respect to controls, both during migraine attacks with photophobia and following headache relief with sumatriptan. Hyperexcitability was not present in the interictal phase
Huang et al. (28)	7 MwA, 4 MwoA episodic	Interictal	Event-related fMRI with visual stimulus (striped patterns)	Increased activation in visual cortex of migraineurs respect to controls
Descamps et al. (29)	21 MwoA episodic	Interictal	Event-related fMRI with visual stimulus (faces, short interstimulus intervals)	Repetitive visual stimuli in migraine showed an altered hemodynamic refractory response respect to controls, possibly confirming lack of interictal habituation
Datta et al. (30)	25 MwA, 25 MwoA	Interictal	Event-related fMRI with visual stimulus (checkerboard on/off pattern every 15 s)	Increased BOLD response to visual stimulation in V1 and LGN in MwA patients compared to both MwoA and controls
Hougaard et al. (31)	20 MwA episodic	Interictal	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Increased BOLD response to visual stimulation in downstream visual network areas (inferior frontal gyrus, superior parietal lobule, intraparietal sulcus, and inferior parietal lobule) of symptomatic aura hemispheres compared to controls
Griebe et al. (32)	18 MwA episodic	Interictal	Event-related fMRI with visual stimulus (optokinetic drum with colored figures)	Increased activation in visual motion perception areas (bilateral V5 complex and left area V3) as well as cuneus and precuneus
Maniyar et al. (33)	10 MwoA episodic	Ictal premonitory phase; induced attacks with GTN	$H_2^{15}O$ PET	Increased activation of cuneus (BA18, part of the extrastriate visual cortex) and right precentral gyrus (BA4) in patients with photophobia in the premonitory phase vs. baseline phase, respect to patients without photophobia
Niddam et al. (34)	26 MwA, 26 MwoA	Interictal	Resting-state fMRI (seed based; ROIs in salience network and dorsal attention network)	Decreased connectivity between the anterior insula and extrastriate areas (including V3A) in MwA compared to both MwoA and controls. The reduced connectivity correlated with headache severity

(Continued)

TABLE 1 | Continued

References	Patient cohort	Migraine phase and attack type	Methodology	Main results
Tedeschi et al. (35)	20 MwA, 20 MwoA	Interictal	Resting-state fMRI (ICA)	Increased functional connectivity in the right lingual gyrus (within the resting-state visual network) in migraine aura patients, respect to migraine without aura and controls
Amin et al. (36)	16 MwoA	Interictal and ictal; induced attacks with PACAP38	Resting-state fMRI (seed based; ROIs in salience network, default mode network, and sensorimotor network)	Decreased connectivity in the sensorimotor network with the left visual cortex. Increased connectivity in the DMN with the visual cortices
Coppola et al. (37)	18 MwoA	Interictal	Resting-state fMRI (ICA)	Decreased connectivity between the default mode network and the visuospatial system
Hougaard et al. (38)	16 MwA	Interictal, ictal during aura	Resting-state fMRI (ICA + seed based; ROIs in cortical visual areas and areas of pain)	Increased functional connectivity between V5 and the ipsilateral middle frontal gyrus of the hemisphere contralateral to the perceived visual aura symptoms, following visual aura attack
Faragó et al. (39)	18 MwA, 35 MwoA	Interictal	Resting-state fMRI (ICA)	Increased amplitude of resting activity fluctuation in the lateral visual network in MwA patients respect to MwoA and controls
Arngrim et al. (40)	5 MwA	Interictal, ictal during aura; induced attacks with hypoxia, sham hypoxia, or physical exercise	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Reduced BOLD response in patients reporting scotoma and increased response in patients with positive aura symptoms. Bi-hemispherical BOLD changes in patients with bilateral visual symptoms
Lisicki et al. (41)	20 MwoA	Interictal	[18F]-FDG PET (with VEPs)	Increased neuronal activation-to-resting glucose uptake ratio in the visual cortex in patients
Lisicki et al. (42)	19 MwoA	Interictal	Resting-state fMRI (seed based)	Increased functional anti-correlations between the right temporo-parietal junction and the visual cortex in patients
Russo et al. (43)	17 MwA, 18 MwoA	Interictal	Event-related fMRI with noxious trigeminal heat stimulation	Increased activation of visual network (lingual gyrus, inferior parietal lobule, inferior frontal gyrus, and medial frontal gyrus) and midline-inferior cerebellum in patients with MwA compared to healthy controls and MwoA
Arngrim et al. (44)	15 MwA	Interictal, during hypoxia	Event-related fMRI with visual stimulus (dartboard on/off pattern every 18 s)	Greater hypoxia-induced decrease in BOLD following visual stimulation in visual areas V1, V2, V3, V4

The opposing findings of increased and decreased gray matter volumes within the motion network in migraineurs are difficult to interpret. Variations within technical acquisition or image processing could be a relevant cause. Another important element could be the differences among study populations. Some authors investigated predominantly episodic (47, 49) while others exclusively chronic (50) migraine; others did not distinguish between the two (51, 52). Given that volumetric differences in area V5 and the cerebellum were associated with attack frequency (51) and acute medication intake, respectively (50), this is an aspect that certainly needs to be taken into account in the planning of future studies.

Spectroscopy Investigations

The use of MRS has increased the already expanding knowledge on visual cortex activation in migraine, by studying *in-vivo* neuronal metabolism. ^{1}H-magnetic resonance in particular allows to measure concentration of N-acetylaspartate (NAA), creatinine (Cr), glutamate (Glx), GABA, and lactate. Several studies performed with this technique in migraineurs—mostly with visual aura—have shown alterations of the visual system.

One paper investigating visual cortex metabolism in MwA, MwoA, and controls subject to visual stimuli, showed that photic stimulation caused a more sustained decrease of NAA and concomitant increase in lactate in MwA patients respects to the other groups, which the authors argue could highlighting potential abnormal mitochondrial function in aura subjects (54). This dysfunction was confirmed by Sandor et al., who studied visual cortex lactate changes in MwA following prolonged visual stimulation, and found that compared to controls or subjects with sensory or motor aura, patients with visual aura displayed abnormally elevated lactate levels, even at rest (55).

With simultaneous transcranial direct current stimulation (tDCS), VEP recording and spectroscopy in MwA patients, Siniatchkin et al. were able to show that occipital areas in migraineurs are characterized by altered homeostasis and cortical information processing (56). In the healthy controls of the study, excitatory and inhibitory baseline tDCS, respectively, triggered either an increase or decrease in Glx/Cr ratio, which could be reversed by photic stimulation. Migraineurs, however, showed decreased Glx/Cr ratio in response to both types of tDCS

TABLE 2 | Main structural neuroimaging studies showing alterations of the visual network in migraine with (MwA) and without aura (MwoA).

References	Patient cohort	Methodology	Main results
Granziera et al. (47)	12 MwA 12 MwoA	DTI, cortical thickness	Increased cortical thickness in V3A and V5 in migraineurs respect to controls. Reduced fractional anisotropy in V3A and LGN in migraineurs
Rocca et al. (48)	7 MwA 8 MwoA	DTI	Altered tractography in optic radiations of migraineurs with visual aura respect to controls and patients without aura
Zhang et al. (49)	32 MwoA	VBM, DTI, SBM	Increased GM volume in the lingual gyrus, fusiform gyrus, and parahippocampal gyrus in patients respect to controls. Increased cortical thickness and gyrification index in lateral occipital cortex in patients
Coppola et al. (50)	20 MwoA, chronic	VBM	Decreased GM volume in left V1/V2 in patients respect to controls
Palm-Meinders et al. (51)	52 MwA 32 MwoA	VBM	Decreased GM volume in V3 and V5 in migraineurs respect to controls. V5 changes correlated with disease activity
Gaist et al. (52)	166 MwA	Cortical thickness	Increased cortical thickness in areas V2 and V3A in migraineurs with visual aura
Lisicki et al. (53)	20 MwoA	VBM	No differences in GM volume in patients respect to controls; positive correlation between GM volume in BA 17 and mean VEP amplitude

stimulation, and importantly this did not to return to baseline in response to visual stimulus.

Another study in migraine with visual aura patients showed a 10% reduction in occipital cortex GABA concentrations respect to controls, as well as significant correlations between glutamate levels and BOLD response to visual stimulation that was not seen in controls. This suggested an altered excitation-inhibition coupling in MwA patients (57). Finally, a recent paper assessed the levels of visual cortex glutamate in both MwA and MwoA, finding higher Glx levels in migraineurs without aura compared to controls (58).

Overall, these studies suggest abnormal cortical processing of visual information and lack of habituation in between attacks in migraineurs, possibly due to an underlying metabolic dysfunction.

The picture that emerges from imaging across different modalities, is that of multiple functional, structural, and metabolic abnormalities affecting the visual network of migraineurs. The motion network in particular seems to be most significantly affected. This is true both for the extensive functional alterations found in the primary visual processing areas of V1/V2, which have specific sub-compartments involved in motion detection, as well as for the structural differences that multiple studies have uncovered in areas V3A and V5.

MIGRAINE WITH AURA

By far the most common clinical manifestation of aura is represented by visual symptoms that are prototypically characterized by an arc-shaped scintillating scotoma (59), although a high variability in symptomatology across and within patients has been recorded (60). The phenomenon of migraine aura has interested clinicians and researchers since its earliest descriptions. In recent decades, the mechanism of aura has become better understood, particularly thanks to seminal neuroimaging studies (61).

The most likely electrophysiological event underlying aura is cortical spreading depression (CSD), first described by Leão in the 1940s (62) and characterized by a wave of neuronal hyperexcitation followed by a sustained depression, traveling at a rate of 2–6 mm/min.

The most prominent evidence linking aura to CSD has come from a study involving the near-continuous recording of a patient with two aura attacks through the use of functional MRI (22). This showed that retinotopic progression of visual aura symptoms was congruently linked to an increase and successive decrease of BOLD signal, starting in cortical area V3A of the extrastriate cortex and progressing contiguously over the occipital cortex. Area V3A is linked to both motion processing and luminance contrast; it further has a retinotopic representation of the opposite hemifield (63). A more recent study in five MwA patients confirmed this link between BOLD changes and aura symptoms, and even showed that clinical heterogeneity in aura—such as prominence of positive or negative symptoms—corresponds to differences in BOLD signaling in the visual cortex. This paper in fact showed that the typical scotoma is associated with a reduced BOLD response likely caused by the depression in neural activity linked to CSD, whereas positive symptoms are linked to an increase in BOLD (40).

One debate regarding migraine aura has centered on the question of whether it represents a separate entity with respect to MwoA, and whether migraine pain can actually be caused by CSD itself.

A theory linking migraine pathogenesis to "silent CSD attacks" largely relies on animal studies showing that CSD can activate trigeminovascular neurons (64). The study by Cao et al. failed to find evidence in support of this hypothesis however, showing rather that activation of substantia nigra and red nucleus anticipates occipital cortex changes in spontaneous and visually triggered migraine with aura attacks (23). A more recent study demonstrated that, following visual aura attacks, there is increased connectivity between the pons and the somatosensory

cortex and between V5 and the ipsilateral lower middle frontal gyrus; however, it found no differences in connectivity between visual cortex and pain areas (38).

Taken together, these studies seem to suggest that brainstem mechanisms contributed to the generation of pain attacks in both MwA and MwoA, and that involvement of the cortex in aura is a subsequent, parallel phenomenon.

Altered excitability of the visual pathways certainly plays a prominent role in the pathophysiology of MwA. Several neuroimaging studies have shown hyperexcitability of both primary and secondary visual cortices, even outside of the attacks.

Vincent et al. first showed that, following visual activation simulating the typical "zigzag lines" percept of aura, patients showed enhanced interictal reactivity of the extrastriate cortex respect to healthy subjects (24). MwA patients also show a stronger BOLD activation in the primary visual cortex and lateral geniculate nuclei compared to both healthy volunteers and MwoA patients, even when matched for levels of visual discomfort (30). Further, in the affected hemisphere of migraineurs with aura, response to visual pattern stimulation has shown to be increased in several downstream areas of the visual network involved in perception of motion, oculomotor control, visual attention and spatial memory (31). This is also seen following more complex forms of optokinetic stimulation (32). Finally, in response to an hypoxia challenge, patients with aura exhibit a greater decrease in BOLD signaling following visual stimulation, possibly due to higher blood oxygen extraction secondary to increased cortical excitability or to an abnormal vascular response (44).

Neuroimaging studies have also shown altered functional connectivity in MwA. Niddam et al. showed that MwA, compared to MwoA, had weaker fc between anterior insula and V3A, suggesting abnormal connections between the limbic and visual systems in aura (34). Faragó et al. found that MwA subjects present resting-state alterations within the lateral visual network respect to controls and MWoA, with increased amplitudes of resting BOLD fluctuations in the cingulate cortex, superior parietal lobule, cerebellum and bilateral frontal regions (39). Tedeschi et al. compared resting-state connectivity in the ictal phase of MwA vs. MwoA and controls, finding stronger fc within the visual network, particularly the extrastriate regions within the lingual gyrus (35). Interestingly, this resting-brain alteration was not limited to the aura phenomenon and was not correlated with clinical parameters or morphological differences, leading the authors to hypothesize that increased extrastriate cortical connectivity could represent a functional biomarker of MwA, differentiating it from MwoA and the non-migrainous brain. The same group has also recently demonstrated an abnormal response to trigeminal nociceptive stimulation in the lingual gyrus, inferior parietal lobule and cerebellum of MwA patients. This confirms the involvement of areas of higher visual processing in MwA, and possibly shows that functional integration between visual and trigeminal pain networks could represent a key pathophysiological mechanisms underlying migraine with aura (43).

Overall, these studies show that both lower and higher visual processing is impaired in aura patients, ictally and interictally. The visual cortices generally present hyperexcitability in response to visual stimulus in migraine with aura. Further, functional connectivity seems to be increased within the visual network and conversely decreased between the visual network and other key brain structures in MwA. Even if these characteristic are not limited to MwA, they certainly seem to be more prominent in this subpopulation.

PHOTOPHOBIA

Typically, light can either exacerbate ongoing migraine pain (photic allodynia), or it can be perceived as very bright or uncomfortable (photic hypersensitivity). Photophobia and migraine pain are directly correlated, with light stimuli causing lower thresholds to pain in trigeminal innervated locations in migraineurs (65, 66), and painful trigeminal stimulation leading to decreased visual discomfort thresholds (5). Importantly, photophobia prevalence appears to be independent of migraine aura (65). Nonetheless photic sensitivity is a key aspect of migraine biology, representing not only a prominent feature of the attack (67), but commonly present in the premonitory (68) and interictal phases also (69).

Photophobia is also frequently experienced as part of the visual snow syndrome (19), underlying the important pathophysiological link between these two conditions.

Several studies have investigated the mechanism of photophobia in migraine, with one prominent paper that identified a pathway through which photic signals from the retina converge on nociceptive pathways mediating migraine pain (70), likely explaining the exacerbation of headache by light.

In a $H_2^{15}O$ PET study, Boulloche et al. showed that in response to light stimulation migraineurs had increased activation of visual network areas—specifically the cuneus, lingual gyrus and posterior cingulate cortex—respect to controls (6). Furthermore, this increased activation was potentiated by trigeminal pain, demonstrating a close interrelation between light perception and the trigeminal nociceptive pathway. The same group then directly investigated ictal photophobia in spontaneous attacks of MwoA, finding that light sensitivity was linked to an increased activation in the visual cortex present during the attack, involving the areas of the lingual gyrus and the cuneus (27). With the same technique, Maniyar et al. studied photic sensitivity in premonitory phase of glyceryl trinitrate (GTN) induced attacks of MwoA and found that premonitory photic hypersensitivity is linked to activation of extrastriate visual cortex, specifically Brodmann areas 18 and 4 (33).

In a functional MRI study on interictal chronic migraineurs, authors found an altered connectivity between the anterior insula and pulvinar of patients with migraine, which could explain, at least in part, the abnormal perception of visual stimuli as painful (71). The pulvinar is relevant in selecting salient visual stimuli (72) and has a direct role in the integration between trigeminal pain and visual inputs (70) through a pathway involving the optic nerves and dura-sensitive spinal trigeminal nucleus neurons (73).

These studies suggest that migrainous photophobia is characterized by diffuse associative visual cortex abnormalities,

and that these are possibly linked to abnormal sensory processing in thalamic structures, particularly the pulvinar.

VISUAL SNOW

Visual snow is a neurological disorder characterized by a continuous visual disturbance that takes the form of uncountable tiny flickering dots covering the whole visual field (74). This static disturbance is often referred to as "snow;" it is typically black and white but can also be colored, flashing, or transparent. In the more complex visual snow syndrome, patients experience several other visual symptoms, that can be of neurological origin—such as palinopsia, photophobia, and nyctalopia—or originate directly from the optic apparatus. The latter are called "entoptic phenomena" and manifest in the syndrome with various combinations of blue field entoptic phenomenon (BFEP), floaters, self-light of the eye, and/or spontaneous photopsia (19).

Even if visual snow represents an entity distinct from both migraine without aura and typical migraine aura, comorbid migraine is present in up to 80% of visual snow cases, significantly complicating its phenotype (75–77). In particular, VS patients who have comorbid migraine present an increased chance of having non-entoptic visual symptoms. Further, some cases of VS has been reported to start with an aura episode (18).

To date there has been only one neuroimaging investigation on VS syndrome, and this was an [^{18}F]-FDG PET study performed on 17 patients (75). This study demonstrated that patients with VS exhibit increased brain metabolism in the area of the right lingual gyrus compared to healthy volunteers. The distribution of hypermetabolism was very similar to the area also shown to be directly linked to ictal photophobia in migraine (27), further supporting the hypothesis of a pathophysiological overlap between the conditions.

Toward a Model for Visual Snow

The lack of recognition of the visual snow condition, which was only characterized very recently, has posed a challenge to understanding the biology underlying this disorder. The consistency of the clinical description offered by affected patients allows to hypothesize a common, general, pathophysiological mechanism, although it is also possible for different aspects to be more relevant in-between subjects.

We here outline possible theories on the visual snow pathogenesis, proceeding anatomically from the periphery onto higher areas of visual processing, and hypothesizing on a common biology underlying the condition by analyzing the different features that characterize it.

The first, most obvious, explanation for VS is that it is directly or indirectly triggered by an eye disease. Several ophthalmologic cases can present with clinical features of "static" similar to visual snow. The authors themselves (FP/PJG) received an unpublished report of VS in a subject diagnosed with X-linked Retinitis Pigmentosa. Indeed a de-afferentation syndrome, in which even a temporary alteration in retinal firing causes a dissociation between peripheral sensory input and central visual perception, would explain the similarity of visual snow to tinnitus, a highly common comorbidity (74) and in some respects the auditory counterpart of visual snow. A similar mechanism is also present in the classic hallucinatory condition of Charles-Bonnet syndrome (CBS), where progressive loss of visual function causes hypo-connectivity from the visual periphery to the brain and gives rise to hallucinations (78). It is also tempting to explain the associated entoptic phenomena of VS syndrome as something arising plainly from the eye, as they are indeed typically described in ophthalmic disorders (79) and can even be present in healthy individuals as a consequence of floating strands of vitreous or white blood cells within the microvasculature stimulating retinal neurons (80–82).

The main counter-argument to interpreting VS as a purely eye phenomenon however, lies primarily in the absence of ophthalmic disorders, a required criterion for the diagnosis of VS (19), and also in the normality of basic eye electrophysiology, such as ERG or VEPs, reported in VS cohorts (74, 76). This does not exclude that perhaps some cases of visual snow might be caused by eye disorders. In this respect it is interesting to recall that in certain examples, CBS hallucinations are characterized by simple flashes, dots of light, or palinopsia, an important feature of VS syndrome (83). More case studies are clearly needed to further elucidate the interaction of eye disorders and visual snow-like phenomena.

A second theory on VS pathophysiology involves a direct thalamic dysfunction. In a process known as thalamo-cortical dysrhythmia, a dissociation exists between sensory inputs from the thalamus and its projections to the cortex. This mechanism was first described by Llinas in tinnitus (84), and is characterized by an increase in unusual, large-scale and coherent thalamo-cortical low-frequency oscillations. These delta and theta oscillations are likely caused by a switch from tonic to high-frequency thalamic bursting—due to protracted cell hyperpolarization—and ultimately determine a disintegration of sensory perception at the cortical level. It is certainly possible to hypothesize a role for thalamo-cortical dysrhythmia in visual snow. Potentially, an underlying homeostatic imbalance of visual pathways, either from altered retinal activity or genetic predisposition, could cause a disinhibition of projections from the posterior thalamus to primary and secondary visual cortices and parietal cortex as well—explaining palinopsia and a continuous perception of movement—thus affecting normal visual perception (76).

Interestingly, the thalamo-cortical dysrhythmia hypothesis also seems to be relevant for migraine pathophysiology (85), where a functional disconnection of the thalamus is thought to be contributing to the abnormal habituation deficit repeatedly observed (86).

In a more simplistic view, the thalamus could be responsible for VS symptoms through a localized increase in activity of the LGN or the pulvinar. The pulvinar is part of the "thalamic matrix" and projects diffusely to the cortex, playing a significant role in cognition and attentive stimulus processing (87). Recent studies have confirmed that the pulvinar can facilitate attention-related communication across widespread neuronal networks including higher-order sensory cortices (88) and, as mentioned before, it has a clear role in photophobia. In the future, neuroimaging studies focused on these nuclei will help clear the role of thalamic dysfunction in visual snow.

A third option could be to hypothesize VS as a purely cortical phenomenon. In visual hallucinatory syndromes, the percept of hallucinations has been shown to correspond to a dysfunction in the cortical area where that particular perception is represented (89). If the "cortical dysfunction theory" were true, we should therefore expect altered brain structure, compensatory neuroplasticity or functional activity to be constrained to visual association/motion areas. It is known that topological visual disorders caused by hyper-function in V1/V2 areas can present with hallucinations similar to visual snow (90). Further, a recent case of sporadic Creutzfeldt-Jakob disease presenting with features of visual snow has been reported in the literature (91). These cases are, however, exceptional and they would certainly not explain most cases of VS in which no gross central nervous system abnormalities are found.

A more complex explanation of the role of the cortex could involve a widespread dysfunction of higher-order visual processing areas, particularly the extrastriate cortex. Certainly the cited PET study, showing increased metabolic activity in the lingual gyrus, points to this (75). There have also been important neurophysiological (92–94) and behavioral (95) studies demonstrating an altered processing and dishabituation in the visual network of the VS brain.

The dorsal visual network, involved in processing visual motion, is likely to play a role in a condition characterized by the perception of constantly moving objects. The motion network is part of what has now been renamed as the "how-pathway" (96) and spreads from V1 dorsally to the parietal lobe, involving visual motion area V5 located in the temporo-parietal-occipital junction (97).

Finally, an altered connection between visual networks and other brain networks involved in salience, cognition and interoception is possible in a disorder like VS. Vision is a dynamic, active process in which top-down influences are seen at all stages of the visual hierarchy—with the exception of the retina—and control various functional properties of vision, particularly attention (98). We can hypothesize that visual snow may be characterized by a general altered excitability and connectivity of the visual network with either the salience and/or DMNs, which typically exert top-down influence on the visual cortex, = or the dorsal and ventral attentional networks, which have been abundantly implicated in theories of visual hallucinations (99, 100).

The final, overarching framework that we propose for visual snow encompasses the three aforementioned hypotheses. If a combination of peripheral, subcortical and cortical dysfunctions were all at play, either in different subjects or in different moments of the natural disease history, this would explain not only the main symptom of the snow common to all patients, but also the variety of symptoms characterizing the VS syndrome. Similarly to a model that has been used to explain tinnitus and is potentially involved in chronic pain as well (101), we could imagine that subcortical spontaneous activity normally

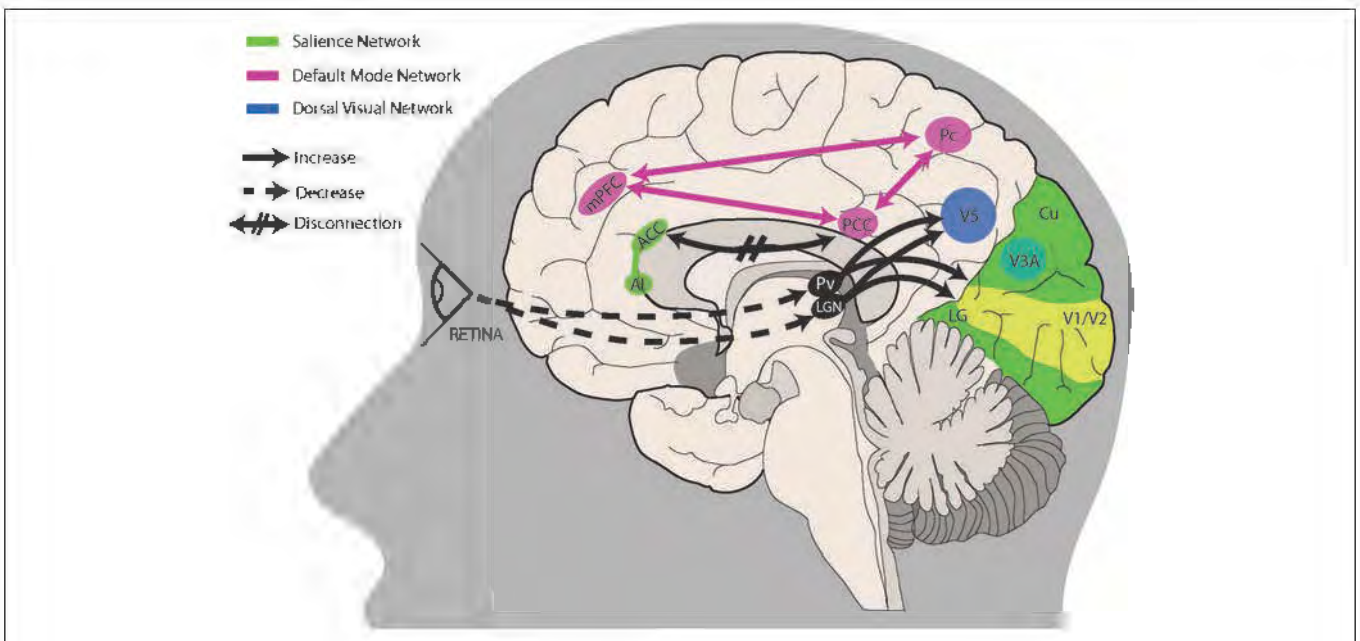

FIGURE 1 | A proposed model for visual snow pathophysiology. Altered peripheral visual stimulation or a form of genetic predisposition could induce dysrhythmic connections between thalamic structures and cortical visual areas. The lateral geniculate nucleus (LGN) and pulvinar (Pv) in particular are directly connected to motion area V5 and the lingual gyrus (LG). Relevant to visual snow biology is the motion processing network, which is composed of areas within the primary visual cortex (V1/V2), area V3A within the cuneus (Cu), area V5 located ventrolaterally among the lateral occipital sulcus and inferior temporal sulcus, and Brodmann area 7 in the precuneus (Pc). Structures pertaining to the default mode network (PCC, posterior cingulate cortex; Pc; mPFC, middle prefrontal cortex) and/or the salience network (AI, anterior insula; ACC, anterior cingulate cortex) are involved in salience and interoception. Disruption of these networks, possibly through altered connectivity between cortical areas, could also play a role in visual snow pathophysiology. See main text for a more in-depth explanation.

ignored and considered as erroneous by the brain in normal conditions, might for various reasons increase in salience and be considered as the default visual perception, particularly if the hierarchical sensory processing networks in the brain do not correct this faulty perception. This model would certainly explain the continuous background perception of the simple static or snow, but also the more complex phenomena typical of the syndrome: palinopsia, entoptic phenomena, photophobia and even nyctalopia, which could in fact simply represent an increased perception of the "noise" when no other stimulus is present. **Figure 1** summarizes the salient aspects of this theory, showing the most important brain structures and connections likely involved in visual snow pathophysiology. Neuroimaging studies will be particularly useful in the future to determine the strength of this reasoning, as well as the role of the different mechanisms in VS biology.

A continuous dysfunction of large-scale visual processing networks, in particular of the motion network, through this or other mechanisms in visual snow possibly constitutes a link to its "cousin" condition of migraine, in which manifestations of altered visual processing, although not predominant, constitute an important aspect of a disease characterized by generalized alterations of sensory processing.

CONCLUSIONS

In summary, modern neuroimaging has allowed to detect several functional, structural and metabolic changes affecting multiple elements of the visual network in migraineurs, both with and without aura. These abnormalities help explain some of the key features of the condition, such as abnormal sensory processing, photophobia and the aura phenomenon, and further link it to the growingly recognized neurological syndrome of visual snow. In this condition, which is likely on a similar pathophysiological spectrum as migraine, multiple elements (i.e., cortical hypermetabolism, thalamo-cortical dysrhythmia, brain network dysfunctions) could be at play in the generation of a persistent visual illusion.

AUTHOR CONTRIBUTIONS

FP wrote the first draft of the manuscript. DF and OO'D revised the initial drafts and gave scientific contribution. PG edited the final version of the manuscript.

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Migraine with aura is associated with impaired colour vision: Results from the cross-sectional German DMKG headache study

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Abstract

Background: Hypersensitivity to light, noise and odour are pivotal clinical characteristics of migraine associated with enhanced cortical excitability and dysfunctional habituation. However, little is known about the integrity of basic sensory functioning in migraine on a population-based level.

Methods: A total of 129 participants with migraine (105 without aura, MwoA, 24 with aura, MA) and 522 healthy controls without headache 12 months prior to baseline were included from a sample of the DMKG study and underwent standardised clinical sensory testing of smell, taste, hearing and vision.

Results: After adjustment for age, sex, smoking status and history of head injuries, the chance of impaired colour perception was significantly higher in MA compared to controls (odds ratio, OR = 3.20; 95% CI = 1.20–8.53) and MwoA (OR = 3.62; 95% CI = 1.31–9.97). Compared to MwoA, MA also had an increased chance of smell (OR = 3.20; 95% CI = 0.98–10.42) and taste (OR = 2.58; 95% CI = 0.90–7.40) impairment.

Conclusions: In this cross-sectional, population-based study on sensory functioning in migraine participants, colour vision was impaired interictally in MA compared to MwoA and controls.

Keywords

Migraine, aura, sensory threshold, vision, headache

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Introduction

Migraine is a complex disorder of sensory processing affecting different parts of the central nervous system (1). Photo- and phonophobia are landmarks for the diagnosis of migraine with (MA) and without aura (MwoA) (2). More recently, osmophobia has been recognised as a third relevant correlate of ictal – but also interictal – sensory dysregulation (3,4). In recent studies the prevalence of photophobia was as high as 76.4%, phonophobia 85.1% and osmophobia 47.7% among the participants (5).

However, only a limited number of studies have assessed the integrity of the involved sensory systems using qualitative or quantitative testing. These studies were mostly conducted at specialised headache centres, inferring the risk of a selection bias (6–11). While some epidemiological studies assessed both hypersensitivity to light, noise and smell as well as subjective sensory impairment (12), only very few have used objective testing such as in a door-to-door approach as in our study (13).

Therefore, participants in a large population-based study on primary headaches in Germany were analysed to elucidate whether thresholds of the visual, olfactory, gustatory and auditory system were altered in MA and MwoA patients.

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Methods

Study procedure and population sample

The Dortmund Health Study (DHS) is part of a large epidemiologic project funded by the German Migraine and Headache Society (DMKG). The DHS aimed to assess the prevalence of headache types, cardiovascular and other chronic diseases, and their impact on everyday life among those affected (14). The study was conducted 2003–2004 and included face-to-face interviews followed by standardised tests of sensory thresholds and functioning including smell, taste, hearing and vision. The detailed study procedure is described elsewhere (14). In short, a random sample of the total population stratified by age and sex was drawn from the population register of the city of Dortmund. Participation was restricted to ages 25 to 75 years.

The study was approved by the local ethics committee of the Medical Faculty of the University of Münster and the Westphalian Chamber of Physicians. Informed consent was obtained by all participants prior to inclusion into the study.

A total of 1312 participants took part in the interview-assessment and subsequent testing of sensory performance. For the present analysis migraine cases (participants with definite or probable migraine) and controls (participants without headaches during the 12-month period prior to the interview) were identified within the DHS ($n = 797$). Out of these we excluded participants with insufficient command of the German language ($n = 122$) and missing values in sensory performance testing ($n = 24$) summing up to a total of 651 participants.

Headache assessment and classification

A structured interview on the diagnosis of primary headaches was designed based on the International Headache Society's criteria for headache classification which were current at the time the study was planned and conducted (ICDH-2) (2). This interview allowed the assessment of the six- and 12- month period prevalence of migraine and tension-type headache (14,15).

Participants who reported a headache during 12 months prior to the interview were subject to further questions about their headache symptoms (such as headache frequency, duration, character, location and presence of accompanying features and aura symptoms). Based upon these characteristics, the headache was classified as definite MwoA (IHS-code 1.1) or MA (IHS-code 1.2.1). If not all diagnostic criteria were met, the headache was classified as probable migraine (IHS-code 1.6) without or with aura. Thus, the definition of migraine included probable ($n = 48$) or definite migraine ($n = 81$) diagnoses. In the present study, 98% ($n = 47$) with probable migraine did not fulfil IHS criterion B: "Headache attacks lasting 4–72 hours" as already described in Pfaffenrath et al. (14).

Sensory testing

Sensory functioning was assessed in four modalities: vision, smell, hearing and taste. An impairment of the respective modality was assessed and classified as follows:

Olfactory testing. Smell was tested using Sniffin' Sticks (12-stick version, Burghart, Wedel; Germany), which are pen-like odour-dispensing devices commonly used in clinical practice and research (16). The sticks enable tests of odour discrimination and odour identification (17). Participants had to identify 12 common odours in a multiple-forced choice test using a list of four descriptions for each odour (18,19). Odours were presented to the participants by placing each of the 12 sticks subsequently in front of both nostrils for three seconds. Smell impairment (hyposmia or anosmia) was assumed if participants identified six or less out of the 12 odours (19).

Gustatory testing. Taste was tested in an identification task using the four basic tastes (sweet, sour, salty and bitter) at suprathreshold concentrations (sweet: sucrose, 1.5 g; sour: citric acid, 0.75 g; salty: sodium chloride, 1.125 g; bitter: quinine hydrochloride, 7.5 μg; all test substances were dissolved in 15 g water) (19). Approximately 0.1 ml of each tastant was sprayed on the middle of the participants' tongue. They were then asked to identify the taste according to a list with the four taste descriptors. After each taste, participants flushed their mouth with water (19). Taste impairment was assumed when participants did not identify all four tastes correctly. A sum score was created by adding 1 for each correctly identified gustatory sample (out of a maximum of 4). In addition, the self-rated taste intensity was measured on a scale from 1 (weak) to 10 (intensive). Participants were asked to rate the perceived intensity for each of the four tastes, resulting in a score from 1 to 40. Then the average taste intensity was calculated as the mean intensity of all four tastes.

Visual testing. Monocular visual acuity was measured using a standard Snellen chart. If applicable, patients were tested wearing their current correction. Vision impairment was defined to be present if participants had a visual acuity of 80% or less. Colour perception was tested by the use of Ishihara plates (20). These charts present different numbers consisting of colour spots grounded on a different-coloured background, so that colour-deficient people cannot or just barely

perceive the numbers (20). Participants were asked to identify the number presented on the colour chart. In total, 14 charts were presented out of which the average of correctly identified colour charts was estimated. If participants identified less than 13 colour charts, a colour-perception impairment was assumed.

Auditory assessment. Hearing was tested using a screening test with hearing thresholds of 30 dB by means of a portable device. Three frequencies (1000 Hz, 2000 Hz and 4000 Hz) were tested subsequently, starting with the right ear. A pure-tone of 30 dB was presented to the participant in a two-alternative forced-choice task. If the participant did not perceive the auditory stimulus, sound-pressure was increased to 40 dB. This procedure was repeated up to a sound-pressure of 80 dB. Then hearing impairment was assessed separately for both ears first. If the auditory threshold was greater than 30 dB in one of the three frequencies, auditory performance was considered moderately impaired. A severe impairment was assumed if the threshold was greater than 30 dB in at least two frequencies. The final definition of hearing impairment encompassed a combination of the auditory performance of both ears. If a moderate impairment was present in both ears, or if a severe impairment was present in at least one ear, the auditory function was defined as being impaired.

Combined sensory assessment. Since it was illustrated in other studies that sensory impairments overlap frequently (19,21,22), we estimated the frequency of a multiple sensory impairment. We defined a multiple sensory impairment to be present if three out of the four investigated sensory impairments overlapped.

Statistical analysis

Continuous variables were described with means and standard deviations, and differences among groups were examined with analysis of variance (ANOVA). Because taste and smell scores were not normally distributed, Kruskal-Wallis test was used instead. Differences in categorical variables were compared using chi-square test or Fisher's exact test (if cell number was 5 or less).

All impairment variables were dichotomous. Whether the chance of sensory impairment was higher in migraine compared to controls was tested by logistic regression. We calculated unadjusted as well as adjusted odds ratios (OR). The latter were adjusted for age, sex, smoking status and history of head injury since these variables were associated with either group, outcome or both. Adjusted group means were estimated by least square means using *t*-tests to identify differences between groups. All analyses were conducted using the statistical software SAS version 9.2.

Results

Participant characteristics

A total of 651 participants (522 controls and 129 cases) were analysed. As illustrated in Table 1, 105 out of the 129 migraineurs had MwoA and 24 MA. Participants with migraine were significantly younger than controls ($p < 0.01$). There were also more women in the migraine groups compared to controls ($p < 0.01$). The prevalence of current smokers ($p = 0.84$), diabetes ($p = 0.11$) or obesity ($p = 0.30$), defined as body mass index (BMI) ≥ 30), was not different between groups. However, there were more participants with depressive symptoms ($p < 0.01$) or a history of head injuries ($p < 0.01$) in the group of participants with migraine.

Sensory assessment

Impairment in at least one sensory modality was frequent but multiple sensory impairments were uncommon, as illustrated in Table 2. There was a group association for any or multiple impairments

Table 1. Epidemiological characteristics.

	Controls ($n = 522$)	MwoA ($n = 105$)	MA ($n = 24$)
Age, mean (SD)	58.2 (12.1)	46.7 (11.4)	45.5 (11.5)
Women,% (*n*)	43.0 (227)	82.2 (88)	79.2 (19)
Current smoker, % (*n*)	19.9 (105)	23.4 (25)	16.7 (4)
History of head injuries, % (*n*)	5.9 (31)	12.2 (13)	20.9 (5)
BMI $\geq$30, % (*n*)	28.4 (148)	21.0 (22)	29.2 (7)
Diabetes, % (*n*)	9.8 (51)	3.8 (4)	4.2 (1)
Depressive symptoms[a], % (*n*)	10.0 (52)	30.5 (32)	33.3 (8)

MwoA: migraine without aura; MA: migraine with aura; SD: standard deviation; BMI: body mass index.
[a]Measured by the Center of Epidemiological Studies Depression Scale (score of $\geq$16).

Table 2. Prevalence of sensory impairments.

	Controls ($n = 522$)	MwoA ($n = 105$)	MA ($n = 24$)
Any sensory impairment, % (n)	88.3 (461)	75.2 (79)	95.8 (23)
Multiple sensory impairments, % (n)	29.3 (153)	7.6 (8)	29.2 (7)
Olfactory impairment, % (n)	24.3 (127)	10.5 (11)	25.0 (6)
Gustatory impairment, % (n)	20.8 (109)	14.3 (15)	29.2 (7)
Visual impairment, % (n)	35.1 (183)	28.5 (30)	20.8 (5)
Colour perception impairment, % (n)	56.5 (295)	47.6 (50)	75.0 (18)
Auditory impairment, % (n)	51.7 (270)	20.0 (21)	29.2 (7)
Self-perceived taste intensity, mean (SD)	19.9 (6.8)	20.4 (7.2)	20.2 (6.2)
Smell score, mean (SD)	10.2 (1.8)	10.9 (1.1)	10.3 (2.2)
(median (range))	(11.0 (12.0))	(11.0 (5.0))	(11.0 (10.0))
Taste score, mean (SD)	3.7 (0.7)	3.8 (0.5)	3.7 (0.6)
(median (range))	(4.0 (3.0))	(4.0 (3.0))	(4.0 (2.0))

MwoA: migraine without aura; MA: migraine with aura; SD: standard deviation.

($p < 0.01$). In more detail, a significant association between group and olfactory ($p < 0.01$) as well as auditory ($p < 0.01$) and colour perception impairment ($p = 0.03$) but not visual ($p = 0.31$) or gustatory ($p = 0.47$) impairment could be found with a higher prevalence as shown in Table 2. The average self-perceived taste intensity did not differ between groups ($p > 0.76$). The same was true for the average taste score ($p = 0.18$). However, the smell score was significantly different between groups ($p < 0.01$).

After adjustment for age, sex, history of head injuries and smoking status, MA also had a higher and statistically significant chance of impaired colour vision compared to controls (OR = 3.20; 95% confidence interval (CI) = 1.20–8.53) and MwoA (OR = 3.62; 95% CI = 1.31–9.97) (see Table 3 for further details). Furthermore, MA showed a tendency to olfactory (OR = 3.20; 95% CI = 0.98–10.42) and gustatory (OR = 2.58; 95% CI = 0.90–7.40) impairment compared to MwoA, in line with high OR and large CI. The number of correctly identified tastants (sum score) and their subjective intensity did not differ between groups after adjustment.

Association with photo-, osmo- and phonophobia

In participants with migraine 79.8% (81.9% in MwoA and 70.8% in MA) reported photophobia during attacks. Phonophobia was reported by 83.0% (83.8% and 79.2), while osmophobia was present in 24.8% (24.8% in MwoA and 25.0% in MA). No relevant association was found between the presence of osmophobia and impaired olfactory perception (OR = 0.98; 95% CI = 0.29–3.36), phonophobia and auditory impairment (OR = 2.54; 95% CI = 0.54–10.29) and photophobia and impaired colour vision (OR = 1.43; 95% CI = 0.60–3.41).

Discussion

In this large population-based study a detailed assessment of headache type and sensory functions was conducted and the association of MA as well as MwoA and sensory functioning examined. After adjustment for potential confounders the chance of colour perception impairment was clearly higher in MA participants. Furthermore, we observed an increased chance of olfactory and gustatory impairment in MA participants even though this missed statistical significance. The prevalence of visual and auditory impairment, as well as the perceived intensity of basic tastes, did not differ among groups. There was also no significant association between olfactory function and the reported proportion of osmophobia, between auditory impairment and phonophobia and between colour vision and photophobia. Thus, our results do not support the idea of a general sensory dysfunction in migraine.

Osmophobia, which is associated with altered activity in the antero-superior temporal gyrus and the piriform cortex (23), was reported by 25% in our population, which corroborates findings of Kelman (24.7%) in a sample of 673 migraine patients treated at a specialised headache centre (4). The only study using a face-to-face approach similar to ours detected osmophobia in 48% of patients (5). Prevalence found in other tertiary headache centres was higher: 46% by Blau and Solomon (3), 44% by Zanchin and colleagues

Table 3. Comparisons of sensory performance between groups.

		Raw OR (CI)	Adjusted OR (CI)[a]
Olfactory impairment	MwoA vs. control	0.36 (0.19–0.70)	0.74 (0.36–1.53)
	MA vs. control	1.03 (0.40–2.67)	2.38 (0.83–6.83)
	MA vs. MwoA	2.85 (0.93–8.69)	3.20 (0.98–10.42)[b]
Gustatory impairment	MwoA vs. control	0.63 (0.35–1.14)	0.81 (0.43–1.55)
	MA vs. control	1.56 (0.63–3.86)	2.10 (0.80–5.47)
	MA vs. MwoA	2.47 (0.88–6.96)	2.58 (0.90–7.40)[b]
Auditory impairment	MwoA vs. control	0.23 (0.14–0.39)	0.70 (0.38–1.30)
	MA vs. control	0.38 (0.16–0.94)	1.34 (0.45–4.00)
	MA vs. MwoA	1.65 (0.61–4.49)	1.91 (0.59–6.20)
Vision right eye	MwoA vs. control	0.52 (0.29–0.91)	0.72 (0.38–1.35)
	MA vs. control	0.41 (0.12–1.39)	0.63 (0.17–2.25)
	MA vs. MwoA	0.80 (0.21–2.98)	0.87 (0.23–3.38)
Vision left eye	MwoA vs. control	0.93 (0.56–1.53)	1.52 (0.85–2.71)
	MA vs. control	0.44 (0.13–1.51)	0.80 (0.22–2.92)
	MA vs. MwoA	0.48 (0.13–1.74)	0.53 (0.14–2.02)
Colour perception	MwoA vs. control	0.70 (0.46–1.10)	0.89 (0.60–1.41)
	MA vs. control	2.31 (0.90–5.91)	3.20 (1.20–8.53)[c]
	MA vs. MwoA	3.30 (1.21–8.97)	3.62 (1.31–9.97)[c]
Self-perceived taste intensity Adjusted means (95% CI)	MwoA vs. control	20.4 (19.1–21.7) vs. 19.9 (19.3–20.5), $p = 0.46$	19.8 (18.1–21.4) vs. 20.2 (19.0–21.3); $p = 0.60$
	MA vs. control	20.2 (19.1–21.7) vs. 19.9 (19.3–20.5), $p = 0.82$	19.7 (16.8–22.5) vs. 20.2 (19.0–21.3); $p = 0.74$
	MA vs. MwoA	20.2 (17.5–23.0) vs. 20.4 (19.1–1.7), $p = 0.89$	19.7 (16.8–22.5) vs. 19.8 (18.1–21.4); $p = 0.96$

CI: confidence interval; MwoA: migraine without aura; MA: migraine with aura; OR: odds ratio; CI: confidence interval.
[a]Adjusted for age, sex, smoking status and history of head injuries.
[b]Relevant association due to high OR and large CI despite missing statistical significance by a narrow margin.
[c]Significant results (with $p < 0.05$).

(24) and 62% in Taiwan (25). Highest rates were found in 71% in a Japanese cohort of MA patients and in 49% of MwoA (26).

Little is known on the integrity of the olfactory system in migraine. Snyder and Drummond found an impaired interictal olfaction in MA and MwoA patients compared to healthy controls using vanillin (6). Similarly, Hirsch reported hypo- or anosmia in 18% of 76 patients with migraine (27). As a limitation, a control group was not included and only pyridine odour threshold was tested with a putative trigeminal co-activation. While both studies corroborate our findings, it was specific only for MA patients in our study.

Only recently Marmura and colleagues reported impaired olfactory ability during migraine attacks in MwoA and MA patients as determined with the University of Pennsylvania Smell Identification Test (UPSIT) (28). While baseline olfaction did not differ from a healthy control group, UPSIT scores shortly after an attack were numerically lower than at baseline. In line with our observation, the majority of patients (66%) with a relevant impairment of olfaction suffered MA.

In contrast, olfaction among 80 Japanese migraine patients in a neurological outpatient service did not differ from 30 controls, while aversive ratings for certain scents were significantly higher among migraine patients, especially those with MA (26). Interestingly, both phenomena were not associated in our cohort as well, which supports the concept of two different and independent pathophysiologic mechanisms.

As olfactory input underlies serotonergic modulation in the olfactory bulb via the $5HT_{2c}$ receptor (29), serotonergic dysregulation as part of migraine biology could explain hyposmia. Alternatively, altered mitochondrial Ca2+ signalling in the olfactory cortex

which was identified as a crucial element in olfactory signalling (30) could be causal.

In a first study from a specialised headache centre, self-reported taste abnormalities were found in 24.6% of MA and MwoA patients (4). In a subsequent report of Kelman and Tanis, self-reported taste abnormalities were present in 827 of 1025 (80.7%) MA and MwoA patients (7). However, it was not differentiated between taste impairment and gustatory hypersensitivity and no quantitative testing was performed. Approximately 90% of what is putative gustatory impairment can actually be contributed to olfactory impairment (31). This emphasizes the importance of sensory testing, especially as anosmic patients are often unaware of their situation (31).

Saisu and colleagues were the first to examine interictal differences in taste by means of standardised testing in migraine patients and controls and found no differences in the prevalence of hypo- or hypergeusia (26). In contrast, the higher ORs for impaired taste in MA in our study imply a reduced taste perception which may in part be explained by the different methodology. In the former clinic-based study, no adjustments for potential confounders were made and the classification of taste anomalies was different.

In a Belgian questionnaire-based study ($n = 134$) on interictal sensory symptoms in migraine, more patients indicated reduced visual acuity (14.2%) and nocturnal vision (14.9%) in the headache-free interval than an increased visual acuity (9.7%) and improved colour vision (9.0%) (12). Patients with at least one visual change were more likely to suffer from ictal photophobia. As a limitation, no objective sensory testing was conducted. These findings are in contrast to a large study from the 1970s which assessed uncorrected and (if needed) corrected visual acuity, the presence of latent and manifest squint for both near and distant vision and convergence as well as accommodation (13) in a total of 168 men and 246 women from a random population sample from Wales. Apart from hyperphoria in near vision no significant differences between participants with and without migraine could be identified. Likewise, a relevant interictal reduction of visual acuity was not found in another smaller sample (32). Our data thus add evidence that visual acuity is not altered in migraine patients.

However, more complex examinations of the visual system yielded subtle differences between migraine patients and controls. Harle and Evans found an impaired stereopsis and a minutely increased prevalence of heterophoria and aligning prism as compared to controls (8). In addition, they identified an increased risk of pupil anomalies, visual field defects and pattern glare (33). Diminished interictal sensitivity in short-wavelength automated perimetry has also been found in 50% of MA and MwoA patients (32).

Anomalies in colour vision have been described by Shepherd, who reported deficient colour discrimination in migraine patients attributed to S-cone mediated detection of light at short wavelengths corresponding to blue light (9,10). In contrast, in our sample Ishihara plates were used, not allowing further assessment of tritanopia (respectively blue vision). It is important to note that our results are supported by the male prevalence in the control group since impaired colour vision is more prevalent in males because of x-chromosomal transmission. This could point to a disturbance in the parvocellular system as part of the primary visual cortex in areas rich with mitochondrial cytochrome oxidases where blobs and interblobs are located which play a crucial role in the complex process of colour vision (34). As a mitochondrial deficit of energy metabolism has been suspected in MA patients (35–37), it is tempting to assume an altered mitochondrial energy metabolism in the visual cortex of MA patients. Similar to our findings in the olfactory system, impairment of colour vision does not correlate with photophobia, suggesting two different pathophysiologic mechanisms.

Photophobia has been associated with retinal pathways not involved in image-formation which modulate the activity of dura-sensitive thalamocortical neurons (38). The prevalence of photophobia in our cohort is similar to that in a multicentre study from 12 Latin American urban communities using a face-to-face questionnaire (5).

Our findings of normal auditory thresholds in a representative population sample from Germany are supported by a controlled study on a sample of 58 patients with migraine (mainly MwoA) from a headache outpatient clinic from Egypt compared to 40 healthy controls (11). However, up to two-thirds of the migraine patients had at least one anomaly in the advanced electrophysiological testing including auditory brainstem response, transient evoked otoacoustic emissions and distortion product otoacoustic emissions. Likewise, Bolay and colleagues could not detect any significant difference in pure tone audiometry and speech discrimination scores between 53 migraine patients (37 with MwoA) and 41 healthy controls (39), similar to another study from Turkey (40). But, on a subclinical level a contralateral suppression of transiently evoked otoacoustic emissions was found.

In a long-term follow-up (median nine years) of a cohort of 61 patients with vestibular migraine from a specialised centre, a mild bilateral sensorineural hearing loss was present in 18% of the patients (41), which suggests a higher risk of auditory impairment in

patients with a previous history of vestibulocochlear dysfunction.

As for phonophobia, the prevalence in our sample was similar to the findings of the community-based study from Latin America (both around 80%). In these individuals, a brainstem dysfunction at the medial olivocochlear complex or a disturbed synaptic transmission between outer cochlear hair cells and olivocochlear efferents could be causal for the generation of phonophobia.

Limitations

As group sizes became relatively small for the MA group after exclusion of participants without sufficient knowledge of the German language, we cannot exclude that analyses were partly underpowered.

The sensory testing paradigm was chosen to allow mobile testing by specifically trained interviewers without a medical background as this was the only feasible setup for a large scale epidemiological study with a broad range of sensory modalities covered. As a limitation of this mostly binary classification into abnormal or normal sensory functioning, subtle subclinical anomalies could have been missed as shown by other studies.

Our controls tended to be older and suffer from diabetes more frequently, therefore, worse sensory performance than in the migraine group would be expected. As this is clearly not the case, it strongly supports the validity of our findings.

Conclusion

In our study, colour vision was significantly impaired in MA patients in a population-based sample. However, general basic sensory functioning was largely unimpaired in our representative sample without evidence for a general sensory dysfunction in migraine present between attacks.

Clinical implications

- In this population-based study, colour vision as well as smell and taste were altered in participants suffering from migraine with aura (MA) compared to those with migraine without aura (MwoA) and healthy controls.
- Visual acuity and basic performance of the auditory system did not differ between these groups; therefore, no evidence for a clinically relevant general interictal sensory dysfunction in migraine was found.
- Disturbances of colour vision in migraine have been reported before and may be due to a mitochondrial dysfunction in the primary visual cortex in MA patients.

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Conflicts of interest

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vision

Article

No Evidence of Reduced Contrast Sensitivity in Migraine-with-Aura for Large, Narrowband, Centrally Presented Noise-Masked Stimuli

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Abstract: Individuals with migraine aura show differences in visual perception compared to control groups. Measures of contrast sensitivity have suggested that people with migraine aura are less able to exclude external visual noise, and that this relates to higher variability in neural processing. The current study compared contrast sensitivity in migraine with aura and control groups for narrowband grating stimuli at 2 and 8 cycles/degree, masked by Gaussian white noise. We predicted that contrast sensitivity would be lower in the migraine with aura group at high noise levels. Contrast sensitivity was higher for the low spatial frequency stimuli, and decreased with the strength of the masking noise. We did not, however, find any evidence of reduced contrast sensitivity associated with migraine with aura. We propose alternative methods as a more targeted assessment of the role of neural noise and excitability as contributing factors to migraine aura.

Keywords: migraine with aura; psychophysics; contrast sensitivity; aura; cortical excitability; neural noise; spatial frequency

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1. Introduction

1.1. Background

The exact pathophysiology of migraine is still unclear, however the prevalence of photophobia and phonophobia (aversion to light and sound, respectively) that occur during the attack [1], or even in the absence of a headache [2], suggest that a migraine is a disorder of sensory processing [3]. Furthermore, visual discomfort to certain patterns and sensitivity to flickering light are commonly reported sensory triggers of migraine. Additionally, between 4% and 7% of people with migraine also experience sensory disturbances immediately preceding the onset of an attack [4]. These disturbances, or aura, while primarily visual, can occur in any sensory modality. Those with migraine aura typically experience hallucinations immediately before the onset of the headache [5], although aura can also occur without the headache [2]. Visual aura typically consists of expanding "fortification spectra" (shimmering zig-zag patterns) and a central scotoma (area of temporary blindness), although there are many other types of more complex aura hallucination [6].

Therefore, understanding the variances in sensory processing between those with migraine and those without may provide an insight to the underlying mechanisms of migraine. Compared to controls, people with migraine aura show heightened behavioural responses to sensory stimuli [7], increased EEG amplitude of the early visual components [8–10] and a higher susceptibility to phosphenes elicited by neurostimulation [11–14] between attacks. These findings are thought to represent an index of general cortical excitability [7,15,16], whereby there is a heightened response to incoming stimuli. Importantly, Brigo et al. [17]'s meta-analysis of susceptibility to phosphenes (as a proxy for cortical excitability) suggested the effect is specific for migraine aura, not migraine without aura. Behavioural

responses have also been identified to be greater in migraine with aura than in those without aura [18,19]. There has been a suggestion that the two subtypes are distinct [20], although this is debated [21], and so the current study will focus on migraine with aura exclusively.

1.2. Contrast Sensitivity

Contrast sensitivity, the degree of contrast required to detect a stimulus, is often measured using sine-grating stimuli (see Figure 1) [22] as a function of their spatial and temporal frequencies. These stimuli are particularly useful for behaviourally investigating cortical hyperexcitability, which may occur as (i) a result of a reduced ability to ignore internal noise [22,23] or (ii) reduced inhibitory controls between neurons in the early visual processing areas [24]. Detection (or discrimination) of these gratings relies on the excitatory and inhibitory interactions between neurons. If there is a heightened response to incoming stimuli in those with migraine aura, it might be predicted that they should outperform controls on behavioural measures of contrast sensitivity. However, several studies have found reduced, rather than increased, contrast sensitivity when tested using static 4 cpd (cycles per degree) gratings [25–28].

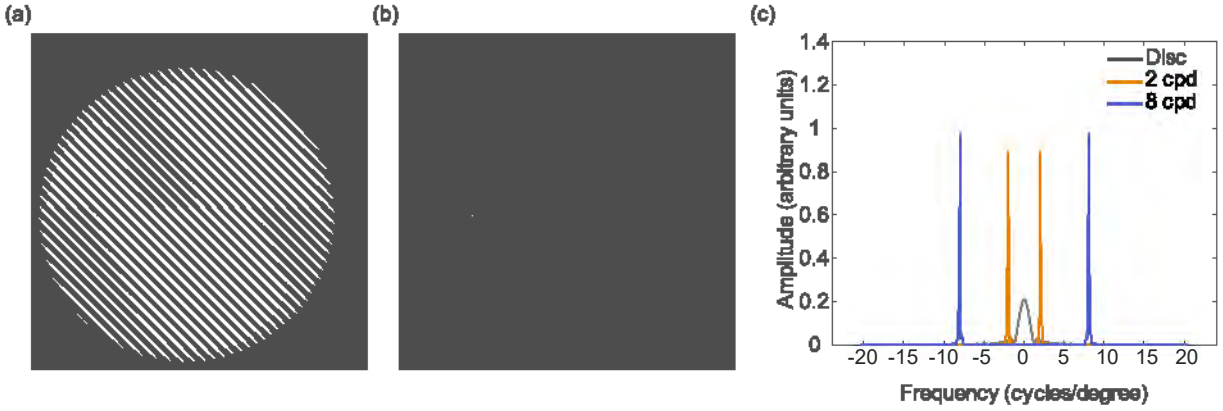

Figure 1. Schematic diagram of the stimuli used in the current experiment: (**a**) the 8 cpd target sine grating (exact spatial frequency content will vary as this is dependent on distance). (**b**) the target and Gaussian noise mask. (**c**) The Fourier transform of the stimuli, showing frequency plotted against amplitude (arbitrary units) for the disc used by Wagner et al. [18] (grey) the 2 cpd (orange) and the 8 cpd (blue) stimuli. The disc stimulus covers a wider range of spatial frequencies compared to the sine gratings that bias the visual system to preferred pathways.

Reduced sensitivity has also been found to flickering gratings, in particular 10–20 Hz flicker [29]. A reduction in contrast sensitivity was found only for low spatial frequency stimuli by Benedek et al. [30]. In contrast, Yenice et al. [31] found reduced contrast sensitivity for a range of spatial frequencies (1.5 to 18 cpd). This was a substantial effect, with a mixed (aura and without aura) migraine group showing just half the contrast sensitivity of a control group.

Other authors however find no difference in contrast sensitivity between migraine and control groups. Using a 3 cpd peak Gabor stimulus, McColl and Wilkinson [15] showed a trend towards poorer baseline contrast sensitivity in both migraine with and without aura groups, but this was not statistically significant. Although there was a reduction in performance in all groups from adding a 3 cpd grating mask (whether simultaneous with stimulus onset or asynchronous), there was no differential effect between the groups. Tibber et al. [32] also showed no differences between migraine aura, without aura and control groups for detecting a 4 cpd peak Gabor patch at cardinal or oblique angles. Asher et al. [33] found a small increase in contrast sensitivity in migraine with aura for centrally-presented 4 cpd Gabor patches, and Aldrich et al. [34] found no difference in contrast discrimination performance for 2.6 cpd Gabor stimuli presented against a 10% or 50% contrast pedestal.

Some studies have found no differences in overall contrast sensitivity [35], but losses in specific areas of the visual field when the stimuli flicker at 9 Hz or above [35]. This may result in smaller targets being missed. Additionally, this visual field loss seems to be worse just after the attack, then improves gradually, however this was in one observer reporting migraine without aura. Other studies have found differences in contrast sensitivity in the periphery only, at 12.5 degrees [36], and 10 degrees [37] eccentricity. Therefore, the current experiment will use large stimuli, covering a large area of the visual field, to allow for the potential deficits in specific areas of the visual field to be detected. Overall, research into contrast sensitivity in migraine with aura shows mixed results, and it is unclear what the reason for these differences might be [22].

1.3. Noise

Several researchers have found no differences in contrast sensitivity under optimal conditions, but that sensitivity is reduced when the stimuli are masked by adding external noise [18,38,39]. Wagner et al. [18] suggested that this was due to increased internal noise in response to a stimulus (neuronal response variability) in those with migraine aura.

1.4. Relation between Neural Noise, Contrast Sensitivity and Aura

The possibility that migraine with aura, in particular, is associated with an increase in neural noise, may help to understand the reason for the occurrence of the aura itself. The physiological correlate of migraine aura is thought to be a cortical wave of spreading depolarisation and depression [40]. This wave of neural excitation, followed by a period of reduced activity, has been used to account for the visual fortification (or zig-zag) patterns, and subsequent scotoma, experienced during a visual aura, respectively. Reaction-diffusion models of cortical spreading depolarisation and depression have been used to show how these self-sustaining patterns of activity can occur [41]. In these models, networks of neurons become susceptible to hallucinations through the balance of their excitatory and inhibitory interconnections (see [42] for a detailed review). An initial, localised occurrence of high activity is also required to trigger the spreading depolarisation. Increased levels of internal noise (additive or multiplicative) [18], or an increased gain on the responses to external stimuli [7,22] could both contribute to a greater susceptibility to the triggering of cortical spreading depolarisation and depression.

In summary, those with migraine aura have tended to show heightened sensitivity to visual stimuli [7], but poorer performance on contrast detection tasks, possibly due to an increased variability in neuronal responses to a stimulus (multiplicative internal noise) [18]. It could be the case that, while the increased levels of excitation result in greater overall activity, not all of this activity is specific to the stimulus. Such an increase in both signal and noise levels could reconcile the hyperexcitability found in migraine with aura with the fact that this does not lead to increased contrast sensitivity [7,22], but does predispose to visual aura.

1.5. Spatial Frequency—Which Spatial Scales of Processing Are Affected?

The spatial scale at which potential deficits in contrast sensitivity occur has not been the focus of much of the previous literature, with many studies using only one spatial frequency, e.g., [25–28].Where this has been looked at in detail [30], one study found that reduced contrast sensitivity in migraine with aura for static stimuli viewed at relatively high (photopic) luminance levels was confined to lower spatial frequencies, below 4 cycles/degree, and not found for spatial frequencies above this. Another study found reduced contrast sensitivity for all spatial frequencies between 1.5 and 18 cycles/degree [31] in migraine (not specifically migraine with aura). The work of Wagner et al. [18] and webster et al. [39], showing deficits in sensitivity only at high noise levels, used disc stimuli. These are low-pass (containing predominantly low spatial frequencies) but spatially localised (since small stimuli were used), and so are not well-suited to scale-space analysis. Therefore, in the current experiment, we used large, narrow band stimuli, with low and

high spatial frequencies, in order to assess whether these noise-masking differences in contrast sensitivity occur for both coarse scale and fine scale mechanisms, respectively. In these stimuli, contrast energy is concentrated narrowly around a specific spatial frequency peak (Figure 1). Since contrast sensitivity across the visual field may be patchy, and associated especially with more peripheral vision [36,37], large stimuli were used. This also had the desirable effect of creating stimuli with a narrow spatial frequency bandwidth.

Analysis of the effects of spatial scale on contrast sensitivity can also, in some circumstances, be used to identify which visual pathways might be responsible for any deficits in processing. There are predominantly two visual areas responsible for the early encoding of visual information, processing information at different spatial scales. Around threshold levels of contrast, the magnocellular pathway is predominantly sensitive to coarse scale, low spatial frequencies below 1.5 cycles/degree. In contrast, the parvocellular system is predominantly sensitive to fine-grained information at spatial frequencies above this value [43–45]. Several authors have suggested that low-contrast stimuli favour the magnocellular pathway [46,47], based on single-cell recordings [48]. Other studies however have shown similar losses in contrast sensitivity in animal models for parvocellular lesions compared to magnocellular lesions [49], and that stimulus contrasts needed to elicit responses are similar for M and P cells in the owl monkey, but saturation levels are different [50].

By choosing appropriate stimuli, scale-space analysis can be used to some extent to investigate which of these two main pathways is the more affected. Although there are some reports of deficits in contrast sensitivity restricted to low spatial frequencies [30], consistent with a greater influence of the magnocelluar pathway, other studies have suggested that these effects occur at a range of frequencies [31], and are not associated exclusively with the magnocellular pathway [37]. The isolation of magnocellular from parvocellular processing using psychophysical techniques is difficult to achieve using only a single stimulus dimension, as in the current study, requiring the use of stimuli with a low spatial frequency, high temporal frequency, low contrast, low (scotopic) luminance, and adaptation to this luminance level [51]. The motivation for including spatial frequency in the current study was to assess how this affected contrast sensitivity and masking differences in migraine with aura [18,30,31,39], rather than specifically to assess the contributions of magnocellular and parvocelluar pathways to these effects.

1.6. The Current Study

Knowing the spatial scale at which any potential deficits occur is important for our understanding of the mechanisms involved in these differences. However, only one prior study has assessed this comprehensively, and this was for a mixed group of participants with and without aura [31]. Therefore, the aim of this study was to assess differences in contrast sensitivity at different masking noise levels, at low and high spatial frequencies exclusively in people with migraine with aura. To do this, contrast sensitivity was estimated at different noise levels for low and high spatial frequency sinusoidal grating stimuli. In line with previous research [18,52], we predict that deficits will only be found at high noise levels, not low noise levels. Since deficits in contrast sensitivity do not appear to be associated with a particular visual processing stream [37], we predict that these deficits could be for either fine, or coarse spatial scale, or both.

2. Methods

2.1. Participants

A total of 39 observers were tested. The categorisation of observers into groups was undertaken using the criteria of the Headache Classification Subcommittee of the International Headache Society [5]. All observers completed the experiment regardless of group. However, only data from individuals in the control or with aura group were included [17–19].

All observers were screened using a questionnaire by the experimenters (JA or PH). All observers had normal or corrected to normal vision. Inclusion as a control observer

required no history of severe headaches, migraine, or aura. Migraine observers were tested interictally and were required to be free from migraine for 3 days either side of the day of testing. The data for 3 migraine observers were excluded as a result of experiencing an attack within 3 days of their testing day. After the classification process, there were 17 controls (9 females, mean age of 23.5 years) and 14 with migraine with aura (7 females, mean age of 31.7 years; see Table 1); 5 observers were excluded after being assessed as either migraine without aura, non-headache-free controls or migraine with aura not meeting inclusion criteria. No observers used prophylactic medication for migraine, and no observers were taking any substance that would affect cognition or perception. All experiments were conducted in accordance with the World Medical Association Declaration of Helsinki (2013) and were approved by the University of Essex ethics committee. All observers gave written, informed consent and received payment or course credit for their participation.

Table 1. Migraine with aura observers' reports of clinical features.

Observer	Sex	Age	Frequency (Per Month)	Duration (Years)	Prior Attack
OB4	M	22	1–3	7	8 days
OB7	F	20	1–3	12	>3 days
OB8	M	29	<1	6	3 weeks
OB10	M	20	1–3	5	1 week
OB14	M	20	<1	2	>3 days
OB18	M	24	1–3	6	>3 days
OB20	M	62	<1	3	2 months
OB21	F	40	1–3	15	1 month
OB22	F	50	3–10	37	10 days
OB26	F	19	<1	9	>3 days
OB35	M	22	1–3	8	>3 days
OB40	F	31	1–3	21	>3 days
OB41	F	59	3–10	44	4 days
OB42	F	26	1–3	16	1 month

2.2. Apparatus

Stimuli were presented using a Sony Trinitron 2100 monitor with a screen resolution of 1280 × 1024 pixels and a vertical refresh rate of 100 Hz. The luminance response of the monitor was measured and calibrated using a Minolta LS-110 photometer. The luminance of the mid-grey background was 38.5 cdm^2 and the maximum luminance of the monitor was 74 cdm^{-2}. One pixel subtended 1.47 arc min. A Datapixx CRT Driver (Vpixx Technologies, Saint-Bruno, QC, Canada) was used to achieve 16-bit control of contrast levels. Stimuli were generated and presented using MATLAB and the Psychophysics Toolbox extensions [53–55]. Responses were made via the left and right arrow keys on a standard keyboard.

2.3. Stimuli

Stimuli were presented on a mid-grey background. The target stimuli were centrally presented sinusoidal gratings, with a spatial frequency of 2 or 8 cycles per degree, windowed with a circular aperture with a radius of 9 degrees, tapered with a Gaussian with a standard deviation of 0.98 degrees. The contrast of the target was manipulated: there were 10 contrast levels (0.05%, 0.01%, 0.02%, 0.3%, 0.45%, 0.5% , 0.75%, 1%, 2%, and 5% Michelson contrast). Each grating was presented at an orientation of ±45° from vertical, randomly selected with equal probability on each trial. In separate blocks of trials, static Gaussian white luminance noise with a standard deviation of 0. 3.5, 7.0, or 14.5 cdm^{-2} was used to mask the stimuli. This Gaussian noise was also tapered with the same window as the target stimulus.

2.4. Procedure

Observers were positioned at a viewing distance of 60 cm from the display, using a chin rest for support. The task consisted of a two-alternative-forced-choice (2AFC) procedure to report the orientation of the target grating. A central fixation cross was presented throughout the experiment. The stimulus, consisting of the target and mask, was presented for 360 ms. At the end of this time it was replaced by a blank grey screen and fixation cross while the participant responded. Participants completed either the 2 cycles/degree or 8 cycles/degree stimuli first, in random order. For each frequency, trials were blocked by noise level, and the order of presentation of these four blocks was also randomised. With each block, each of the 10 contrast levels was presented 20 times, given 200 trials per block. The order or presentation of these trials was randomised.

3. Results

The current study investigated the effect of increasing stimulus noise in contrast detection for a migraine with aura group in comparison with a control group. This was conducted both for low and high spatial frequency stimuli. For each contrast level in each condition, the percent correct was converted to $d^{'}$, as a measure of each observer's sensitivity to that stimulus (Figure 2). A 4-way, group × luminance contrast × noise level × spatial frequency, ANOVA was used to assess how sensitivity was affected by each of these factors. There was no main effect of group ($F(1,29) = 1.605$, $p = 0.216$, partial $\eta^2 = 0.052$), meaning that overall there was no difference in sensitivity between people with migraine with aura and the control group. There was a main effect of contrast ($F(9,261) = 343.1$, $p < 0.001$, partial $\eta^2 = 0.922$) reflecting the increase in correct responses with increasing stimulus contrast. There was a significant main effect of spatial frequency ($F(1,29) = 524.0$, $p < 0.001$, partial $\eta^2 = 0.948$), and a significant frequency-by-contrast interaction ($F(9,261) = 62.40$, $p < 0.001$, partial $\eta^2 = 0.683$), reflecting greater sensitivity to the lower spatial frequency. There was also a significant effect of noise ($F(3,87) = 106.9$, $p < 0.001$, partial $\eta^2 = 0.787$) and a significant noise-by-contrast interaction ($F(27,783) = 16.728$, $p < 0.001$, partial $\eta^2 = 0.366$), reflecting the reduction in correct responses with increasing noise level. A significant frequency-by-noise level interaction ($F(3,87) = 10.28$, $p < 0.001$, partial $\eta^2 = 0.262$) indicated a greater effect of noise at the higher spatial frequency.

There was a significant group-by-noise level interaction ($F(3,87) = 2.751$, $p = 0.047$, partial $\eta^2 = 0.087$). Sensitivity was greater in the migraine with aura group at the higher noise levels, but not at the lowest noise level. The group-by-contrast ($F(2,261) = 1.564$, $p = 0.126$, partial $\eta^2 = 0.051$) and group-by-frequency ($F(1,29) = 0.891$, $p = 0.353$, partial $\eta^2 = 0.030$) interactions were not significant.

There was a significant frequency-by-noise-by-contrast interaction ($F(27,783) = 21.97$, $p < 0.001$, partial $\eta^2 = 0.420$). The three-way interactions did not, however, indicate any differences between the two groups, since none of the group-by-frequency-by-contrast ($F(9,261) = 1.55$, $p = 0.131$, partial $\eta^2 = 0.051$), group-by-frequency-by-noise ($F(3,87) = 0.778$, $p = 0.510$, partial $\eta^2 = 0.026$) and group-by-noise-by-contrast ($F(27,783) = 0.685$, $p = 0.765$, partial $\eta^2 = 0.023$) interactions was not significant. The four-way group-by-frequency-by-noise-by-contrast interaction was also not significant ($F(27,783) = 1.401$, $p = 0.087$, partial $\eta^2 = 0.046$).

The contribution of migraine duration to noise-masked contrast detection in the migraine group was assessed using using a 3-way ANOVA (luminance contrast × noise level × spatial frequency) with migraine duration as a covariate. There was no significant main effect of duration ($F(1,12) = 0.625$, $p = 0.444$, partial $\eta^2 = 0.050$) and no significant 2-way, 3-way, or 4-way interactions between duration and frequency, noise or contrast.

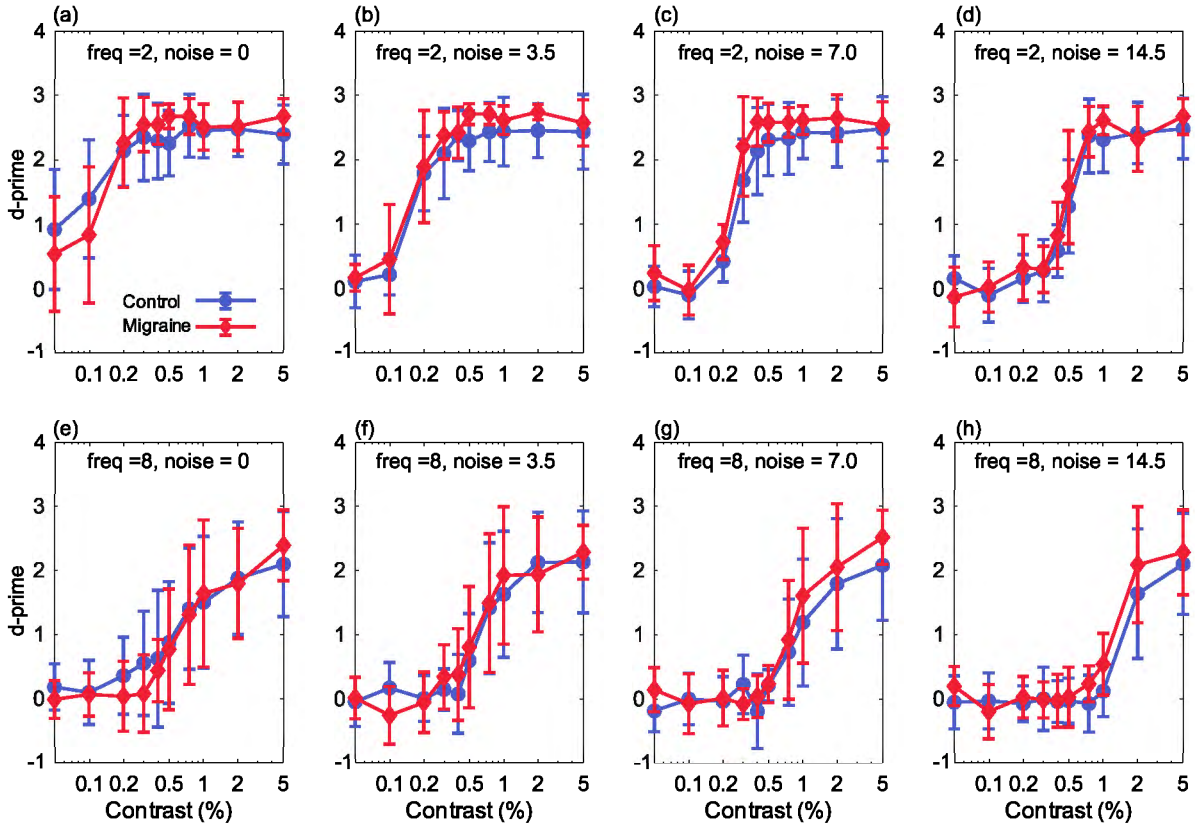

Figure 2. The results showing percentage Michelson contrast, spatial frequency against d' (sensitivity) for the 2 cpd stimuli (top row) and the 8 cpd stimuli (bottom row), for increasing levels of Gaussian noise (n): (**a**,**e**) 0 noise (sigma of the Gaussian function = 0), (**b**,**f**) sigma is 3.5, (**c**,**g**) sigma is 7, (**d**,**h**) sigma is 14.5. Error bars show ±1 standard deviation.

To assess any differences in effects across scale, for each spatial frequency, d' values were analysed using a 3-way contrast × noise × participant group mixed design ANOVA.

For the 2 cycles/degree stimuli, there was a main effect of contrast ($F(9,261) = 423.9$, $p < 0.001$, partial $\eta^2 = 0.936$), reflecting the increase in correct responses with increasing stimulus contrast. There was also a significant effect of noise ($F(3,87) = 119.4$, $p < 0.001$, partial $\eta^2 = 0.805$) and a significant noise-by-contrast interaction ($F(27,783) = 28.73$, $p < 0.001$, partial $\eta^2 = 0.498$), reflecting the reduction in correct responses with increasing noise level. A significant main effect of group ($F(1,29) = 5.21$, $p = 0.030$, partial $\eta^2 = 0.152$) and a significant group-by-contrast interaction ($F(9,261) = 2.40$, $p = 0.012$, partial $\eta^2 = 0.077$) were found, reflecting better overall performance in the migraine with aura group in comparison with the control group. The noise-by-group ($F(3,87) = 1.63$, $p = 0.189$, partial $\eta^2 = 0.053$) and noise-by-contrast-by-group ($F(27,783) = 1.10$, $p = 0.331$, partial $\eta^2 = 0.037$) interactions were not significant.

For the 8 cycles/degree stimuli, there was a main effect of contrast ($F(9,261) = 136.4$, $p < 0.001$, partial $\eta^2 = 0.825$), again reflecting the increase in correct responses with increasing stimulus contrast. There was a significant effect of noise ($F(3,87) = 22.8$, $p < 0.001$, partial $\eta^2 = 0.440$) and a significant noise-by-contrast interaction ($F(27,783) = 9.88$, $p < 0.001$, partial $\eta^2 = 0.254$), reflecting the reduction in correct responses with increasing noise level. For this spatial frequency, there was not a significant main effect of group ($F(1,29) = 0.302$, $p = 0.587$, partial $\eta^2 = 0.010$) or a significant group-by-contrast ($F(9,261) = 1.249$, $p = 0.265$, partial $\eta^2 = 0.041$) or group-by-noise ($F(3,87) = 1.90$, $p = 0.135$, $\eta^2 = 0.062$) interaction. The noise-by-contrast-by-group ($F(27,783) = 1.05$, $p = 0.402$, partial $\eta^2 = 0.035$) interaction was also not significant.

Performance was overall very similar between the two groups, and we did not find the expected reduction in sensitivity in the migraine with aura group at higher levels of noise. Performance was in fact slightly better in the migraine with aura group for low spatial frequency stimuli, although this difference was very small, as can be seen in Figure 2 (top row). The manipulations of the stimulus variables of contrast and noise level produced larger effect sizes (partial η^2 around 0.5 or above) than the group differences for the low spatial frequency stimuli (partial η^2 around 0.15 or below). On average, across all conditions, the increase in d' value in the migraine with aura group for low spatial frequency stimuli, relative to the control group, was 0.155 (0.209).

4. Discussion

This study aimed to investigate contrast sensitivity under varying noise conditions in those with migraine with aura for two spatial frequencies, allowing for scale-space analysis. For the low spatial frequency stimuli, there was better performance in the migraine with aura group compared to the control group, for the higher levels of stimulus contrast. There were no differential effects of noise between groups. There were no group main effects or interactions for the high spatial frequencies.

4.1. Interpreting the Contrast Response Functions

The firing rate of each neuron depends on the contrast of the stimulus, where the firing rate increases above baseline as contrast increases and saturates as contrast intensifies. Plotting these responses typically shows a sigmoidal shape [56,57]. The contrast response function (CRF) illustrates the effect of contrast in visual processing. It has been suggested that detection of contrast can be improved by "raised attention" which increases the effective contrast. Based on the single cell recordings two models have been proposed to describe how attention and perception interact to improve contrast detection [58], *contrast gain* and *response gain*. Contrast gain is characterised by a shift in the psychometric function that is interpreted as a change to the threshold, where the threshold describes a response accuracy at chance level [59]. When directing attention to a specific location, sensitivity at that location is increased. Directed attention increases responses at low contrasts more than high contrasts [60]. This is consistent with an increase in physical or effective contrast, where performance saturates at higher contrast, and corresponds to the multiplication of contrast required to reach threshold. Response gain models predict that attention multiplies a neuron's firing rate by a constant gain factor, whereby stimuli with increasing contrast will show an additive increase in firing rate [59,60] and are are characterised by a change in the slope and upper asymptote of the psychometric function [59].

The responses to increasing noise levels in the current study show a rightward shift in the CSF, (see Figure 3), indicative of reduced effective contrast, particularly for low spatial frequencies. There was no notable change to the slope or shift of the curve between migraine and control groups. While responses to high spatial frequency targets also display a tendency towards a rightward shift with increasing noise these were less pronounced than at low spatial frequencies.

Differences in sensitivity in migraine have been interpreted in previous studies using the perceptual template model [61]. This takes account of the efficiency of encoding, and the effects of additive and multiplicative noise on sensitivity. Changes in these parameters affect the slope of the psychometric function. Previous studies have focused not on the shape of the psychometric function, but on changes in threshold, and found that thresholds tended to increase only at high external noise levels [18,39]. In contrast, we found that the performance of control and migraine with aura groups was similar across all noise levels.

In general the slope of the curve was lower for high spatial frequency conditions (compared to low spatial frequency) with poorer performance at baseline (lower asymptote) as noise increased, possibly indicating reduced response gain [58]. Response gain has been linked to an overall increase in firing rate [59], suggesting the units are simply responding

more overall for high spatial frequency targets with increasing external noise. However, again, these were similar across migraine and control groups.

To summarise, for low spatial frequency targets, there appears to be a multiplicative reduction in effective contrast at threshold as noise increases in both migraine and control groups. Contrary to previous work [18,19,39], there was no evidence of increased multiplicative internal noise in migraine compared to control groups in the current study. For high spatial frequencies, increasing noise slightly reduced effective contrast at threshold. However, there appears to primarily be reduced performance at baseline, increasing the contrast required at the lower asymptote. This could be indicative of increased response gain, which is linked to overall increase in overall firing rate [59]. However, once again, there is no evidence of a difference between those with migraine aura and controls.

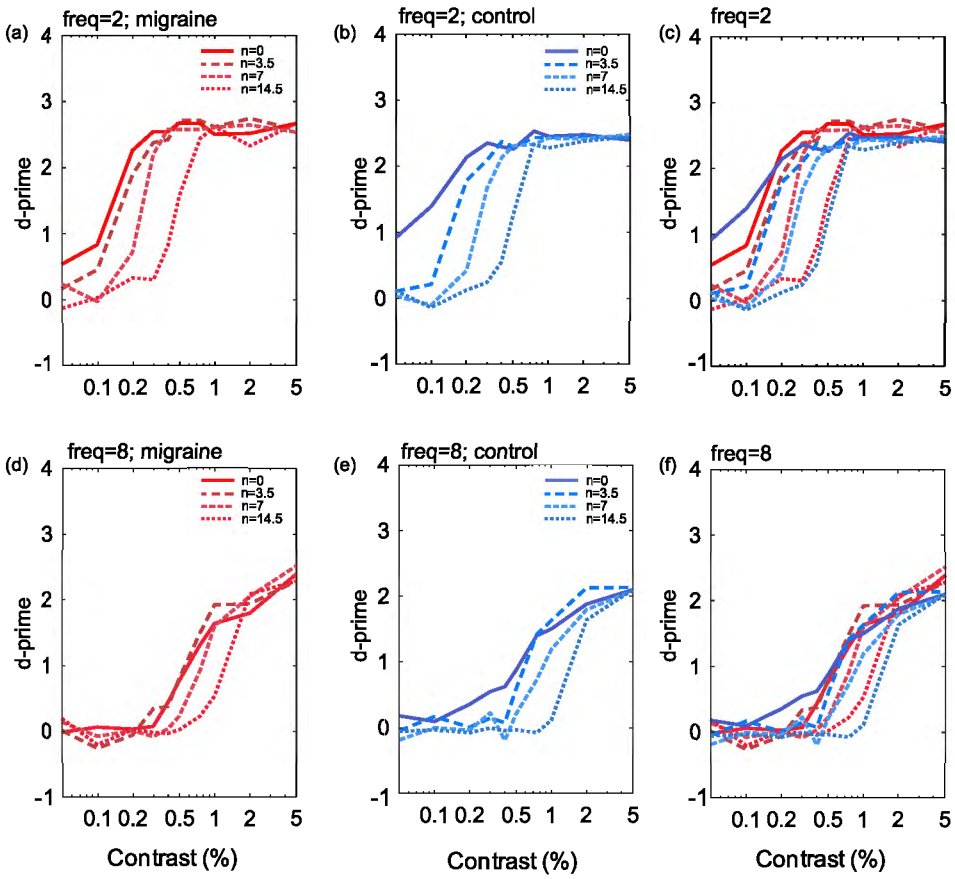

Figure 3. The results showing percentage Michelson contrast spatial frequency against d' (sensitivity) for the 2 cpd stimuli (**a**–**c**) and the 8 cpd stimuli (**d**–**f**). Noise is plotted for each of the four levels independently for control (**b**,**e**) and migraine groups (**a**,**d**) and finally combined groups (**c**,**f**) by frequency.

4.2. Effects of Increasing Noise Levels

The low spatial frequency effect suggests that the differences in contrast sensitivity are more consistent with the contribution of the magnocellular system rather than the parvocellular system. However, these stimuli will not necessarily *isolate* the two pathways, but bias towards the favoured one [45]. The magnocellular system favours the lower spatial frequencies, and is thought to have a dominant role in processing transient visual stimuli. This might explain findings that those with migraine show increased performance for detecting briefly presented stimuli [62]. This is speculative, as in the current study all stimuli were presented at much longer intervals, and had a broader temporal frequency spectrum, than those required to see the benefit of briefly presented stimuli. To attempt to isolate the transient system, narrowband stimuli, and masks, with low spatial frequency, high

temporal frequency, presented at scotopic luminance levels could be used [44,45,51,63,64]. This was beyond the scope of the current study, which focused on understanding how differences in contrast sensitivity in migraine with aura are influenced by spatial frequency and masking noise.

There was no differential group effect of increasing noise levels. It was expected that those with migraine with aura would show poorer contrast sensitivity at high noise levels, in line with previous research [18,52]. This was not found to be the case; our results do not show any evidence of increased additive or multiplicative internal noise in those with migraine aura on a contrast sensitivity task. This could be due to the choice of noise mask.

It is possible to measure internal noise using equivalent noise paradigms, which allow for estimations of internal noise, as well as the impact of adding external noise to the stimulus [65]. Performance at low noise levels is limited by the internal noise in the system itself, and the sampling efficiency. At high noise levels, the externally-added noise is much greater than the internal noise, rendering its effect negligible. The linear amplifier model (LAM) is one of the most straightforward ways of thinking about equivalent noise tasks. This model estimates the observer response as a linear combination of the contrast of the target, the noise internal to the system, and the noise associated with the target. The linear amplifier model assumes a linear response to increasing noise, which is not the case in contrast sensitivity tasks. In order to overcome this, a non-linear model can be fitted, with a gain control term. When using this non-linear model, it is not then possible to differentiate internal noise estimates from this gain control parameter. Therefore Baldwin et al. [66] suggested that pedestal noise masks could actually confound non-linear responses to the noise, from sources such as cross-channel suppression, rather than allowing for the estimation of internal noise. In the case of contrast sensitivity, a "zero-dimensional" noise mask can be added, instead of pedestal noise levels [67]. The "zero-dimensional noise" mask consists of contrast jitter of the target itself, rather than overlaying a separate white noise mask. By using the contrast jitter mask, rather than a pedestal mask, the possibility on non-linear effects of the mask can be differentiated, as it will limit effects such as cross-channel suppression.

The equivalent noise paradigm has been used in those with migraine, however this showed no differences in threshold performance between those with migraine and those without [68]. However, this was a mixed migraine group, rather than a purely migraine with aura group. The equivalent noise paradigm has also been applied by Tibber et al. [23] using a staircase method in the dimensions of motion, orientation, and size perception. They found a trend towards increased internal noise for motion perception in those with migraine, which was not statistically significant when corrected for multiple comparisons [23]. For motion, the high noise was added by changing the standard deviation of the dot trajectories, rather than adding additional "noise dots". Again, the participants in this study were a mixed migraine group. It is possible that internal noise differences are specific to those experiencing migraine with aura, and so it would be good for future research to investigate this in an exclusively migraine with aura sample.

4.3. Migraine Duration

One reason for the lack of effects could be the duration of the migraine history of the participants. It is important to note that those with migraine with aura do not always show evidence of increased cortical excitability. Afra et al. [69] did not show a difference in baseline VEP (visually evoked potential) amplitude, although there was a facilitation of the response with repeating blocks of visual stimulation. Khalil et al. [8,70] found increased VEP amplitude, but only in those who had experienced migraine with aura for less than 10 years; those experiencing migraine with aura for longer than this showed a *reduced to normal* VEP amplitude. Khalil et al. [28] reported reduced contrast sensitivity, as well as P100 response amplitude (the positive peak in VEP at 100 ms) to 4 cpd gratings in those with migraine aura, and this related to the length of time the person had experienced migraine (accounting for age). The implication of these findings are that long-term repeated

attacks may result in structural damage in the neural tissue that normalise the amplitude of the P100 response. Tibber et al. [32]'s participants had experienced migraine for around 15 years on average, which might explain the lack of findings. The participants in our study had experienced migraine with aura for between 2 and 44 years, with an average duration of around 14 years. 6 out of the 14 migraine participants had experienced migraine for more than 10 years, this may have diluted any effect. However, our analysis albeit with a small sample size, suggest there was no effect of migraine duration on contrast sensitivity.

4.4. Conclusions

In this study, we assessed whether contrast sensitivity deficits in migraine with aura would be evident only at high levels of external noise, and whether any such effects are influenced by the spatial frequency of the target stimuli. We conclude, however, that such estimates of contrast sensitivity using traditional stimuli and noise masks in those with migraine aura may not be the best tool to identify sensory processing differences between groups. Although contrast sensitivity provides an overall measure of visual sensitivity, there are many facets to the potential differences in people with or without aura that it is unable to capture. This is likely to account for the fact that previous findings are not robust [22], with some studies showing impaired contrast sensitivity [18,25,27,30,31,37,71,72], and others [15,32–34,39,73] showing no such deficits.

Contrast sensitivity is one of the most basic visual functions. It may be the case that differences in migraine aura are due to more complex mechanisms. For example, visual processing deficits across a range of conditions have been particularly associated with the dorsal processing stream [74], which depends on dynamic, low-frequency information. However, stimuli intended to isolate this "magnocellular function" are not precise in restricting processing to this channel [75]. Robust findings have tended to be for global motion stimuli (see [22] for a review), processed at higher stages of visual processing such as cortical area V5/MT [76]. This suggests that at this global stage of processing, rather than the earlier, local encoding stages assessed by contrast sensitivity measures, that will provide a clearer understanding of sensory differences in migraine. These studies have also suggested that differences might be particularly associated with a reduced ability to exclude noise [23], and that this might also be associated with an increased gain in response to external stimuli [7,22]. The use of zero-dimensional noise stimuli, rather than traditional contrast pedestals and noise masks, is better able to provide reliable measures of sensory noise and non-linear transduction of stimuli. Additive noise masks may invite other processes, such as cross-channel suppression [66], which may also differ in migraine.

The characteristics of individual participants, their long-term and short-term history of migraine and their migraine subtype are important considerations. Visual processing differences in migraine with aura are not necessarily shared by those without aura, for example [18]. Where differences are observed, they may be influenced by the length of time for which an individual has experienced migraine [70], and vary across the migraine cycle [77,78]. Together, these considerations suggest that measures of contrast sensitivity, at a single point in time, may not provide the most diagnostic assessment of sensory processing in migraine, and may account for the heterogeneous results that have been reported from such measures.

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Informed Consent Statement: All observers gave written, informed consent and received payment for their participation.

Data Availability Statement: The data that support the findings of this study are openly available at https://osf.iokeajc/, accessed on 17 June 2021.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

cpd	cycles per degree
CRF	Contrast Response Function
EEG	Electroencephalogram
LAM	Linear Amplifier Model
VEP	Visual Evoked Potential

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ORIGINAL ARTICLE

Ocular morbidity on headache ruled out of systemic causes—A prevalence study carried out at a community based hospital in Nepal

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KEYWORDS
Binocular vision anomalies;
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Abstract
Purpose: The association between ophthalmic anomalies and headache still needs to be investigated largely. We aimed to look for it in the context of a rural community hospital of Nepal.
Methods: Hundred patients with headache were investigated for ophthalmic anomalies after the probable systemic association was ruled out. All the patients were first examined by general physician, otorhinolaryngologist and psychiatrist. Ocular evaluation consisted of detailed refractive, binocularity assessment and anterior and posterior segment examination. Data were analyzed using *t*-test, chi-square test, multiple logistic regression, odds ratio as well as frequency and percentages.
Results: Female above the age of 17 suffered more ($p < 0.05$). Frontal headache was more common than occipital ($p > 0.05$). In students and housewives frontal headache was more common (OR 3.467, 0.848–14.174; 95% CI and 1.167, 0.303–4.499; 95% CI). Refractive error was associated with frontal headache (OR, 1.429, 1.130–0.806, 95% CI). On presentation, 88% had visual acuity 6/9 or better. Forty-four percent had refractive error among whom astigmatism was more frequent (63.63%) followed by hyperopia (27.27%) and myopia (9.09%). Known eye problems were significantly associated with refractive error and binocular vision anomalies ($p < 0.001$). Convergence insufficiency (16.25%) and fusional vergence (11.25%) deficiencies were common among unstable binocularity.
Conclusion: Ocular anomalies co-exist with headache complains very frequently. Refractive and binocular vision anomalies need to be largely investigated in all headache patients. It is important to get a good headache history so that patients can be referred to the appropriate specialist.

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PALABRAS CLAVE
Anomalías de visión binocular;
Insuficiencia de convergencia;
Cefalea;
Errores de refracción

Morbilidad ocular sobre cefalea descartada entre las causas sistémicas: estudio de prevalencia llevado a cabo en un hospital de una comunidad en Nepal

Resumen
Objetivo: La asociación entre anomalías oftálmicas y cefalea todavía debe investigarse a fondo. Nuestro objetivo fue examinarlo en el contexto de un hospital de una comunidad rural de Nepal.
Métodos: Se examinaron cien pacientes con cefalea en busca de anomalías oftálmicas una vez descartada una posible asociación sistémica. Todos los pacientes fueron explorados por un médico general, un otorrinolaringólogo y un psiquiatra. La evaluación ocular consistió en un examen detallado refractivo de la binocularidad y un examen del segmento anterior y posterior. Los datos se analizaron utilizando la prueba de la t, la prueba de la χ^2 al cuadrado, regresión logística múltiple, razón de probabilidades, así como frecuencia y porcentajes.
Resultados: Las mujeres mayores de 17 años sufrieron más ($p < 0,05$). La cefalea frontal fue más frecuente que la occipital ($p > 0,05$). En estudiantes y amas de casa fue más frecuente la cefalea frontal (OR 3,467, 0,848 - 14,174; IC del 95% y 1,167, 0,303 - 4,499; IC del 95%). El error de refracción se asoció con cefalea frontal (OR, 1,429, 1,130-0,806, IC del 95%). En la presentación, el 88% tenían una agudeza visual de 6/9 o mejor. Un 40% presentaron errores de refracción, entre los cuales el más frecuente fue astigmatismo (63,63%), hipermetropía (27,27%) y miopía (9,09%). Los problemas oculares conocidos se asociaron de manera significativa con error de refracción y anomalías de visión binocular ($p < 0,001$). La insuficiencia de convergencia (16,25%) y los déficits de vergencia fusional (11,25%) fueron frecuentes en la visión binocular inestable.
Conclusión: Las anomalías oculares coexisten muy frecuentemente con casos de cefalea. Las anomalías de refracción y de visión binocular deben investigarse a fondo en todos los pacientes con cefalea. Es importante obtener buenos antecedentes de cefalea para poder remitir a los pacientes al especialista adecuado.

Introduction

Headache has been defined as the pain located above orbitomeatal line.[1] It is one of the frequent reasons to seek a consultation with health care practitioners.[2] It is a difficult condition to establish the actual cause. Diagnosis and treatment is often an impossible task without the correct views of etiology.[3]

Primary headache (headache without underlying disorders) prevalence varies with age, 9–11% in school children.[4] The preponderance of headache is higher in female. In more than 80% patients, headache starts before age 40 with a lower prevalence rate at an advanced age (>50 years).[5] Similarly, highly conflicting prevalence has been observed in different countries as 21.2% in the US,[6] 96% in Denmark,[7] and past-year prevalence ranges from 13.4% in the US,[6] to 87.3% in Canada.[8]

The evidence in the literature for a strong association between oculo-visual problems and headache is weak.[2] Still patients who believe that appropriate ocular examination and treatment help to lessen their headache visit optometrists' and ophthalmologists' very frequently.[8,9] Headache being one of the most common neurological symptoms has often been associated with Parkinson's disease, multiple sclerosis and myasthenia gravis. Nishimoto et al. revealed that in headache associated with myasthenia gravis, mild ocular symptoms are associated which range from slight degree of diplopia or ptosis which fluctuates dynamically and might lead to the worsening of headache.[10] Harle and Evans report that in migraine headache often binocular vision anomalies in the form of decompensated heterophoria and reduced stereopsis might be present in subtle form.[2]

Ophthalmological studies on headache have reported the role of different ocular diseases like acute glaucoma, uveitis, optic neuritis[11] and visual anomalies like refractive errors and accommodative and vergence deficiencies.[12] The uncorrected refractive errors are often believed to be associated with frontal and/or occipital headache.[13] Eye strain as a direct cause of headache has long been debated.[14,15] Very frequently a careful eye examination and a possible correction of the defect has been observed to reduce headache symptoms.[1] Thomas et al. noted that 21% of people with headache consult an eye care practitioner which is almost similar to those (27%) who seek a consultation with a general medical practitioner.[9] Whittington reported that among more than 1400 consecutive patients attending for refraction, 45% complained of headache.[16]

Patients who fail Sheard's criterion (Prism Fusional Vergence less than twice the near phoria) are expected to suffer from headache symptoms.[17] In 1966, Gordon et al.[18] claimed that minor refractive error (RE) often caused more headache and symptoms of eyestrain than major RE. Ciliary muscle strain has also been suggested as possible source of headache.[19] To the authors' knowledge, there has not been any reports on exploring the ophthalmic share of headache symptoms among the Nepalese people who present to a general hospital.

The aim of this study was to investigate whether reported headache complaints of patients attending the general ophthalmic clinic are associated with ophthalmic anomalies.

Methods

Patients

This study has a descriptive cross-sectional design. It was conducted in the Ophthalmology Department of Dhulikhel Hospital over a period of three months from March 2010. The hospital covers the rural population of approximately 1.9 million people from Kavrepalanchowk, Sindhu-palchowk, Dolakha, Sindhuli, Ramechhap, Bhaktapur and other surrounding districts. Hospital targets mainly the people with low socio-economic status who do not have access to the well facilitated health care services. It has provided services to 50 out of 75 districts of the country so far.[20]

We included only the patients with headache who were referred from the medical, otorhinolaringology (ENT) or psychiatry Out Patient Department (OPD). The diagnosis of primary headache was based on International Classification of Headache Disorders: 2nd edition (ICHD-II), based on physical and neurological examinations and head CT and/or MRI. Criteria for eye consultation were set as follows: all the patients needed to undergo thorough systemic evaluation with appropriate tests carried out. The appropriate investigation was ordered by the respective departments. The patients without definite diagnosis were then referred for eye examination. Only the patients with headache of more than three months duration were included in the study.

Each alternate patient complaining of headache (irrespective of nature/location/intensity) was included in the study with unrestricted random sampling method regardless of age, sex and referral. Alternate patients were chosen because it gave a plenty of time for the examination to be carried out in each patient in detail. Blood pressure was measured in each patient to look for undiagnosed hypertension. None of the patients had undiagnosed hypertension. Patients with other diagnosed systemic diseases such as migraine, sinusitis, and dental caries or women with menstrual migraine and/or women taking oral contraceptive pills were excluded from the study. Age groups of the patients were categorized as school children (<17 years), non-presbyopic adults (<40 years) and presbyopic adults (>40 years). This research was approved by the institutional research committee of Dhulikhel Hospital. The tenets of the Helsinki declaration were followed. Full informed consent was obtained and participants were able to abstain or withdraw from the research at any time without having to give a reason. No participants withdrew after they had arrived at the clinic. It was ensured that the clinician was masked about the identity of the patients with headache participating in the study and those excluded from the study, so that all the tests would be performed with equal emphasis to every patient.

Assessments

Headache questionnaires

The first part of the evaluation consisted of a structured interview conducted by one of the medical interns and utilizing a headache questionnaire. The questionnaires were based on an article ''How to take a history of head or facial pain'' by Blau.[21] The questionnaires surveyed demographic data (e.g. sex, age, and occupation), headache occurrence and characteristics, headache onset and timetable (categorized into morning, afternoon, evening, during the night, or none) and pain topography (categorized into back, front, left sided, right sided or diffuse). The presence or absence of accompanying symptoms (nausea, vomiting, photophobia, phonophobia) and visual aura were assayed, as were treatment patterns (non-pharmacological measures or medications or spectacles), the presence or absence of aggravating factors (including physical or visual effort), family history, history of trauma, dental caries, sinusitis, menstrual disturbances and oral contraceptive pills intake in females.

Patients were asked to estimate the average number of hours spent daily in visually straining tasks (e.g., reading, watching television, and working with a computer) and whether headaches accompanied those tasks.

Visual acuity assessment

Presenting visual acuity was measured for each eye and for both eyes together at distance (6 m) with internally illuminated Snellen's Chart. Near vision was recorded at a distance of 33 cm with good illumination with reduced Snellen's Chart.

Refractive assessment

Retinoscopy was done with a retinoscope at the working distance of 50 cm estimating refractive status of patients objectively, which was followed by subjective refraction in which the patient's response to the corrective lenses was assessed. Patients with dissimilar objective and subjective findings, fluctuating refractive status, below 15 years of age, and patients with binocular vision anomalies (BVA) underwent cycloplegic retinoscopy (1% cyclopentolate). In these patients subjective refraction was done after three days, when the cycloplegia effect dissapeared completely. Spherical and astigmatic deviations were measured to the nearest 0.50 D. Astigmatic axes were measured to the nearest five degrees, negative cylinders being used for all measurements. The degree of ametropia was stated as follows: patients with Spherical Equivalent Refractive Error (SERE) of -0.25 and +0.25 Dioptres (D) were considered as emmetropic, SERE > +0.50 D was considered as hyperopia and SERE > -0.50 D was considered as myopia. Astigmatism was defined as the cylindrical component of the refractive error more than 0.50 D. All examinations were carried out by the single observer (optometrist), who did not know the results of the headache questionnaire.

Binocular Vision Assessment (BVA)

Cover test was performed at a distance of 6 m and 40 cm with an opaque occluder. A small non-accommodative target was used to control accommodation. The type and direction of

heterophoria or heterotropia were recorded. Ocular motor functions were evaluated in six cardinal gazes. The Near Point of Convergence (NPC, which is the nearest distance from the eyes to which eyes can converge without experiencing diplopia or subjective discomfort) was assessed with a Royal Air Force (RAF) rule (an instrument used to measure NPC and accommodative amplitude). Amplitude of Accommodation (AA, it is the difference in the focus power of the eye while fixating from near to far) was measured in each eye separately and binocularly later with push up method. The first sustained blur was then noted (the carrier of the RAF rule which contains N series letter target is moved toward the patient resting the rule pad on cheeks. The patient is asked to state when letters become blurred; the first sustained blur is noted as the dioptric distance from the eye.).

Binocular Vision Assessment (BVA) except cover test was not carried out on presbyopes because they are assumed to demonstrate vergence dysfunction due to loss of accommodative convergence. Fusional reserves were measured with a vertical bar prism using an accommodative target. Distance divergent (base-in) followed by convergent (base-out) reserves were recorded as three values, the blur point, the break point, and the recovery point. Near base-in and base-out fusional reserves were recorded in the same way. Heterophoria was measured first, followed by divergence amplitudes and then convergence amplitudes so that each test did not have effect on other.

Other examinations

Slit lamp bimicroscopy and detailed fundus examination were carried out to rule out ocular pathology. Intraocular pressure was measured with Goldmann tonometer on all the patients. Patients whose diagnosis remained inconclusive on eye examination were referred to other departments such as medical, ENT or psychiatry as required and elicited by headache history for further investigation.[1]

Data analysis

For data analysis we included only the right eye in every patient when there were two readings for two eyes because findings in both the eyes of same individual are generally likely to be similar.[22] Statistical analysis was done by calculating *t*-test to compare the means of two groups, chi-square test for non parametric data, multiple logistic regression to explore relationship between headache and occupation, odds ratio to explore risk of headache site with refractive and binocularity status as well as frequency and percentage to estimate the prevalence. Statistical software 'Statistical Package for Social Sciences, version-11.5' was used to analyze data. Statistical significance was set at $p < 0.05$.

Results

Study population

A total of 100 patients with headache complaints participated in the study. Non-participation was due to severe headache while presenting to the OPD. Few patients were excluded because of the systemic diseases under investigation and which required simultaneous ocular consultation (like Hypertension, raised intracranial pressure, pregnancy induced migraine, suspected sinusitis, menstrual disturbances). Female gender predominated in the study (63%).

Table 1 Reported headache with age, sex and previous examination ($N = 100$).

Age group (years)	Sex (no.)		Previous examination (%)	
	Male	Female	Yes	No
<17	11	9	14	6
<40	18	42	33	22
>40	8	12	12	13
Total	37	63	59	41

Age distribution and previous eye examination

Most of the headache complaints were in non presbyopic adults with females' outnumbering males in each age category, except for school children (Table 1). Fifty-nine percent of the patients had previous eye examination among which 41% had ocular morbidities. Twenty-four patients (24%) had previous eye examination within six months. The female preponderance is not significant for the age below 17 years ($\chi^2_2 = 5.538$, $p = 0.063$) but it is highly significant for age above 17 years ($p = 0.026$).

Profile of headache

In 35% people headache lasted for one year. Some complained of long standing headache of more than one year even lasting up to nine years (one patient). The pattern of headache site with the occupation is presented in Table 2.

In multiple logistic regressions, we observed that the frontal and occipital headache is relatively determinant for both students and housewives (Table 3). It is seen that the unstructured odds ratio was significant with the occupations and site of headache but the *p* value is more than 0.05.

Previous eye examination was observed to be a risk factor both for refractive error; OR 1.213 (0.924–1.593, 95% CI) and binocular vision anomalies; OR 3.97 (0.111–1.417 in 95% CI). Six and seven patients each with RE complained of temporal and diffuse headache respectively. In four patients with BVA diffuse headache was present. Uncorrected RE was observed to be a risk factor for frontal headache (Table 4). None

Table 2 Percentages of reported site of headache complains with occupation ($N = 100$).

Occupation	Frontal	Occipital	Temporal	Diffuse	Total
Students	26	6	3	5	40
House wife	14	9	5	8	36
Others	9	5	4	6	24
Total	49	20	12	19	100

Table 3 Relation between occupation and site of headache (for most frequently observed values).

Occupation	Site of headache	Statistics		
		p value	Unstandardized coefficient	Odds ratio (95% CI)
Students	Frontal	0.084	1.243	3.467 (0.848–14.174)
	Occipital	0.670	0.365	1.440 (0.269–7.714)
	Temporal	0.914	−0.105	0.900 (0.133–6.080)
House wives	Frontal	0.823	0.154	1.167 (0.303–4.499)
	Occipital	0.699	0.300	1.350 (0.295–6.183)
	Temporal	0.940	−0.065	0.938 (0.173–5.070)

Table 4 Statistical relation between oculo-visual anomaly and reported site of headache. The statistics includes Pearson χ^2 tests and odds ratio with 95% confidence interval (CI).

Ocular anomaly	Site of headache			Statistics	
	Frontal	Occipital	Total	Odds ratio (95% CI)	*p*-Value
BVA	5	0	5	1.429 (1.130–1.806)	0.155
RE	22	9	31		

BVA, binocular vision anomalies; RE, refractive error.

of the patients had BVA leading to occipital and temporal headache.

Visual acuity and refractive examination

Most of the patients had normal to subnormal visual acuity (Table 5). Forty-four percent of the patients had refractive error. All of them were corrected with appropriate prescription which was evident through retinoscopy. Known eye problem was significantly associated with refractive error and BSV anomalies ($\chi^2_1 = 11.225$, $p = 0.001$). Eight early presbyopes were prescribed the near vision glasses.

Table 5 Summary table.

Ocular morbidity	Frequency (%)
Visual acuity	100 (100)
6/6–6/9	88 (88)
6/12–6/60	10 (10)
<6/60	2 (2)
Refractive error	44 (44.00)
Hyperopia	12 (27.27)
Myopia	4 (9.09)
Astigmatism	28 (63.63)
Binocular vision anomalies (non presbyopic, N = 80)	23 (28.75)
Convergence insufficiency	13 (16.25)
Poor fusional vergence	9 (11.25)
Intermittent exotropia	1 (1.25)
Others	7 (7)
CVS	5 (5)
Established glaucoma	1 (1)
Glaucoma suspect	1 (1)

Binocular Vision Assessment (BVA)

Orthoptic examination was carried out on 80 non-presbyopic patients (Table 5). Seventy-one patients had orthophoria; eight had exophoria with good recovery. Fusional vergence satisfying Sheard's criteria was measured in 71(89%).

Discussion

The prevalence of refractive errors (44%) in this group of this community was higher than that reported by different authors of other parts of the world. Cameron[23] estimated a low prevalence of refractive error related headache in a sample of 50 patients referred for ocular examination and Jain et al.[24] in an observational study conducted in India reported only 1.48% (of 202 patients) prevalence of refractive errors in headache patients. These discrepancies are from the patient enrolment. They have included every patient of headache without speciality consultation. We observed 28.75% patients with headache to have poor binocularity of which 16.25% (out of 80 non-presbyopic patients) had receded Near Point of Convergence. This prevalence of convergence insufficiency is less than that of Gupta et al.[25] in India (49%), Romania[26] (60.4%) and Patwardhan and Sharma[27] (71.4%) in India. These discrepancies might be because of the different working environments of the patients. Gordon[15] also cites poor binocular status as a potential source of headache. The literature also provides anecdotal support for the hypothesis that certain optometric anomalies, especially decompensated exophoria, may be prevalent in headache.[28] A large number of patients with BSV anomalies in our study might be correlated to these observations. Although these data imply that Nepalese people from rural areas have more ocular problems leading to headache, the differing prevalence of these morbidities in different countries must be accounted for economical and

psychological well being because these people might be exaggerating their headache symptoms. Moreover, these discrepancies could be because of the patient enrolment being very selective in our study where all the non ocular causes of headache were excluded. The higher proportion of people with previous eye examination in this study suggests that these people think that their eyes are culprit behind their headache. Our observations for the prevalence of headache in uncorrected refractive errors are in accordance with that of Gil-Gouveia and Martins.[14]

This study provides further evidence that headache is more common in female ($p > 0.001$) similar to observation noted by Hendricks et al.[29] We observed that every six patients out of ten have headache in the non-presbyopic adult group with females having more than two fold (2.33 fold) prevalence over male. Headache prevalence in this particular age group might be because of the psychological stress caused by educational pressures for career development, emotional factors and family conflicts. Female preponderance could be because of the culturally set factors and the effects of male dominated society which may lead to psychological stress.[30] Prevalence rate of headache has been observed to increase at the age of 13, particularly among girls because of puberty.[4] In our study, patients in the school age comprised of 20%. Headache in this age group could be because of home and school environment which puts pressure for better performance in the studies.

Some authors believe that spectacles for the correction of low degree of refractive errors is just a placebo[15] while others claim it to be an effective method to ameliorate headache symptoms.[29] Our results also suggest the claim that low degrees of refractive errors are associated with headache because 88% of these patients had been presenting visual acuity of 6/6 and 6/9. One hypothesis states that even the minor degree of astigmatic errors of refraction causes changes to visual perception that alter the hyperexcitability in the visual cortex of the brain of headache sufferers.[30] Astigmatic blur may exacerbate the perception of striped patterns which are thought to be important in the visual triggers of different types of headaches.[31] Another hypothesis could be the neurotic personality traits which mean that the patients with headache demand low degrees of refractive error correction.[32,33] It is possible that refractive error could have an association with headache having no impact on the severity but the uncorrected refractive error exacerbates the headache symptoms.[2] We have observed that the prevalence of astigmatism is higher than that of hyperopia and myopia (63.63%, 27.27% and 9.09%). Our study is in an agreement with that of Patwardhan and Sharma who claim the same trend in refractive error prevalence in headache patients.[27]

The prevalence of computer vision syndrome observed in our study (13%) is similar (9–12%) to that of the United States.[28] The patho-physiology of headache associated with prolonged VDU use resides within the ocular surface abnormalities, accommodative spasms, dry eyes and/or extra-ocular etiologies.[34]

The first limitation of our study is that our patients were recruited from a hospital outpatient clinic population with a small sample size, so these results may not be representative of the general population as a whole. Second, we did not perform visual field testing as all the patients were first examined by different category of medical specialists which examine headache patients and all the possible non ocular causes were ruled out. Visual field testing has a core role in the differentiation of ocular and non ocular headache which needs to be included among the wide range of ophthalmic tests. Third, the inadequate patient masking is the probable reason to reveal high prevalence of ocular morbidity. Our strong point is the very selective patient enrolment. We have excluded every headache with known etiology.

In conclusion, this study provides the evidence that ocular morbidities and headache symptoms are linked very frequently. Thorough refractive evaluation and binocularity evaluation are important in headache. It is important to get a good headache history so that patient can be referred to the appropriate specialist for the management of headache and hence live a better quality of life.

Conflicts of interests

None.

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Review Article

Persistent and Repetitive Visual Disturbances in Migraine: A Review

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Visual disturbances in migraineurs, such as visual aura, are typically episodic, that is, associated with the headache attack, and overlaid by head pain and other symptoms that impact the patient. In some patients, however, visual symptoms are dominant due to frequency (migraine aura status), duration (persistent migraine aura and other persistent positive visual phenomena), or complexity (visual snow syndrome). These syndromes are more rare and challenging to classify in clinical practice resulting in a lack of systematic studies on pathophysiology and treatment. We aim at describing clinical features and pathophysiological concepts of typical migraine aura with a focus on cortical spreading depression and differentiation from non-typical migraine aura. Additionally, we discuss nomenclature and the specifics of migraine aura status, persistent migraine aura, persistent positive visual phenomena, visual snow, and other migrainous visual disturbances. The term migraine with prolonged aura might be a useful bridge between typical aura and persistent aura. Further studies would be necessary to assess whether a return of the classification category eventually helps diagnosing or treating patients more effectively. A practical approach is presented to help the treating physician to assign the correct diagnosis and to choose a medication for treatment that has been successful in case reports of these rare but disabling conditions.

Key words: migraine aura, migraine aura status, cortical spreading depression, persistent migraine aura, visual snow, prolonged migraine aura

Abbreviations: BOLD blood oxygenation level dependent, CSD cortical spreading depression, ICHD International Classification of Headache Disorders, VS visual snow

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INTRODUCTION

Migraine is characterized by recurrent episodes of headache with specific features.[1] It is well known that migraine is associated with visual symptoms.

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Some of them are useful in making a diagnosis (photophobia), others enable sorting in to subgroups, notably migraine with aura.

The International Classification of Headache Disorders (ICHD) defines aura as reversible, focal neurological symptoms in association (prior or during) with – or even independent from – a migrainous headache that typically lasts less than 60 minutes.[1] In our own clinical experience, most visual symptoms of migraine patients can be dealt with using such a general approach since visual symptoms are short-lasting and overshadowed by the severity of headache and other associated symptoms such as nausea or movement sensitivity. However, a small proportion of patients are predominantly affected by visual symptoms that can be prolonged or even persistent. Recently, several studies have addressed patients with persistent visual symptoms in migraine mainly from a phenotypical or pathophysiological perspective with scarce data on treatment options.[2-7]

Here, we review the current literature on the severe forms of migraine aura[1] – including migraine aura status, prolonged and persistent migraine aura – as well as visual snow,[5] a condition that often occurs with comorbid migraine with aura and consists of a continuous TV-snow like visual disturbance in the entire visual field that comes along with persistent palinopsia, photophobia, impaired night vision as well as excessive floaters, and other entoptic phenomena. First, we discuss the hallmarks of typical migraine aura from a clinical and pathophysiological perspective. Second, we introduce the different temporal courses of visual aura (migraine aura status, prolonged aura, and persistent aura) with clinical data on treatment and prognosis. Third, the phenotype of visual snow syndrome will be described in detail and distinguished from persistent migraine aura. We finally aim at offering a practical approach to the clinician who sees patients with persistent visual problems allowing a correct diagnosis and some first treatment options. However, when not successful, patients should not be dismissed as malingerers but should be sent to headache centers that might offer research options to increase our understanding by offering systematic studies on these rare conditions.

METHODS

In September 2015, a literature search in PubMed was performed using the key words "migraine aura," "migraine with aura" combined with "visual" and words indicating information on the temporal course: "duration," "persistent," " prolonged," and "status." Further key words were "visual snow" and "static." Further, articles from the reference list of relevant articles were screened, and articles known to be relevant by the authors were considered. For migraine aura status, persistent or prolonged migraine aura and visual snow, case series or smaller studies were selected when describing symptoms, time course, or treatment. For episodic migraine aura, we aimed at describing the typical time course and therefore excluded single case reports or smaller case series. Further, we excluded hemiplegic migraine, migraine with brainstem aura, and retinal migraine.[1]

A limitation of this review is that it presents mainly case series of rare conditions thus not allowing to differentiate between natural course, placebo, and the true efficacy of treatment.

EPISODIC VISUAL DISTURBANCES IN MIGRAINE

Typical Migraine Aura.—Aura derives from the ancient Greek αὔρα, meaning "breeze, soft wind." Traditionally, it has been used for describing a distinct atmosphere or quality associated with something. For migraine, perceptions or symptoms registered in association, typically prior, to the headache itself could be sensed as the "atmosphere" around the most striking symptom. Based on this, it has been recognized for decades that the headache phase divides the entire migraine attack into 3 distinct phases, the most striking headache phase, the preceding prodromal phase, which includes both the premonitory and, in those who get it, the aura phase, and the solely headache-free postdromal phase.[8] When viewed from a distant perspective, the broad Greek meaning of "breeze" summarizes probably all abnormalities realized by patients before the beginning of head pain, although the term has evolved to mean much less. A reasonable division that will be

used in the following paragraphs is the distinction between premonitory symptoms, typical migraine aura and other symptoms.

Most patients can predict the onset of their migraine headache.[9] However, it is unlikely that patients therefore suffer from migraine with aura. It is much more likely that patients have some premonitory symptoms, which are present in nearly 80% of patients.[9,10] Despite the recognition of these symptoms over some decades, little is known about the pathophysiology of the earliest phase of the migraine attack. Consistent with the symptoms experienced by patients, such as tiredness, yawning, and thirst, functional neuroimaging has revealed hyperperfusion of the hypothalamus and periaqueductal gray during the premonitory phase suggesting diencephalic and/or mesencephalic origin.[11]

In contrast, typical migraine aura is striking in its clinical presentation and has been subject to continuing efforts in respect of clinical phenotyping and pathophysiological research. The International Classification of Headache Disorders (beta version of the third edition, ICHD-3-beta) summarizes: Typical aura consists of "visual and/or sensory and/or speech/language symptoms ... and is characterized by gradual development, duration of each symptom no longer than 1 hour, a mix of positive and negative features, and complete reversibility."[1] In other words, these criteria require highly specific values of the following parameters: (i) neurological symptoms affecting vision, sensory, and/or language, (ii) dynamics involving development (spreading, succession) and duration (5–60 min), (iii) unilaterality, and (iv) association with headache. Importantly, as not all polythetic criteria are required, yet the mention of each one offers its face-valid importance to clinicians and illustrates an important teaching and clinical practice issue of the use of the criteria.

Typical Migraine Aura and Cortical Spreading Depression.—One of the main features, which differentiates typical visual aura from other transient neurological conditions such as transient ischemic attack or an epileptic seizure, is the slow progression of symptoms. This character is unique to migraine aura and might be important to understand the basis of migraine aura pathophysiology. Liveing suggested in 1873 a "nerve storm" was responsible for the symptoms.[12] Lashley was able to map his aura retinotopically and concluded that the symptomatology reflected a cortical process progressing with a speed of 3 mm/minute across the primary visual cortex.[13] In 1944, the Brazilian neurophysiologist Leão identified a wave of inhibition in the electrocorticogram of rabbits spreading at a rate of 2–3 mm/min centrifugally from an electrode of stimulation.[14] He called this phenomenon cortical spreading depression (CSD) and commented on its similarity to migraine aura.[15] Apart from one short note by Milner in 1959 on a possible correlation between the scotomas of migraine aura and CSD of Leão,[16] no attention was given to this observation, likely due to the prevailing hypothesis that migraine aura was caused by a vasospasm and cortical ischemia. In 1981, however, Olesen et al demonstrated a wave of oligemia during clinical aura starting from the occipital area progressing rostrally[17] at a velocity of about 2 mm/min irrespective of arterial territories.[18] This was inconsistent with an ischemic hypothesis and suggested that aura is primarily a neuronal event that is accompanied by vascular changes. In a seminal work, Hadjikhani et al were able to trigger typical visual migraine aura by exercise and demonstrated in functional MRI a change of blood oxygen level dependent (BOLD)-response to checkerboard-pattern stimulation over time consisting of a reduction of amplitude and an initial increase followed by a decrease (depression) of mean BOLD signal.[19] Importantly, when looking at the time course of the migraine aura, this pattern progressed over the occipital cortex from posterior to rostral in congruence with the patient's experience (from the center of the visual field centrifugally) suggesting a spreading depression of BOLD response (Fig. 1). The velocity of this spread was 3.5 mm/min similar to the CSD from Leão,[14] suggesting that indeed typical migraine aura is a consequence of CSD also in human.

Typical Migraine Aura and Silent Areas of Cortex.—Interestingly, the cortical area that first depicted the pattern of depressed BOLD response

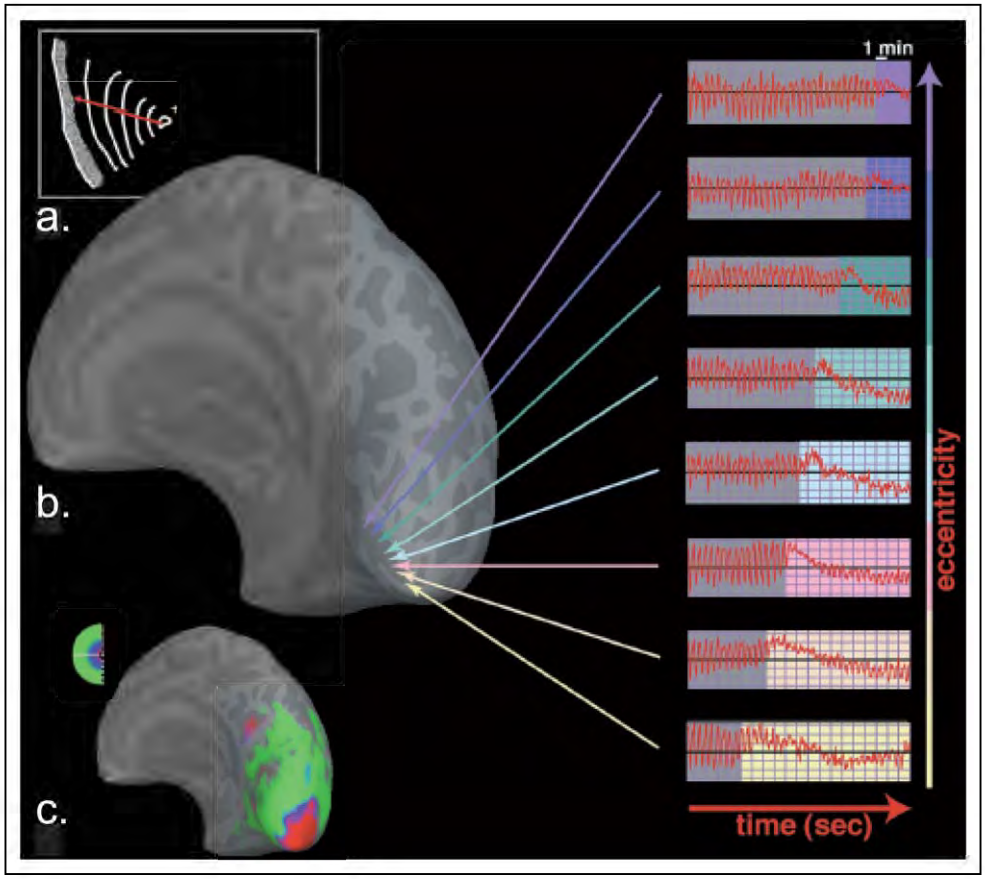

Fig. 1.—Cortical spreading depression has been first identified in the invasive electrocorticogram of rabbits by Leao.[14] After stimulation, the electrocorticogram flattens. This "depression" moves centrifugally from the stimulation electrode ("spreading") at a velocity of 2–3 mm/min with subsequent recovery after about 10 min. Such behavior has been associated with typical visual migraine aura in human that starts in the center of the visual field and progresses centrifugally as shown in the insert of the figure (a), modified after Hadjikhani et al.[19] (Copyright (2001) National Academy of Sciences, United States). The authors have used functional MRI assessing the BOLD-response to checkerboard stimulation during typical migraine aura and found a "depression" of the amplitude "spreading" over the occipital cortex (b) in a retinotopical manner (c) suggesting that cortical spreading depression can occur in migraineurs and might be the correlate of migraine aura. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to checkerboard visual stimulation was outside the striate cortex in area V3a, which belongs to Bordmann area BA19 in respect of microstructure.[19] This suggests a distant origin of CSD that gets symptomatic no earlier than when reaching an eloquent cortical region, such as the primary visual cortex. This is supported by a work from Hansen et al,[20] who analyzed more than 1000 visual auras of an individual patient over almost 18 years. The most frequent time courses of the visual symptoms were consistent with the classic visual aura starting in the center of the visual field and then spreading centrifugally in one hemifield over about 30–60 min.[20] However, a substantial proportion of auras were different, either starting from the periphery or disappearing from the visual field and then reappearing at a distant location.[20] This is important since it suggests that (i) aura can be initiated at different locations in the occipital cortex or even outside the visual cortex and (ii) CSD can "travel" through "silent areas" when symptoms disappear by exiting the visual field and reappear by reentering. Despite these intra-individual variations, this work further underlines that many characteristics of visual auras remain stable and that CSD is an excellent model mechanism of the symptomatology. Another

clinical aspect that could allow us to better understand the different behavior of CSD is the study of the succession of aura symptoms. Two different aura symptoms, such as visual and sensory might reflect the involvement of different brain areas, such as the visual and sensory cortex, which may start sometimes simultaneously and, in other cases, in succession.[21] In the latter case, the textbook explanation is that CSD spreads gradually from visual to sensory areas,[22] whereas in the first case a multifocal CSD might exist or a single CSD originates in a silent area of the brain that later on involves 2 eloquent areas at the same time.

Typical Migraine Aura Without Headache.—Not all typical migraine aura episodes are followed by or associated with migraine headache. In a sample of 4000 subjects, Russell and Olesen[23] identified 163 subjects with migraine with aura, of which 62 (38% of migraine with aura) also had typical migraine aura without headache with 7 having exclusively aura without headache (4% of migraine with aura and 0.2% of all). This illustrates the close link between the aura and head pain generation.[24,25] Nevertheless, not all patients with aura developed headache suggesting that both are still separate phenomena. This is strongly supported by the discrepancy of animal studies and clinical studies on migraine prevention: phenytoin,[26] carbamazepine,[27] and ketamine[28] are able to block CSD in animal models without substantial effect on migraine prevention in human.[29,30] Lamotrigine is effective in preventing migraine with aura[31-33] without actually affecting migraine without aura.[33,34] Such differential effect on aura in comparison to migraine, that is, headache, prophylaxis is supported by Bogdanov et al,[35] who demonstrated a marked effect of lamotrigine on CSD, whereas the migraine/headache prophylactic medication valproic acid was clearly less effective on CSD. Lamotrigine thus might be quite specific for aura but not headache prevention.

Non-Typical Migraine Aura.—The variability of visual symptoms in migraine is considerable,[23,36-42] and several possible variables could generate these symptoms as a consequence of CSD: Some have been studied, such as different characteristics within a single visual aura[39,40] or duration and succession of each symptom as described by Hansen et al[20]; others are hypothetical and still need to be assessed systematically, such as color of visual disturbances (for positive phenomena), frequency of flickering (for intermittent phenomena), or shape/location in the visual field. All this variability might be linked to different behavior of CSD or to different location in the (supplementary) visual cortex.

The question remains about the classification of the remaining visual symptoms that might occur prior to, or early on during, migraine attacks but do not reflect premonitory symptoms nor are consistent with clear CSD. Are these CSD in "silent" areas or are these fundamentally different neuronal mechanisms? For instance, it is commonly agreed that a fortification spectrum that may gradually spread right or left in a laterally convex shape is a visual aura. In contrast, not everybody would agree that blurred vision or vision "like looking through heat waves or water" involving the entire visual field is migraine aura in the sense of CSD. Such symptoms have been reported as migraine aura in different studies[38-40] and reports.[43] Moreover "blurred/foggy vision" was considered only when associated with other types of visual illusions, and ended up to be the most common visual symptom.[39]

As a clinician, it might be helpful to identify evidence by accessing information on the symptoms occurring together with the visual symptom in dispute: (i) Does the symptom occur in the same attack with other typical visual aura symptoms or does it occur only independently? (ii) Are the symptoms experienced solely by patients with a typical migraine aura biology? (iii) Does the visual symptom share some properties of typical aura phenomenology, such as spreading, duration, location in the visual hemifield/both eyes or co-occurrence with other, clearer aura symptoms? Although a non-specific symptom, such as visual blurring, may have a different behavior (eg, being more frequently located in the entire visual field without spreading), it cannot be proven that it is not caused by CSD of otherwise "silent" cortical areas, nor can it be established to be due to a CSD-like

phenomenon. This is consistent with a hypothesis by Hansen et al that the transient transformation of visual aura from a curvilinear positive wavefront into a circular scotoma could have been due to a crossing of CSD from V1 to V2.[20] It can be argued that indistinct symptoms are best classified as such; we use the term – Other Visual Disturbance – to invite thought since classifying them all as Typical Aura is both not evidence based and leads to cessation of thinking about their pathophysiology. Assessing such non-classic symptoms using neuroimaging or neurophysiological studies might be necessary to understand whether the pathophysiology behind the variations of visual symptoms in migraineurs is similar to CSD. Since such studies typically require group-comparisons, exact clinical phenotyping of the individual symptom is necessary in the first place. Second, study groups need to be homogeneous in respect of the symptom without a priori assuming that all visual symptoms are aura and can be interspersed without impact on the study results.

In summary, there are congruent data from clinical and paraclinical findings that typical migraine aura is a result of CSD in the visual cortex. Similar data do not exist for other visual symptoms in migraine. Therefore, clinical practice and especially clinical studies should differentiate between typical migraine aura and other visual symptoms.

TEMPORAL VARIATIONS OF MIGRAINE VISUAL AURA

According to ICHD-3-beta, typical migraine aura develops gradually over more than 5 min and lasts between 5 and 60 min. Now as polythetic criteria, the criteria do not set absolute limits, but do offer face validity issues. For example, there is current evidence that a substantial proportion of episodes otherwise fulfilling criteria for typical migraine aura deviate in respect of migraine aura duration: Taking into consideration the limitations mentioned above in respect of what should be called typical migraine aura as a consequence of CSD, a prospective study by Russell et al[41] reported that the visual disturbances of typical visual aura had an acute onset in 8 attacks out of 51 (16%). No other prospective studies confirmed this data while retrospective studies reported a rate ranging from 3%[23] to 21%.[39] Little is known on the exact duration of aura symptoms.[44] Viana et al focused on temporal aspects of migraine aura.[21] Results showed that symptoms lasted for more than 1 hour in a substantial proportion of auras (14%–21%). Twenty-six percent of patients had at least one aura (out of 3 recorded) with one symptom lasting longer than 1 hour.[21] Visual auras of duration longer than 1 hour are not uncommon, and the transition to more problematic time courses of migraine aura might be smooth.

ICHD-2[45] dispensed with the ICHD-1[46] term migraine with prolonged aura. Intra-individually, patients typically have auras of duration shorter than 60 min, but can also have longer durations. In one prospective study, 6 patients out of 54 patients with migraine with aura had 3 consecutive auras with at least one symptom lasting for longer than 1 hour, whereas 8 patients experienced aura duration for longer than 1 hour in only 1 attack out of 3.[21] In our opinion the term prolonged aura, while not required in a polythetic system, adds face validity to the classification. Whether a return to this previous term in the classification has clinical utility would be a matter of future research.

Some Definitions.—Typical migraine aura is common. In our own clinical experience, patients often present with a long history or even family history and have learned to cope with the occurrence of these visual symptoms, although some are more severely affected with consequences for everyday life, such as driving or career choice. Visual symptoms can further be the main problem (i) in the case of repetitive frequent episodes (migraine aura status), (ii) persistent visual aura, or (iii) persistent other visual symptoms (ie, different from previous visual auras). Such conditions appear to be rare, and only few case reports or case series have been published. Often, they pose substantial challenges to the patient and the treating physician. ICHD-3-beta defines the following temporal variations of migraine aura:

i. Migraine aura status (ICHD-3-beta code A1.4.5) is listed in the appendix of ICHD-3-beta and

defined as the occurrence of at least 2 aura episodes per day on at least 3 consecutive days. For that, secondary forms have to be excluded, such as reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome and arterial dissection.[1]

ii. Persistent visual aura without infarction (ICHD-3-beta code 1.4.2) is a visual aura – typical in nature for the patient – that lasts for longer than 1 week. Appropriate tests are able to exclude secondary causes, such as strokes or other structural abnormalities.[1]

iii. In the current classification, there is no term for persistent visual symptoms in migraineurs that do not resemble the previous auras. Whether such symptoms can be included in (ii) persistent visual aura without infarction is currently unknown. In fact, the literature often does not clearly distinguish between both despite the striking clinical difference. As we will discuss below, we would recommend keeping persistent visual phenomena strictly separated from persistent migraine aura for reporting to appropriately approximate pathophysiology and treatment.

MIGRAINE AURA STATUS

Among 8821 patients with migraine with or without aura, a retrospective study identified only 4 patients with migraine aura status (at least 2 attacks per day for at least 5 days), suggesting that this is a rare condition. All patients were female and had a history of migraine with aura. Mean duration of aura status was 4 weeks, 3 of these 4 patients had further episodes of aura status and 2 responded to treatment with lamotrigine,[47] although separating natural history must be challenging here. A history of migraine with aura seems to be prerequisite for this condition, but it remains unclear why some patients develop aura status when most patients do not. In one study, 2 patients had association with hyperhomocysteinemia and heterozygous mutation of the methylene tetrahydrofolate reductase-encoding gene with improvement after therapy with acetazolamide and folic acid.[48] Haan et al reported 7 patients with migraine aura status, of whom 3 were treated successfully with acetazolamide. Repetitive attempts to reduce medication failed in the first weeks and migraine aura status recurrence was successfully controlled by restarting acetazolamide. Two patients were finally able to stop medication, suggesting that acetazolamide might suppress the symptoms without actually stopping the underlying pathophysiological process.[49] In the early description by Haas et al,[50] 2 patients were described with repetitive visual phenomena in homonymous visual fields. One patient had a colorful pinwheel-like visual phenomenon lasting several minutes that occurred several times per day over about 5 weeks with a marked decrease during treatment with aspirin and cyproheptadine. The other had a history of typical migraine aura consisting of a flashing C-shaped perception that moved centrifugally over about 20 min. In contrast to this, the patient had "migraine aura status" over about 2 weeks when he experienced concentric grey lines "like ripples in a pond" in the right visual field lasting several seconds and occurring about 100 times per day. Retrospectively, it might be open to discussion whether to call this "migraine aura status" since the events did not resemble previous auras and did not clearly reflect CSD what brings us back to the basic problem of what to call migraine aura as discussed above.

Due to the rarity of the condition, Joao et al have suggested loosening the criteria by requiring only 3 episodes in a maximum of 3 days.[51] In their own series, they identified 8 patients with ICHD-3-beta migraine aura status. By using their own criteria, they confirmed these subjects and 12 in addition, and both groups did not differ substantially from each other except for the female predominance in the non-ICHD-3-beta group. This more liberal approach might allow to study more cases in respect of diagnosis and therapy as concluded by the authors,[51] but it still remains unclear, if both groups actually have a different condition. From a research perspective, it might be best to confine on a few pure cases than on a large number of patients who have a diluted condition.

PERSISTENT MIGRAINE AURA WITHOUT INFARCTION AND PROLONGED AURA

When migraine aura lasts longer than 1 week the term "persistent migraine aura" is applied[1]

provided there is no evidence of infarction in appropriate testing (ICHD-3-beta code 1.4.2). Importantly, there are several aspects that need to be considered: (i) patients have to have a previous history of migraine with aura, (ii) the persistent symptom should be typical for patient's previous auras, and (iii) the criterion of 1 week is based on expert opinion and requires confirmation in the future. Accordingly, patients with a history of migraine or even migraine with aura who have persistent visual phenomena that do *not* correspond to previous auras should *not* be given the diagnosis of persistent migraine aura. The literature has admixed persistent visual aura and what is now widely called visual snow,[5] which we will return to below.

Only case series or small studies have been published suggesting that this is a rare condition. In an early work, Liu et al presented 10 patients with migraine biology and persistent visual phenomena.[52] According to the temporal relation with migraine aura, the authors classified the complaints to being either definitely related to migraine (the persistent visual phenomenon started with migraine aura), probably related to migraine (history of migraine aura and headache during the beginning of the visual phenomenon), or possibly a migraine equivalent (no association with migraine aura or headache). Similar cases have been presented.[53] Wang et al have applied the visual aura rating scale, which assesses similarity to typical migraine aura properties as mentioned above (ie, unilaterality, zig-zag lines, scotoma, gradual involvement, but not duration of 5–60 min since inclusion criterion was persistent migraine aura),[54] on their own patients with persistent visual phenomena and 23 subjects from the literature. They found that the higher the similarity to typical visual aura the higher the likelihood of good outcome.[7] Further, the same group assessed visual cortex hyperexcitability in 6 migraineurs with persistent visual phenomena using visual-evoked magnetic field recording. Comparison to controls with episodic or chronic migraine with or without aura showed that potentiation was highest in patients with persistent visual phenomena. Within this group, potentiation was inversely correlated to disease duration.[3] This suggests that, similar to the early clinical observation by Liu et al,[52] persistent visual phenomena in migraineurs might (i) differ from other migraine spectrum disorders *and* (ii) might represent different subtypes with different relation to migraine, pathophysiology and prognosis. Further, the reduction of potentiation might indicate that the mechanism of such condition "burns out" over time with albeit persisting symptoms. Belvis et al report a patient with history of migraine with brainstem aura who developed a persistent visual disturbance lasting 9 days. From the description, it remains unclear whether the condition developed from an aura typical for the patient, and the presentation ("white and bright particles falling in both visual fields") differed substantially from previous auras ("bilateral and total amaurosis plus bilateral paresthesias") retrospectively doubting the diagnosis of prolonged visual aura[1,55] or "visual snow phenomenon" when applying the appropriate criteria.[5] Bearing these limitations in mind, the authors found signal alterations in the occipital lobe using apparent water diffusion coefficient in the occipital lobe 4 days after the beginning of the symptoms that disappeared 3 days after returning clinically back to normal. Whether this method is useful for studying persistent/prolonged visual phenomena in migraine need to be determined in the future.

Jager et al[4] reported 4 migraineurs with persistent visual symptoms (one with likely visual snow, one seeing "heat waves" in the entire visual field, one having blotches of light in central vision, and one demonstrating an inward shunt of vision). A diagnosis of persistent migraine aura could not be fully established since a direct association with an episode of migraine aura has not been demonstrated for these patients. Patients were extensively studied in MRI using apparent water diffusion coefficient and perfusion studies. In contrast to Belvis,[55] no alterations could be demonstrated. Whether this is due to a difference in disease duration – Jager et al tested patients with symptoms for longer than 3 years[4] whereas Belvis et al tested within 1 week[55] – requires further research. Relja et al reported a patient with persistent visual aura (scintillating scotoma "like a chessboard" in the right visual field)

that occurred after a migraine aura typical for the patient. In SPECT with technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO) there was decreased blood perfusion left fronto-parieto-occipital and right occipital. Similarly, brain perfusion MRI 6 weeks after symptom onset revealed left hypoperfusion that resolved after symptoms improved about 5 months later.[56] Bereczki et al demonstrated a patient with history of visual, sensory, dysphasic, and motor aura who had persistent homonymous hemianopia right. Diffusion weighted imaging revealed purely cortical signal increase, first in the occipital lobe then shifting anteriorly to the temporoparietal cortex and finally disappearing together with a resolution of visual symptoms.[57] Similarly, Kim and Kwon demonstrated cerebral vasogenic edema, cortical hypoperfusion, and hypometabolism in the area corresponding to the symptoms.[58] In summary, electrophysiology, functional brain imaging, and diffusion weighted imaging of patients with persistent visual aura suggest some cortical dysfunction that might represent a correlate of cortical spreading depression, although there still is conflicting data, and the number of patients studied is very limited.

Treatment Of Persistent Migraine Aura.—In respect to treatment there are few data available owing to the rarity of the condition. Chen et al reported 2 patients with persistent visual phenomenon. One had coin-sized white spot in the left hemifield after an attack with migraine without aura; the other had stars persistently flickering in the right hemifield moving eccentrically. Both patients had hypoperfusion in technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO) SPECT in the corresponding occipital cortex contralateral to the side of the visual field deficit. Importantly, both patients responded to treatment with lamotrigine.[59] A case series by Rothrock reported 2 patients who had persistent migraine aura for 2 months and 2 years, respectively, starting after aura episodes that were typical for the patient. Treatment with valproic acid 250 mg bid or 500 mg bid completely resolved the symptoms.[60] Two patients reported by Rozen[61] had prolonged visual aura for 7 days and 2 days that responded to intravenous furosemide. Other patients were successfully treated with prochlorperazine and magnesium.[62] Kaube et al have investigated 25 mg ketamine nasal spray in patients with severe form of prolonged aura in familial hemiplegic migraine and could demonstrate a substantial reduction in duration and severity in 5 of 11 patients.[30] This effect could be only confirmed for a reduction of aura severity but not on aura duration in a study in 18 patients with prolonged aura by Afridi et al, who compared 25 mg intranasal ketamine to 2 mg intranasal midazolam.[63] Limited data therefore would indicate that valproic acid, lamotrigine, furosemide, or ketamine might be useful for the treatment of persistent and prolonged migraine aura.

VISUAL SNOW (VS)

Patients with VS experience the view of a badly tuned analogue television ("TV-snow"), that is, uncountable tiny dots in the entire visual field flickering typically between black and white (Fig. 2a). Symptoms are continuous and present with eyes open and closed. Liu et al presented 3 patients (patient 6, 7, and 8) in group III (possibly a migraine equivalent) due to comorbid migraine without temporal relationship between the onset and headache or aura.[52] In contrast, Wang et al have ascribed a diagnosis of persistent visual aura to 2 subjects with "TV-snow"-like visual disturbance despite a visual aura rating scale score of 0.[7,54] Similarly, 2 VS patients were commingled with 4 subjects who had different complaints, and all 6 were tested as a group of "persistent visual aura" for visual cortex hyperexcitability by using visual-evoked magnetic field recording.[3] Interestingly, cortical hyperexcitability was inversely correlated with disease duration: patients with VS had symptoms for many years suggesting that VS behaved differently from the other visual disturbances in migraineurs, and thus both groups may not be intermixed for research.

Based on the records of 22 patients seen by one of us (PJG) and the results from an internet survey among patients with self-assessed VS, Schankin et al proposed preliminary criteria that were

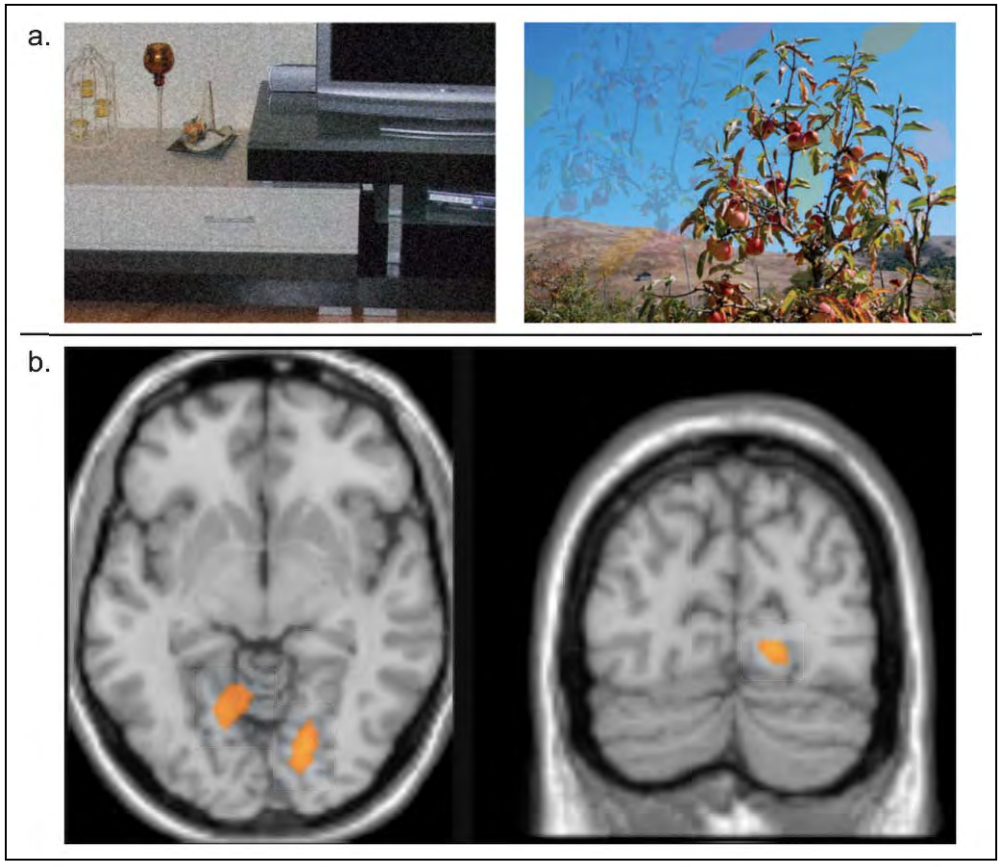

Fig. 2.—Patients with visual snow syndrome suffer from a continuous TV-static-like visual disturbance in the entire visual field (a. left) and additional visual symptoms, such as palinopsia (a. right).[5] Hypermetabolism of the supplementary visual cortex (lingual gyrus in b.) has been demonstrated in these patients supporting an organic origin of the condition involving processing of visual input.[6] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

prospectively tested in 142 patients of whom 78 had VS and unremarkable ophthalmological examination. Almost all patients (72% or 92%) had at least 3 of the following additional visual symptoms resulting in the proposal of diagnostic and research criteria (Table 1): palinopsia (trailing and afterimages), exaggerated entoptic phenomena (floaters, blue field entoptic phenomenon, spontaneous photopsia, self-light of the eye), photophobia, and nyctalopia (impaired night vision).

Symptoms were continuous, and 24% of patients reported having the condition as long as they could remember, whereas the remainder had disease onset at around 20 years. The clinical presentation of continuous presence in the entire visual field of visual symptoms without directed movement or zig-zag lines, but with additional visual symptoms, suggests that VS is part of a unique clinical syndrome that does not resemble typical visual aura. Further, since only 11% of patients had a visual aura around the week of the beginning, VS has to be considered distinct from persistent visual aura. However, 59% of patients had comorbid migraine, and 27% had typical migraine aura suggesting an overlap of pathophysiological mechanisms.[5] In 120 patients with "visual snow syndrome," comorbid migraine was significantly associated with the additional visual symptoms palinopsia, photopsia, photophobia, and nyctalopia as well as tinnitus.[6] Migraine biology therefore seems to aggravate the clinical syndrome, and VS patients with migraine might therefore volunteer for research more likely than those without. A recruitment bias resulting in a false-high prevalence of migraine in patients with VS is thus possible. A similar problem is unlikely for typical migraine

Table 1.—Patients With Visual Snow Often Complain of Additional Visual Symptoms, Suggesting the Existence of a Syndrome

A.	Visual snow: dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.
B.	Presence of at least 2 additional visual symptoms of the 4 following categories:
	i Palinopsia. At least one of the following: after images (different from retinal afterimages) or trailing of moving objects.
	ii Enhanced entoptic phenomena.† At least one of the following: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia.
	iii Photophobia
	iv Nyctalopia (impaired night vision)
C.	Symptoms are not consistent with typical migraine visual aura ICHD-IIIb.[1]
D.	Symptoms are not better explained by another disorder (especially normal eye exams, no previous intake of illicit drugs).

The table depicts preliminary criteria for such visual snow syndrome, modified from Schankin et al.[5]
†Entoptic phenomena are visual symptoms that arise from structures of the visual system. They include photopsia (spontaneous flashes of light), floaters, blue field entoptic phenomenon (uncountable little grey/white/black dots or rings moving in a pulsatile manner over the visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky), or self-light of the eye (colored waves or clouds when closing the eyes in the dark).

aura, since there was no such association indicating a true pathophysiological overlap.

Functional brain imaging with [18F]FDG-PET in patients with VS syndrome (Table 1)[5] showed brain hypermetabolism in the supplementary visual cortex (bilateral lingual gyrus) of Brodmann area 19 (Fig. 2b), but not in the primary visual cortex. Visual snow thus seems to be a disorder of higher visual processing, and not of upstream visual input. This is consistent with patients having normal ophthalmological exam and normal visual evoked potentials.[5]

Importantly, the lingual gyrus might also be important for *adjusting* brightness of light perception. Denuelle et al[64] studied photophobia, which is a clinical hallmark of both migraine and "visual snow syndrome." The authors identified the primary visual cortex as well as the lingual gyrus being more active when visual stimulation with low levels of light during migraine attacks was compared with identical stimulation in the interictal state.[64] Similarly, migraineurs with interictal photosensitivity have thicker cortex in the right lingual gyrus when compared with patients without such photophobia.[65] When taking into account that photophobia means that light of photon energy typically not able to illicit discomfort or pain is actually painful, the lingual gyrus might be important for *adjusting* brightness of light perception.

"Visual snow syndrome" is characterized by VS plus additional symptoms,[5] such as palinopsia, a failure of suppressing the just-seen,[66] enhanced entoptic phenomena (eg, floaters, blue field entoptic phenomenon) that actually represent visualization of the optic apparatus itself,[67] photophobia and impaired night vision. It is, therefore, conceivable that healthy subjects do not see these manifestations due to an *active suppression system* that might be located in the supplementary visual cortex. This suggests that the lingual gyrus might play an important role in this system.[68] Whether this area is of particular relevance for VS or only for one or more of the additional symptoms such as photophobia needs to be determined. In this respect it is important that [^{18}F]FDG incubation occurred in the dark with eyes closed where patients only experienced VS and maybe some self-light of the eye, but not photophobia or palinopsia.[6]

The link between "visual snow syndrome" and the highly comorbid typical migraine aura might be sought in the microstructure of the cortex in the lingual gyrus, which belongs to Broadmann area 19. Hadjikhani et al have identified V3A as the region where earliest functional changes appear during typical migraine aura in functional MRI after visual stimulation,[19] supporting the view that one common pathophysiological concept might cause both conditions. In

the current literature, there are no studies characterizing a pure group of patients with VS on a functional or pharmacological level. One interesting case report by Unal-Chevik and Yildiz found potentiation in repetitive visual evoked potentials in one patient with VS that improved after treatment with lamotrigine in parallel to amelioration of VS.[69] Further, this particular patient depicted occipital bending from left to right. Such bending is not uncommon in subjects without VS,[70] and the unique finding of potentiation with positive response to lamotrigine needs to be prospectively replicated. Our limited understanding of this condition is further reflected in the poor response to treatment by migraine prophylactics or antiepileptic medication[6,71,72] despite the pathophysiological overlap with migraine aura and the evidence of cortical hyperexcitability.[69] Due to the lack of proper studies and only one case report showing some effect by lamotrigine,[69] proper studies of homogeneous patient groups using strict criteria[5] assessing pathophysiology and treatment response will hopefully lead the way to some alleviation of the distressing symptoms of affected individuals.

INTEGRATING THE VISUAL SYMPTOMS OF MIGRAINEURS

Visual symptoms are frequent in migraine patients but often represent a minor problem when compared with the severity of head pain, nausea and movement sensitivity. A small subgroup of patients is predominantly affected by repetitive or persistent visual aura or the migraine-associated phenomenon VS. Approaching a patient with such symptoms in clinical routine is often difficult due to the rarity of the condition and the complexity of patient's history. The following approach has been useful in our clinical practice.

Our view is the patient's history typically reflects their true perception of what they see, and malingering or psychogenic causes are the exception when talking about visual symptoms in migraineurs. The history of "visual snow syndrome," which has often been dismissed as stress-related, attention-seeking, or simply "crazy," taught us that careful history-taking and impartial documentation of symptoms reported by patients over years[2,5] can help to identify patterns of symptoms that result in the definition of a syndrome[5] and studies demonstrating a possible biological origin.[6] History taking should focus on headache including beginning, frequency and phenotype of current and previous headache attacks to establish (i) diagnosis of episodic or chronic migraine and (ii) the presence or absence of visual or non-visual auras. In this respect, the term "typical migraine aura" should be reserved for symptoms that are consistent with cortical spreading depression irrespective of the occurrence prior, together or independently from headache attacks. This should be demarcated from premonitory symptoms such as neck stiffness, photophobia, or concentration problems. With this preparatory work, establishing a diagnosis of migraine aura status or persistent visual aura seems straightforward.

One approach is to limit the diagnosis of persistent migraine aura to patients whose previous aura symptoms persist,[1] and not to those with an aura typical for the subject followed by completely different visual symptoms that then do not go away. These patients may have a persistent aura, with its typical features, however, one needs to be more careful about secondary causality. For visual symptoms that are neither aura nor visual snow, the term other migrainous visual disturbances seems to state what is known. Visual snow can be identified reliably by asking open questions about the view (i) in the dark with eyes open and on white, but not bright paper (TV-snow-like), (ii) of the blue sky (floaters, blue field entoptic phenomenon), (iii) with eyes closed (lava lamp-like self-light of the eye), (iv) of high contrast objects or moving objects (palinopsia) as well as (v) night vision, and (vii) photophobia. When the diagnosis is established, empiric treatment according to the cases published in the literature (Table 2) would be justified. Verapamil, which is often used in clinical practice to treat migraine with aura[73] and hemiplegic migraine,[74,75] would also be an option when other treatments fail. Table 2 further shows that patients with "visual snow syndrome" often have no response to various treatments, whereas the prognosis of the other forms of persistent visual symptoms in migraine seems to be somewhat better. Early referral to

Table 2.—Overview Over Literature on Persistent Visual Phenomena in Migraine and Migraine Aura Status

Diagnosis	Authors, Year	Number of Patients†	Successful Medication (Daily Dosage)
Migraine aura status	Beltramone et al, 2014[47]	4	Lamotrigine in 2 of 4
	Cupini et al, 2007[48]	2	Acetazolamide in 2 of 2, folic acid in 1 of 2 in addition
	Haan et al, 2000[49]	7	Acetazolamide (500–750 mg/d) in 3 of 3 tried
	Haas, 1982[50]	2	Aspirin 650 mg/d and cyproheptadine 12 mg in 1 of 2
Persistent migraine aura without infarction	Liu et al, 1995[52]	3 (1–3)	No response to medication, spontaneous resolution possible
	San-Juan and Zermeno, 2007[53]	1	Possible response to nimodipine
	Wang et al, 2008[7]	4 (3–6)	Propranolol, tompiramate, and lamotrigine improved symptoms in 1 reported, lamotrigine, and topiramate improved symptoms in 1 reported
	Relja et al, 2004[56]	1	Lamotrigine (75 mg/d) was associated with slow improvement
	Kim and Kwon, 2015[58]	1	Corticosteroids (500 mg/d, tapered)
	Rothrock, 1997[60]	2	Valproic acid (500 and 1000 mg/d)
Persistent migraine aura without infarction and prolonged aura (PA)	Rozen, 2000[61]	2 (1 PA)	Furosemide (20 mg i.v./d) in 2 of 2
Prolonged aura	Rozen, 2003[62]	2	Prochlorperazine (30 mg/d), magnesium sulfate (2 g/day)
	Kaube et al, 2000[30]	11	Ketamine 25 mg intranasally in 5 of 11
	Afridi et al, 2013[63]	18	Double-blind ketamine 25 mg vs midazolam 2 mg intranasally: reduction of severity in ketamine group, not duration
Other migrainous visual disturbances	Liu et al, 1995[52]	4 (4–5, 9–10)	No significant response to medication
	Belvis et al, 2010[55]	1	Spontaneous resolution
	Jager et al, 2005[4]	3 (2–3)	No response to medication in 1 reported.
	Chen et al, 2001[59]	2	Lamotrigine (100 mg/d) in 2 of 2
Visual snow	Liu et al, 1995[52]	3 (6–8)	Nortriptyline and carbamazepine resolved palinopsia in 1 of 3; sertraline reduced symptoms by 50% in 1 of 3
	Wang et al, 2008[7]	2 (1–2)	No response to medication in 1 reported
	Jager et al, 2005[4]	1 (1)	No response to medication in 1 reported
	Schankin et al, 2014[5]	78	Individual response not listed. No complete resolution listed by any medication
	Schankin et al, 2014[6]	17	Naproxen in 1 reported, no improvement by medication in 9 reported
	Unal-Cevik and Yildiz, 2015[69]	1	Lamotrigine (100 mg/d)
	Beyer and Gaul, 2015[71]	2	No response to medication
	Simpson et al, 2013[72]	1	No response to medication
	Bessero and Plant, 2014[2]	20	No response to medication

Studies were selected based on the report of a detailed history of the visual disturbance to allow grouping into migraine aura status, persistent migraine aura without infarction or prolonged aura, visual snow, and other migrainous visual disturbances. In the medication column, only successful medication was listed for the purpose of clarity.
†Individual patients listed in parentheses.

headache centers where patients could be included in prospective studies would be the next step when such approach fails.

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Clinical Observations

Positive Persistent Visual Symptoms (Visual Snow) Presenting as a Migraine Variant in a 12-Year-Old Girl

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ABSTRACT

BACKGROUND: Migraine is a common neurological disorder affecting children, in which the headache is often preceded or accompanied by a complex of neurological symptoms known as an aura. Persistent visual symptoms are rare, with typical visual aura sometimes being poorly distinguished from other visual disturbances. **METHODS:** We describe the case of a 12-year-old girl who has experienced persistent, constant symptoms throughout the visual fields of white, bright, jagged spots and black and white flashes with sparkles and dots since May 2010. She also has palinopsia, squiggles, and photophobia. The child's drawing of her visual symptoms helps illustrate the case and illuminate her ordeal. **RESULTS:** The child's visual symptoms have so far been resistant to pharmacological therapy. **CONCLUSION:** Further insight is needed into this debilitating condition to allow effective management in the pediatric population.

Keywords: persistent migraine aura, visual snow, positive persistent visual symptoms, migraine variant

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Introduction

Migraine is a common neurological disorder affecting between 3% and 10% of children.[1] Trends in age and sex distribution consistently show that the incidence increases with age and that a male preponderance in early childhood reverses around the age of puberty.[2] In approximately 30% of sufferers,[3] the headache is preceded or accompanied by a complex of neurological symptoms known as an aura. Visual auras are by far the most common and can include both positive and negative symptoms. Positive symptoms include flashes of light (photopsia), visual hallucinations, and, more commonly, scintillating scotomas or fortification spectra. Negative symptoms include scotomata, visual field defects, tunnel vision, and even complete blindness. When aura symptoms persist beyond 7 days without evidence of infarction, the International Classification of Headache Disorders, second edition, characterizes the condition as persistent migraine aura without infarction.[4]

Sometimes visual disturbances take forms not typical for migraine aura. One such disturbance first described by Liu et al.[5] has been called visual snow or positive persistent visual disturbance.[6] The latter takes the form of continuous disturbance seen in the entire visual field and is characterized by multiple tiny black and white or colored dots or squiggles.[7] Few patients in childhood have been described.

Case Description

We describe a 12-year-old girl with persistent visual disturbance. Since the age of 7 years, she has suffered from migraine, describing throbbing headaches typically on the right side. These were moderate to severe in intensity and associated with nausea, photophobia, and phonophobia. They occurred approximately every 7 weeks. She was not taking any preventive therapy and the headaches were being treated unsuccessfully with paracetamol (acetaminophen). Both her mother and her maternal grandparents also suffer from headache.

Her visual symptoms (Fig) started acutely on waking in May 2010, 4 days after a migraine, and have since matured and persisted. Despite variation in intensity and manifestation, the visual symptoms have been continuous. These consist of white, bright, jagged spots and black and white flashes with sparkles and dots. She describes her vision as blurred throughout much of the day and complains of after images and trails (palinopsia) when she moves her field of vision. She has a degree of

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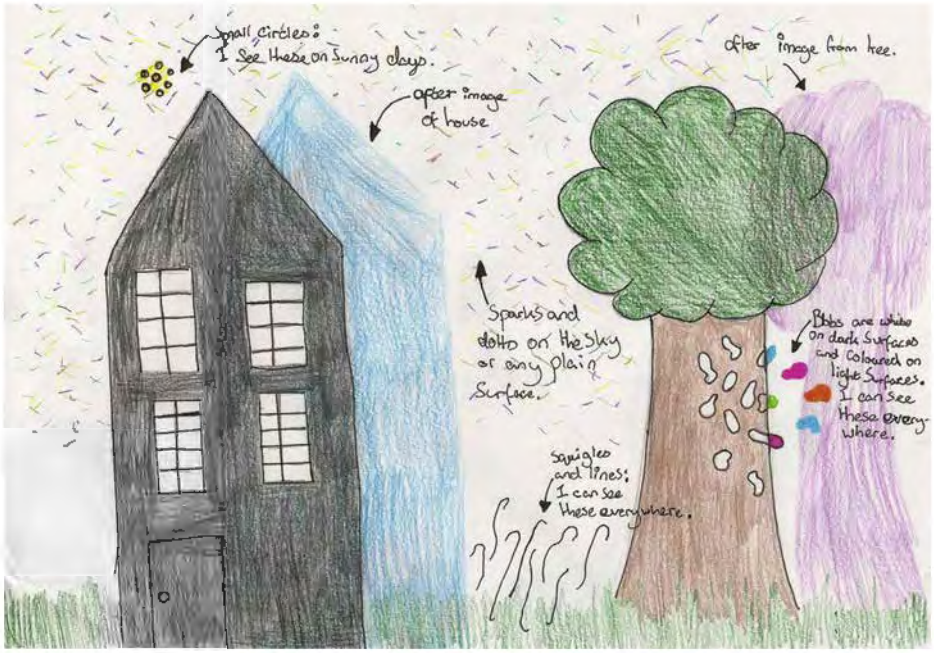

FIGURE.
A drawing produced by a 12-year-old girl to illustrate her persistent visual disturbances associated with migraine. Commencing acutely in May 2010, these visual symptoms have varied in intensity and manifestation, but nonetheless been continuous despite a variety of pharmacological therapies.

photophobia and reports that bright lights can lead to afterimages that can persist for several hours. On one occasion, she suffered from acute loss of half her visual field over several hours. This resolved spontaneously and was not associated with headache. Since the visual disturbances started, she reports some dull pain of a frontal and occipital nature on 5 of 7 days.

Physical, psychological, and neurological examination of the girl revealed no abnormal findings other than some tenderness over the occipital nerves. Basic blood tests including a coagulation profile were normal and an electroencephalograph showed no abnormalities. On ophthalmological assessment she was found to have normal visual fields and good visual acuity with 6/6 vision in both eyes. Her eye movements were normal with no sign of strabismus or nystagmus. Color vision was within normal limits, and on electrodiagnostic assessment her visual evoked potentials were normal and symmetrical, as were the electroretinograms. Examination with a slit lamp revealed healthy anterior and posterior segments of both eyes with no evidence of optic neuropathy or retinal abnormality. Magnetic resonance imaging, including T1, T2, fluid attenuated inversion recovery, and diffusion-weighted images, performed after 6 months of continuous symptoms showed a small arachnoid cyst in the medial left temporal fossa but no specific findings that could account for the girl's symptoms.

Several drugs have been tried since the onset of visual symptoms. On initial presentation, she was prescribed sumatriptan 20 mg nasal spray with no effect. She was then treated with topiramate to a dose of 75 mg twice daily, which has since increased to 100 mg twice daily. Despite dramatically reducing headache frequency, topiramate has had no effect on her visual symptoms. A period of treatment with riboflavin (400 mg twice daily) also had no effect. For 6 weeks, she took flunarizine (maximum 10 mg daily) but this was discontinued because of intolerable side effects (stomach pains) and no apparent improvement in visual symptoms. Two occipital nerve injections (containing 40 mg methylprednisolone and 30 mg 1% lignocaine [lidocaine]) several months apart have also been unsuccessful. Acetazolamide has recently been started at a dose of 125 mg rising to 250 mg twice daily, but this has not led to any improvement.

Discussion

Persistent visual disturbance in children lasting months is unusual. Our specialist clinic has only seen two patients and in these the aura lasted less than a week. In both of these patients, treatment for the migraine resolved the symptoms of aura. In contrast, in this patient, topiramate has been highly effective at controlling the headaches without any beneficial effect on the visual disturbance.

Visual aura in migraine is thought to be explained by cortical spreading depression (CSD),[8] an electrophysiological event whereby a wave of neuronal depolarization originating within the visual cortex is followed by a period of sustained suppression of neuronal activity. The CSD is accompanied by changes in regional cerebral blood flow thought to reflect reduced neuronal activity and metabolism. It has been suggested that *persistent* visual aura may be due to sustained reverberating waves of CSD,[9] perhaps combined with visual cortex hyperexcitability.[10] Single photon emission computed tomography and functional magnetic resonance imaging studies appear to support this theory, showing cortical hypoperfusion associated with symptoms,[11] but to a degree that does not lead to infarction. One would predict from the columnar arrangement of the visual cortex[12] that excitation would produce sharp edges, and this has indeed been shown.[13] Clinically, visual snow (positive persistent visual disturbance) shares little of the phenotype of typical migraine aura.

Several medications have been used to treat individuals with persistent visual aura, including verapamil, aspirin, selective serotonin reuptake inhibitors, tricyclics, carbamazepine, nifedipine, and beta blockers, but with little success.[9] Limited case studies support the use of a number of drugs that have an effect on CSD. Lamotrigine has a downregulating effect on glutamate, which is involved in propagating CSD via N-methyl-D-aspartate receptors.[14] Furosemide disrupts extracellular potassium accumulation, which is thought to be an initiating step in CSD

generation.[15] The enhancing effect on γ-aminobutyric acid (GABA) transmission caused by divalproex sodium (sodium valproate with valproic acid) inhibits spreading depression.[16] Acetazolamide is a carbonic anhydrase inhibitor with some effectiveness through an unknown mechanism of action, although there is some experimental evidence in animals that it reduced the susceptibility of neurons to CSD.[17] Topiramate is also an inhibitor of carbonic anhydrase, but has other properties including blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission, and the inhibition of excitatory pathways through glutamate receptors. There is anecdotal evidence of its efficacy in the treatment of persistent aura.[18] Its use for migraine prophylaxis is clearly established. Flunarizine is a calcium channel blocker that seems particularly effective at treating hemiplegic migraine in children.[19] There is no evidence of its effectiveness in persistent visual symptoms.

Our initial treatment aim in this child was to eradicate the migraine in the hope that the visual disturbance might be helped. So far, this has been unsuccessful. Of the two published cases of persistent visual aura in children, one child responded to oral furosemide after being treated unsuccessfully with atenolol[20] and the other was treated with phenobarbital and amitriptyline, which decreased the frequency of the headaches but had no effect on the persistent visual aura.[5] The former case as described is not one of visual snow and does not inform this condition.

Pediatric cases of visual snow (positive persistent visual disturbance) are extremely important. They clearly demonstrate the problem is unlikely to be merely "psychological" as has been suggested or indeed made up from the internet, because it is unlikely a child would use the internet for that purpose. The fidelity of the symptoms across age groups and cultures suggests a uniform biology whose exploration will allow us to deal with the syndrome properly. We hope our case encourages presentation of others and spurs research.

We thank the patient and her mother for allowing us to report her findings and for providing us with the unique illustration and description of her visual symptoms.

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Prevalence and clinical features of migraine in a population of visually impaired subjects in Curitiba, Brazil

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Cephalalgia

Kowacs PA, Piovesan EJ, Lange MC, Werneck LC, Tatsui CE, Ribas LC, Scapucin L, Marques LEA & Moreira ATR. Prevalence and clinical features of migraine in a population of visually impaired subjects in Curitiba, Brazil. Cephalalgia 2001; 21:900–905. London. ISSN 0333-1024

To investigate the relevance of lacking or diminished visual input on the expression of migraine, we evaluated its prevalence and clinical features in a population of visually impaired subjects. Between September 1999 and April 2000, 203 visually impaired subjects with a headache inventory were surveyed. Those with headache were assessed according to IHS criteria for the presence of migraine. Migraineurs had their symptoms further detailed through an interview and a headache diary. Of the 104 subjects reporting headaches during the last 6 months, 29 had migraine (14.2%). The prevalence of migraine was not influenced by whether the visual impairment was complete or partial. Mean frequency of migraine attacks was 2.7/month. Most subjects (96%) reported severe and/or moderate attacks. Nausea, vomiting, aggravation by activity and phonophobia were reported by 62%, 37.9%, 86.2% and 96.6% of the subjects, respectively. Visual impairment does not seem to influence prevalence of migraine or its clinical features. □ *Blindness, migraine, visual impairment*

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Introduction

The relationship between migraine and the visual system is not limited to the occurrence of visual aura (1) and photophobia (2), but to several ictal and interictal functional peculiarities of the pathways related to visual input and processing (1–7). Drummond (2) has shown that migraineurs present higher glare ratings to light stimulation between migraine attacks, compared with controls. When submitted to flicker stimulation, most migraine subjects present a driving response of their alpha rhythm (3). Potentiation instead of habituation of interictal visual evoked responses to checker-board pattern stimulation is seen in migraineurs compared with controls (4). Wray et al. (5) have shown migraineurs to present a greater sensitivity for low-level visual processing between attacks, a finding suggestive of functional impairment of inhibitory interneurones. Evidence for such impairment has been more recently presented by Mulleners et al. (6), by showing that inhibition of letter recognition at 100 msec was less disturbed by transcranial magnetic stimulation in migraineurs than in controls. Compared with healthy volunteers, migraineurs present lower thresholds for visual discomfort when exposed to progressive light stimuli (8–10). The wave of spreading hypoperfusion that has been shown to occur during attacks of migraine with or without aura usually starts in the occipital lobes before spreading forward (11–13).

Recently, we have shown that intense light stimulation could lower trigeminal and cervical pain perception thresholds (10), a finding that suggested that visual input, by lowering pain thresholds, could facilitate migraine attacks. We have conducted this study in order to determine if the lack of light input or a status of diminished light perception in visually impaired individuals could influence the prevalence and clinical features of migraine.

Population and methods

Between the months of September 1999 and April 2000, 208 subjects from eight centres for visually impaired subjects in Curitiba, Brazil, were randomly recruited. They were personally interviewed, answering structured questions regarding the occurrence of headache in their lifetime. Inclusion criteria were both genders, aged between 16 and 60 years, and presence of total blindness or of a severe visual impairment. Exclusion criteria were cognitive dysfunction, inability to identify more than one type of headache when present, lack of will to participate, and progressive neurological disease. Five patients were excluded, one due to lack of will to participate, two due to the presence of associated psychiatric disorders, and two because of cognitive impairment. Those with headaches were further assessed according to IHS criteria (14) for the occurrence of migraine in their lifetime, in the last year, in the last 6 months, and in the last month. Migraineurs were submitted to an additional inventory to obtain further details of the clinical features of their migraine attacks. All data were collected on a person-to-person basis. They were also submitted to another ophthalmologic evaluation, and were asked to fill out a headache diary with a tactile analogical scale for pain (TAS) (15), specially designed for the study. Regarding their visual impairment, those without any perception of visual stimuli in both eyes were classified as totally blind (ICD-10 category 5), and those with subnormal vision or 'legally blind' (ICD-10 categories 1–4), in whom even after the best optical correction visual acuity in the best eye remained 20/200 (category 1) or lower (categories 2–4, 16). ANOVA, comparison of the proportions (CP test), Mann–Whitney and Student's *t*-test were used to compare data of those totally blind with the findings of those with subnormal vision. Demographics of the population and aetiology of visual impairment are shown in Table 1.

Results

Of the 203 patients interviewed, migraine was diagnosed for any period of life in 34 (16.7%). One patient had not had any headache episode in the last 6 years, one patient had his migraine transformed to a chronic daily headache and in a third patient migraine subsided and a tension-type headache ensued. Thirty-one patients complained about migraine episodes in the last year (15.3%), but two of them had not presented any migraine episode in the last 6 months. Four patients reported another headache associated with migraine: one reported idiopathic stabbing headache, another, headache associated with arterial hypertension, and two others reported tension-type

Table 1 Demographics and clinical features of the study population

	Migraineurs		Non migraineurs		Total	
	n	%	*n*	%	*n*	%
	29	14.3	174	85.7	203	100
Gender						
Males	7	24.1	118	67.8	125	61.6
Females	22	75.9	56	32.2	78	38.4
Age (years ± SD)	31	±10.7	36.0	±16.5	35.3	±15.9
Aetiology						
Congenital	13	44.8	95	54.5	108	53.2
Acquired	13	44.8	62	35.6	75	36.9
Congenital + acquired	3	10.4	14	8.0	17	8.4
Unknown	–	–	3	1.7	3	1.5
Specific aetiology						
Cataract	8	27.6	34	19.5	42	20.7
Glaucoma	2	6.9	32	18.4	34	16.8
Trauma	1	3.4	13	7.5	14	6.9
Retinal detachment	1	3.4	12	6.9	13	6.4
Tumour	3	10.4	8	4.6	11	5.4
Measles	2	6.9	8	4.6	10	4.9
Pigmentary retinosis	1	3.4	6	3.4	7	3.4
Others	7	24.2	32	18.4	39	19.2
Unknown	4	13.8	29	16.6	33	16.2

headaches. All of them knew how to distinguish their other headaches from migraine.

Our results showed a prevalence ratio for migraine of 14.28% for the 6 months preceding the study. Of the 29 visually impaired subjects presenting with migraine in the 6 months preceding the study, seven were male and 22 female. Mean age was 30.6 ± 10.2 years, and there was no difference of age between those totally blind (32.2 ± 7.5 years) and those with subnormal vision (29 ± 11.7 years) ($P = 0.612$, Mann–Whitney). There was no difference in migraine prevalence in the totally blind compared with those with subnormal vision ($P = 0.735$, CP test). Twenty-five subjects (12.3%) had at least a single migraine attack in the month preceding the appointment. Additional details of prevalence data are shown in Table 2.

Characteristics of migraine in those patients presenting with migraine attacks in the 6 months preceding the study were further detailed. They presented a mean of 2.7 attacks in the month preceding the study, with a mean duration of 27.5 h. Unilateral pain during the attacks was reported by 41.37% of the subjects. Phonophobia was reported by 96.55% of the migraineurs. Photophobia was present in 61.1% of the 18 patients with subnormal vision. Nausea and vomiting were present in 62% and 37.9% of the patients, respectively. Most of the patients (86.2%) reported aggravation of the symptoms by activity. Migraine episodes

Table 2 Prevalence of migraine in the subjects studied. Visually impaired subjects ($n = 203$)

	All the migraineurs		Totally blind (ICD-10 category 5)		Subnormal vision (ICD-10 categories 3–4)	
Prevalence	*n*	%	*n*	%	*n*	%
Last month	25	12.3	8	10.3	17	13.6
Last 6 months	29	14.3	11	14.1	18	14.4
Males*	7	24.1	3	27.3	4	22.2
Females*	22	75.9	8	72.7	14	77.8
Last year	31	15.3	12	15.4	19	15.2
Lifetime	34	16.7	14	18.0	20	16.0

n, number of subjects; ICD = International Classification of the Diseases; *data based on the last 6 months' prevalence.

Table 3 Characteristics of the migraine headaches*

	Totally blind ($n = 11$)†		Subnormal vision ($n = 18$)‡			Total ($n = 29$)	
	n	%	*n*	%	*P***	*n*	%
Duration in hours							
4–12	3	27.3	5	27.8	0.694	8	27.6
13–24	4	36.4	8	44.4	0.971	12	41.4
25–72	2	18.2	4	22.2	0.830	6	20.7
Not available	2	18.2	1	5.6	0.651	3	10.3
Characteristics of pain							
Throbbing	10	90.9	13	72.2	0.463	23	79.3
Compressive	–		4	22.2	0.259	4	13.8
Mixed	1	9.1	1	5.6	0.694	2	6.9
Intensity of pain							
Mild	–		1	5.6	0.806	1	3.5
Moderate	5	45.5	6	33.3	0.793	11	37.9
Severe	6	54.5	11	61.1	0.969	17	58.6
Laterality of pain							
Bilateral	4	36.4	7	38.9	0.795	11	37.9
Unilateral	4	36.4	8	44.4	0.971	12	41.4
Shifting sides	3	27.2	3	16.7	0.838	6	20.7

n, number of subjects; *data based on the migraine headaches occurring in the last 6 months; †ICD-10 category 5; ‡ICD-10 categories 1–4; **CP test.

Table 4 Characteristics of the associated symptoms*

	Totally blind ($n=11$)†		Subnormal vision ($n=18$)‡			Total ($n=29$)	
	n	%	*n*	%	*P*§	*n*	%
Aggravation by activity							
Present	10	90.9	15	83.3	0.983	25	86.2
Not present	–	–	3	6.7	–	3	10.4
Unknown	1	9.1	–	–	–	1	3.4
Anorexia	8	72.7	11	61.1	0.814	19	65.5
Nausea	7	63.6	11	61.1	0.795	18	62.1
Vomiting	4	36.4	7	38.9	0.795	11	37.9
Photophobia							
Present	–	–	11	61.1	0.004	11	37.9
Not present	–	–	6	33.3	–	6	20.7
Unknown	–	–	1	5.6	–	1	3.5
Not applicable**	11	100	–	–	–	11	37.9
Phonophobia	11	100	17	94.4	0.806	28	96.6
Aura	2	27.2	2	11.1	0.543	4	13.8

n, number of subjects; *data based on the migraine headaches occurring in the last 6 months; †ICD-10 category 5; ‡ICD-10 categories 1–4; §CP test; **blind subjects.

were reported as severe by 58.6% of the patients. Although patients with subnormal vision reported severe attacks more frequently than those totally blind, this difference was not statistically significant ($P=0.969$, CP test). Four female patients reported migraine with aura. Aura was reported to be auditory by one and visual by three. The auditory aura patient was totally blind and described her auditory aura as bilateral tinnitus. Two of the visual aura patients had subnormal vision, and visual aura was described by both as scintillating scotomata lasting 2–4 min, usually preceding the headaches.

The other visual aura patient had had migraine headaches since adolescence, sometimes preceded by bilateral scintillating scotomata lasting 1 min. She started suffering a progressive visual loss at the age of 30 and her visual aura disappeared. An occipital meningeoma was diagnosed and resected and in the 4 years of follow-up she has remained a migraineur, although her migraine visual aura has remitted. The clinical features of the migraine attacks in the visually impaired patients that reported migraine episodes in the last 6 months are summed up in Tables 3 and 4.

The findings obtained through the application of the TAS will be presented elsewhere.

Discussion

Prolonged exposure to the glare of intense light, particularly to sunlight, has been reported by 30% to 45% of migraineurs to trigger migraine attacks (17, 18). The patient with migraine without aura and with a spreading oligemia described by Woods et al. presented an attack when submitted to complex visual stimuli (12). More recently, Cao et al. have reported attacks of migraine with aura triggered by specific visual stimuli (19). After Moskowitz hypothesized on the role of the trigeminal vascular system in migraine pain (20), Lance postulated the neurovascular hypothesis, emphasizing the role of endogenous or environmental stimuli over the hypothalamus and its efferent pathways projecting to brainstem nuclei, such as the locus coeruleus or the raphe nuclei, on the triggering of migraine attacks (21). Recently, we have shown light stimulation to induce not only discomfort in migraineurs at lower levels than in controls, but also to lower their trigeminal and cervical pain perception thresholds (10), a finding that suggested that visual input, by lowering pain thresholds, could facilitate migraine attacks.

Conversely, attacks beginning in the absence of light, i.e. during sleep, are known to happen in migraineurs (22). Peatfield and Rose have described the case of a woman whose eyes were enucleated in her early childhood, who started to present migraine with aura soon afterwards (23). Her migraine with aura attacks persisted through her childhood, adolescence and adulthood in spite of the lack of visual input.

Disorders of the eyes leading to blindness, especially acute glaucoma, are known to be associated with pain in the head or in the eye. However, the clinical features

of headaches related to eye pathology usually differ from those of migraine (14), although they may rarely mimic migrainous features (24). Pradalier et al. (25) have reported a high prevalence of migraine in a population of patients with glaucoma, a finding that has to be carefully interpreted, as the questionnaire used to diagnose migraine was applied by ophthalmologists not familiar with that condition.

Interestingly enough, the clinical features of migraine attacks described by our patients were very similar to those reported by visually normal individuals (26, 27), but phonophobia was reported at a higher proportion by the visually impaired. Surprisingly, photophobia was reported by a still higher proportion of the individuals with partial visual impairment, in spite of the fact that most of these patients could barely perceive light stimuli. The fact that most patients presented severe visual impairment might explain the lack of significance of the finding of more severe attacks by subjects with partial rather than complete visual impairment, as a larger population would be needed to reach a definite conclusion. There were no differences between the other features of the migraine attacks on totally blind individuals and on those with subnormal vision.

Our prevalence numbers were lower than those found by Bigal et al. (28) and by Sanvito et al. (29) in Ribeirão Preto and São Paulo, mid-eastern Brazil, but these authors have carried out their studies on highly selected populations, as they searched for the prevalence of migraine among the personnel of a university hospital and among medical students, respectively. The study of Barea et al. in Porto Alegre, southern Brazil, reported lower numbers, but it was carried out on a population of a rather lower age bracket (30). The fact that the population studied is highly Caucasian might explain why the migraine prevalence numbers found were very similar to those described in some population-based studies carried out in the northern hemisphere (31, 32). Curitiba is the capital of the state of Paraná, in south–eastern Brazil, located 900 m (3000 feet) above sea level, near the Atlantic margin of the Brazilian Highlands and the headwaters of the Iguaçu river. Since 1654 it has been colonized by Caucasians of Portuguese ancestry. From 1854 to 1914 it received many Italian, German and Polish immigrants, a smaller wave of Syrians and Japanese coming later (33). Caucasians predominated in the 1991 census as Whites made up 81.7% of its population (34), followed by 15.7% of Mulattos, 1.7% of Blacks, and 0.9% of Amerindians and Orientals (34). Further HLA analysis of the different sub-populations confirmed Portuguese, Italian, German and Polish Caucasian haplotypes in 94% of the White population. The other sub-populations revealed a more pronounced interethnic admixture, with Caucasian haplotypes found in 57% of the Mulattos and 25% of the Black population (35).

According to our results, complete or partial visual impairment seems not to affect the prevalence of migraine, as they suggest that lacking or diminished light input does not affect the expression of migraine on predisposed individuals. Our subjects derived from an estimated population of approximately 11 200 visually impaired individuals (36), being thus representative (1.8%). However, our sample of migraine patients was small and a type two error in the statistical analysis cannot be completely excluded.

The finding that the prevalence of migraine is unaffected by diminished or lacking light input suggests that the environmental visual stimuli play a secondary role in the expression of migraine. However, as suggested by the report of phonophobia by most of the patients and of photophobia by the subjects with subnormal vision, the role played by each sensorial channel on migraine expression may depend on the level of activity of that specific sensorial channel in a given individual.

Although our findings suggest that normal visual processing is not a *sine qua non* condition for the expression of migraine, the role of the visual system on migraine pathophysiology remains a challenge to be clarified.

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Prevalence of astigmatism in headache

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Abstract

Aim: To study the prevalence of uncorrected low grade astigmatism as the sole cause of headache.

Materials and Methods: It is a prospective cross sectional study, conducted in the Department of Ophthalmology for 18 months. A total of 400 patients presenting with headache as the single complaint were enrolled in the study. All the patients were evaluated for presence of astigmatism with the help of visual acuity, retinoscopy, keratometry and post mydriatic test and then the follow up was done at 4, 8 and 12 week to see the status of headache.

Results: The prevalence of uncorrected astigmatism among cases presenting with headache as the single complaint was 49.3%. Age of patients ranged from 14 to 35 years with a mean age of 22.85±6.43 years, however, proportion of patients with age ≤20 years was significantly higher among astigmatism cases (50.8%) as compared to that of patients without astigmatism (40.9%). Mean age of astigmatic patients was also lower (21.72±5.53 years) as compared to that of those not having astigmatism (23.94±7.03 years). Majority of patients were females (69.8%). Statistically no significant association between gender and astigmatism was seen.

Conclusion: The findings of the study thus suggested that among cases presenting with headache as the sole cause, prevalence of astigmatism is quite high and treatment of uncorrected astigmatism brought about a phenomenal improvement in symptoms of headache.

Keywords: Astigmatism, Headache.

Introduction

Astigmatism is a Greek word, which has two components, "a" means absence and "stigma" means a point. It is a refractive error (ametropia) that occurs when parallel rays of light entering the non-accommoding eye are not focused on the retina.[1]

Refractive errors are one of he leading causes of headache and among these Astigmatism is of significant importance.[2] Association between refractive errors and headache has been established in various studies in almost all age groups.[3,4] Studies have reported that refractive errors alone cause for nearly 44% of total cases complaining of headache, of which 63.6% have astigmatism.[5]

Although International Headache Society (IHS) in its classification system[6] places Headache Associated with Refractive Errors (HARE) as a separate category of diagnosis of headache with the following diagnostic criteria:

1. Uncorrected [or miscorrected] refractive errors (e.g. hypermetropia, astigmatism, presbyopia, wearing of incorrect glasses).
2. Mild headaches in the frontal region and in the eyes themselves.
3. Pain absent on awakening, and aggravated by prolonged visual tasks at the distance or angle where vision is impaired.

The evidence suggests a close relationship between headache and refractive errors in general and astigmatism in particular.[7-10]

A low magnitude of astigmatism is the most common refractive cause of ocular headaches in young individuals.[11-13] In low grade astigmatism, to obtain distinct vision, efforts of accommodation put a considerable strain on the eyeball and lead to symptom of asthenopia, with headache being the most prominent symptom.[14] A symptomatic relief in asthenopic symptoms has been reported following correction of refractive errors,[15] thus lending strength to the relationship between refractive errors and headache.

Although there is a strong popular belief of causative effect of refractive errors on headache yet there is no definite evidence that refractive errors alone can be a cause of chronic headaches.[16] With this background, the present study was planned to study the prevalence of uncorrected astigmatism as the sole cause of headache and to quantify the minimum extent of astigmatic error which can be responsible for the symptomatic presentation of headache and to evaluate the impact of refractive correction using spectacles on the symptomatic relief of headache.

Despite this relationship being widely assumed, there are limited studies evaluating the prevalence of astigmatism among patients presenting for refractive error assessment with a sole complaint of headache. Moreover, the literature is scarce regarding the systematic assessments studying the impact of corrective measures on the headache complaints.

Materials and Methods

The present study was a prospective cross sectional study, conducted in the Department of Ophthalmology at Era's Lucknow Medical College and Hospital, Lucknow after getting Institutional Ethical clearance.

Inclusion criteria comprised of patients presenting with headache as the sole complaint, aged between15-35 years and giving valid informed consent and excluding those cases having any known disease which may cause or contribute to headache.

Demographic details including age and sex were noted. Thorough ocular evaluation was done on all selected patients both clinically as well as with the help of diagnostic instruments. Visual acuity both with and without pin hole was done using Snellen's charts; both uncorrected and best corrected visual acuity was noted. Retinoscopy was performed to evaluate the astigmatism using Pristley smith retinoscope, Keratometry was performed using Keratometer.

Astigmatism was defined as cylindrical refractive error measured after cycloplegia of more than or equal to 1.5 Diopter in either eye expressed in positive correcting cylinder form.

The astigmatism was further classified as:

Simple myopic astigmatism: when there was myopia in one meridian and emmetropia in the other meridian, *e.g.* -0.50 x 180.

Compound myopic astigmatism: when there was myopia in all meridians, of differing amounts, *e.g.* -0.50 DS/ -0.50DC x 180.

Simple Hypermetropic Astigmatism: When there was hyperopia in one meridian and emmtropia in the other meridians. For example +2.5 DC x 180 (diopter sphere).

Compound Hypermetropic Astigmatism: When there was hypermetropia in all meridians, of differing amounts. An example of compound hyperopic astigmatism is +0.50DS/ +0.50DC x 180.

Mixed astigmatism: When there is myopia in one meridian and hyperopia in the other meridian. An example of this is -0.75DS/ +1.25DC x 180.

All the patients of astigmatism were prescribed glasses and were requested for follow up at 4. 8 and 12 week of using glasses. At each follow up the patients were advised to rate the change in pattern of headache as either complete resolution, improvement, no change or worsening of Headache. The data so collected was subjected to statistical analysis using Statistical Package for Social Sciences, version 15.0. For, categorical data Chi-square test was used whereas continuous data was analyzed using paired 't'-test and student "t"-test. The confidence level of the study was kept at 95% and hence a "p" value less than 0.05 indicated a statistically significant association.

Results

The present study was carried out with an aim to assess the role of uncorrected astigmatism as the sole cause of headache. For this purpose, a total of 400 patients presenting with headache as the single complaint visiting our facility for refractive error evaluation were enrolled in the study. All the patients were evaluated for the presence of astigmatism as per criteria defined in the Materials and Method section of this work. Cases were subsequently grouped as per presence of astigmatism. All the patients with astigmatism were invited to participate in an intervention for correction of astigmatism by suitable spectacles. A total of 140 (71.1%) consented to participate in the study.

All the patients undergoing astigmatism correction were followed up at 4, 8 and 12 weeks.

Table 1: Distribution of cases according to astigmatism status

S.N	Group	No. of cases	Percentage
1.	Group I - with Astigmatism	197	49.3
2.	Group II - No astigmatism	203	50.8

Out of 400 pateints, a total of 197 (49.3%) were found to have uncorrected astigmatism. These patients comprised the Group I of study while remaining 203 (50.8%) did not have astigmatism and comprised the Group II of study. (Table 2)

Table 2: Socio-demographic details

S.N	Age group	Group I (n=197)		Group II (n=203)		Total	
		No.	%	No.	%	No.	%
1.	≤20 Yrs	100	50.8	83	40.9	183	45.8
2.	21-30 Yrs	88	44.7	80	39.4	168	42.0
3.	>30 Yrs	9	4.6	40	19.7	49	12.3
Mean Age±SD		21.72±5.53 (15-35)		23.94±7.03 (14-35)		22.85±6.43 (14-35)	
χ^2=27.56 (df=2); p<0.001							
SN	**Gender**	**Group I (n=197)**		**Group II (n=203)**		**Total**	
		No.	**%**	**No.**	**%**	**No.**	**%**
1.	Male	60	30.5	61	30.0	121	30.3
2.	Female	137	69.5	142	70.0	279	69.8
χ^2=-0.008 (df=1); p=0.929							

SN	VA	Group I (n=197)		Group II (n=203)		Total	
		No.	%	No.	%	No.	%
1.	VA 6/6	137	69.5	163	80.3	300	75.0
2.	VA 6/9	60	30.5	40	19.7	100	25.0
χ^2=-6.6165 (df=1); p=0.013							

Age of all patients ranged from 14 to 35 years. Maximum number of cases (n=183; 45.8%) were aged ≤20 years followed by those aged 21-30 years (n-168, 42%) and >30 years (n=49, 12.3%) respectively.

On evaluating the data in to groups proportion of those aged ≤20 years and 21-30 years was found to be higher in Group I (n=100, 50.8% and n=88, 44.7%) as compared to that in Group II (n=83, 40.9% and n=80, 39.4%) whereas proportion of those aged >30 years was higher in Group II (n=40, 19.7%) as compared to that in Group I (n=9, 4.6%). Statistically, this difference was significant (p<0.001).

Majority of patients were females (n=279, 69.8%). The proportion of females was slightly higher in Group II (n=142, 70%) as compared to that in Group I (n=137, 69.5%) (p=0.929).

Most of patients had visual acuity 6/6 in both the eyes (n=300, 75%). There were (n=100, 25%) patients having visual acuity 6/9 in one or both the eyes. On comparing the visual acuity status between two groups, proportion of those having visual acuity 6/9 was significantly higher in Group I (n=60, 30.5%) as compared to that in Group II (n=40, 19.7%) (p=0.013).

Table 3: Distribution of cases according to type of Astigmatism (n=197)

S.N	Type	No. of cases	Percentage
1.	Simple myopic	170	86.3
2.	Simple hypermetropic	22	11.2
3.	Compound hypermetropic	5	2.5
4.	Compound myopic	0	0
5.	Mixed	0	0

Further, distribution of group I patients into various types of we found that to astigmatism, Simple myopic type was most common (n=170, 86.3%) followed by simple hypermetropic (n=22, 11.2%) and compound hypermetropic (n=5, 2.5%) types.

All the 197 patients with astigmatism were invited to participate in an intervention for correction of astigmatism by suitable spectacles. A total of 180 (n=129, 91.4%) consented for participation. All the patients undergoing astigmatism correction were followed up at 4, 8 and 12 weeks. Final follow up was done at 12 weeks.

However, finally, 40 out of 180 consenting to participate in the study did not complete follow up. Hence, in final assessment only 140 patients were left. The outcome of intervention is being shown for these 140 patients. At first follow up, a total of (n=37, 26.4%) patients were relieved, (n=55, 39.3%) showed improvement, (n=37, 26.4%) showed no change while (n=15, 7.9%) showed worsening in headache

At second follow up, a total of (n=55, 39.3%) patients were relieved, (n=54, 38.6%) showed improvement, (n=22, 15.7%) showed no change while (n=9, 6.4%) showed worsening in headache. At third and final follow up, a total of (n=78, 55.7%) patients were relieved, (n=49, 35%) showed improvement, (n=8, 5.7%) showed no change while (n=5, 3.6%) showed worsening in headache.

Table 4: Statistical evaluation of change between different follow-up intervals (Wilcoxon signed rank test)

S.N.	Comparison	Z	'p'
1.	FU 1 vs FU 2	7.54	0.054
2.	FU 1 vs FU 3	35.9	<0.001
3.	FU 2 vs FU 3	11.9	0.008

On evaluating between the follow-up change in status of patients, though proportion of those showing relief and improvement showed a continuous increase by each follow up, however, the difference was significant only between first vs third (p<0.001) and second vs third (p=0.008) follow up intervals. No significant association was observed between Astigmatism type and outcome.

Table 5: Comparison of Outcome among different astigmatism types

SN	Outcome	Astigmatism Type					
		Simple Myopic		Simple Hypermetropic		Compound Hypermetropic	
At first follow up		n=113		n=22		n=5	
		No.	%	No.	%	No.	%
First Follow Up							
1.	No change	31	27.4	4	18.2	2	40.0

2.	Relieved	45	39.8	9	40.9	1	20.0
3.	Improvement	30	26.5	7	31.8	0	0.0
4.	Worsening	7	6.2	2	9.1	2	40.0
χ^2=10.033; p=0.123							
Second Follow Up							
1.	No change	44	38.9	7	31.8	4	80.0
2.	Improvement	44	38.9	10	45.5	0	0.0
3.	Relieved	18	15.9	4	18.2	0	0.0
4.	Worsening	7	6.2	1	4.5	1	20.0
χ^2=7.066; p=0.315							
Third Follow Up							
1.	No change	66	58.4	9	40.9	3	60.0
2.	Improvement	36	31.9	12	54.5	1	20.0
3.	Relieved	7	6.2	1	4.5	0	0.0
4.	Worsening	4	3.5	0	0.0	1	20.0
χ^2=9.019; p=0.173							

Discussion

Refractive errors and headache are some of the common health problems.[17-19] In different populations the prevalence of refractive errors range from 13 to 80% while incidence of chronic primary headache and sporadic headache are reported to be 15% and 40% respectively.[17] The high prevalence of both problems in general population prompts towards a possible relationship between two. Headache is a recognized symptom associated with refractive errors especially astigmatism. Experimental studies among computer users have shown that induced astigmatism leads to production of symptoms including headache.[17] The present study was carried out with an aim to make a correlative evaluation of uncorrected astigmatism as the sole cause of headache and to assess whether correction of astigmatism has any impact on complaints of headache.

For this purpose, a total of 400 patients presenting with headache as the single complaint visiting our facility for refractive error evaluation were enrolled in the study. The prevalence of astigmatism among these patients was found to be 49.3%. Thus almost half the patients presenting with complaints of headache had astigmatism. Prevalence of astigmatism among headache cases has been reported to vary substantially in different studies using different sampling frames. In one study, Akinci et al.[7] who conducted a case-control study among patients with headache enrolled as cases and controls without headache found the rate of astigmatism to be 19.7%. However, Marasini et al.[11] in their study from Nepal reported this prevalence rate to be 28%. On the other hand, Abolbashari et al.[10] in their study from an Iranian facility reported majority of headache patients (54.1%) to be having astigmatism. In two recent studies from India, the prevalence rates of astigmatism among headache patients were reported to be 41% and 40.8% respectively. The prevalence rates 49.3% as assessed in present study is thus within these ranges and shows that astigmatism remains to be one of the most important underlying morbidities among patients presenting with headache.

Age of patients ranged from 14 to 35 years with a mean age of 22.85±6.43 years, however, proportion of patients with age ≤20 years was significantly higher among astigmatism cases (50.8%) as compared to that of patients without astigmatism (40.9%). Mean age of astigmatism patients was also lower (21.72±5.53 years) as compared to that of those not having astigmatism (23.94±7.03 years). A relationship between type of astigmatism and age has been reported in several previous studies.[17,18] Studies conducted among infants and young children have shown that the prevalence of against-the-rule astigmatism is quite high in infants and toddlers, however, it disappears by the time the children reach school age[17]. Although, the present study did not include too young children, however, the role of age-related disappearance of astigmatism to be the cause behind significantly higher age of patients without astigmatism can be explained to a certain extent on the basis of the phenomenon of disappearance of astigmatism among children with advanced age.

In present study, majority of patients were females (69.8%). Statistically no significant association between gender and astigmatism was seen. The complaints of headache have been reported to be more common in females as evidenced in various epidemiological studies,[17,18] however, the present study failed to find out any association of astigmatism with gender.

Impact of correction of refractive error and astigmatism on headache frequency was also evaluated retrospectively in a study by Akinci et al.[7] who also showed proportion of patients with miscorrected refractive error to be significantly higher in headache cases (16.5%) as compared to controls (2%), thus emphasizing the fact that miscorrected or uncorrected refractive error and astigmatism have a detrimental role on the frequency of headache.

Incidentally, there are limited or almost negligible studies on the relationship between headache and

astigmatism and evaluation of impact of correction of astigmatism on headache despite a plenty of evidence reporting astigmatism prevalence to be higher in headache patients, especially in young age. The present study is probably the first attempt to systematically study the problem and shows that this relationship exists and correction of astigmatism can be helpful in relief from headache. Hence, further studies to evaluate this relationship further in detail are recommended.

Conclusion

The findings of the study thus suggested that among cases presenting with headache as the sole cause, prevalence of astigmatism is quite high and treatment of uncorrected astigmatism brought about a phenomenal improvement in symptoms of headache. The findings of present study thus emphasize the need for evaluation of astigmatism among persons with headache as a sole complaint, especially those in young age. These findings are encouraging, however, given fewer number of studies on the issue require further evaluation. Moreover, considering the subjectivity associated with headache, long-term post-correction follow-up is recommended to confirm whether the treatment effects are lasting.

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REVIEW

Primary headache disorders and neuro-ophthalmologic manifestations

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Abstract: Headache is an extraordinarily common complaint presenting to medical practitioners in all arenas and specialties, particularly primary care physicians, neurologists, and ophthalmologists. A wide variety of headache disorders may manifest with a myriad of neuro-ophthalmologic symptoms, including orbital pain, disturbances of vision, aura, photophobia, lacrimation, conjunctival injection, ptosis, and other manifestations. The differential diagnosis in these patients is broad and includes both secondary, or symptomatic, and primary headache disorders. Awareness of the headache patterns and associated symptoms of these various disorders is essential to achieve the correct diagnosis. This paper reviews the primary headache disorders that prominently feature neuro-ophthalmologic manifestations, including migraine, the trigeminal autonomic cephalalgias, and hemicrania continua. Migraine variants with prominent neuro-ophthalmologic symptoms including aura without headache, basilar-type migraine, retinal migraine, and ophthalmoplegic migraine are also reviewed. This paper focuses particularly on the symptomatology of these primary headache disorders, but also discusses their epidemiology, clinical features, and treatment.

Keywords: headache, migraine, trigeminal autonomic cephalalgias, neuro-ophthalmologic, aura, photophobia

Introduction

Headache is an extraordinarily common symptom and presenting complaint to medical practitioners in all arenas and specialties – particularly for primary care physicians and neurologists, but ophthalmologists as well. A wide variety of headache disorders may manifest with a myriad of neuro-ophthalmologic symptoms, including orbital pain, disturbances of vision, photophobia, lacrimation, conjunctival injection, ptosis, and other manifestations. The differential diagnosis in these patients is broad and includes both secondary, or symptomatic, and primary headache disorders. Awareness of the headache patterns and associated symptoms of these various disorders is essential to achieve diagnostic certainty and therapeutic success.

Secondary causes of headache presenting with neuro-ophthalmologic manifestations have been extensively reviewed elsewhere.[1] Herein, primary headache disorders that prominently feature neuro-ophthalmologic manifestations, including migraine, the trigeminal autonomic cephalalgias (TACs), and hemicrania continua (HC) are reviewed. This review focuses particularly on the symptomatology of these primary headache disorders and the pathophysiology of the neuro-ophthalmologic manifestations, but their epidemiology, diagnosis, and management will also be reviewed.

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Headache classification

A systematic approach to headache classification is essential for both clinical management and research, which spurred the development of the first edition International Classification of Headache Disorders (ICHD-1) in 1988.[2] The second edition (ICHD-2) revised the first edition and is the current standard for headache diagnosis and classification.[3] The ICHD-2 classifies headache disorders into three major categories: (1) primary headaches; (2) secondary headaches; and (3) cranial neuralgias, central and primary facial pain, and other headaches. This review will focus exclusively on primary headache disorders. Most of the common associated neuro-ophthalmologic symptoms have been incorporated into the diagnostic criteria of various primary headaches, such as photophobia in migraine.

Neuro-ophthalmologic symptoms

A host of neuro-ophthalmologic symptoms may occur in primary headache disorders, and are summarized in Table 1.

Photophobia

Photophobia is the clinical term that may encompass three different phenomena, all of which are common in patients with headache: (1) abnormal sensitivity to light; (2) ocular discomfort; and (3) exacerbation of headache by light.[4] Photophobia is described by 66%–88% of individuals with migraine.[5] Three-quarters of patients with migraine with aura report light as their most common trigger.[6] Light exposure can worsen acute migraine, and affected individuals typically escape to a dark place. Photophobia may also interfere with correct visual and color perception as well as induce visual perceptual distortions.[7]

The presence of unilateral photophobia may be clinically useful in the differential diagnosis of primary headaches. Although photophobia is almost always bilateral in patients with migraine – even in the presence of unilateral head pain, it is more often unilateral – ipsilateral to the side of head pain – in patients with TACs and HC.[8] Only 4% of episodic migraine patients with photophobia experience this symptom unilaterally, while 80% of those with episodic cluster headache (CH) and 55% of those with HC have unilateral symptoms.[8]

Pathophysiology

The exact signaling pathways and neurophysiological features of photophobia are not well understood, but are thought to involve the trigeminal afferent pathways with possible input from the pretectal nuclei, occipital cortex, and thalamus. Irritation to any region supplied by the trigeminal nerve can result in photophobia. Recent studies have suggested that the visual cortex is hyperexcitable and a major contributor to the symptom of photophobia in migraine.[5,9,10] Recent positron emission tomography data indeed note the presence of occipital cortex hyperexcitability during migraine attacks and even after migraine alleviation with triptans utilizing low luminous stimulation.[11]

The most likely anatomical localization of photophobia is at the site where the visual and trigeminal nociceptive pathways converge. The anatomic pathway by which light drives migraine pain has been recently identified in a study of migraine patients who were legally blind but still experienced photophobia with light stimulation.[12] The likely candidate locus for such an interaction is a nucleus in the posterior thalamus, which receives input from non-image forming, intrinsically photosensitive retinal ganglion cells and projects to somatosensory cortices.

Visual aura

A classic neuro-ophthalmologic manifestation of migraine is visual aura. Typical visual aura is classically described as

Table 1 Neuro-ophthalmologic manifestations commonly occurring in primary headache disorders

	Photophobia	Visual aura	Autonomic symptoms (ptosis, myosis, lacrimation, eyelid edema)
Migraine	Common, bilateral	Common, binocular, and homonymous	Common but not prominent, usually bilateral
Basilar-type migraine	Common	Common, occurs simultaneously in temporal and nasal fields	Uncommon
Retinal migraine	Common	Monocular, often ipsilateral to the head pain (commonly occurs in patients who also have migraine with typical visual aura)	Uncommon
Trigeminal autonomic cephalalgias	Common, often unilateral	Uncommon but reported	Prominent, strictly unilateral
Hemicrania continua	Common, often unilateral	Uncommon but reported	Prominent with exacerbations, strictly unilateral; also associated with ipsilateral ocular foreign body sensation[98]

having a hemianopic distribution and expanding in the shape of a crescent with a bright, flickering, ragged edge. This arc of scintillating lights, known as the fortification spectrum, may form into a herringbone-like pattern that expands to encompass an increasing portion of a visual hemifield. Visual distortions such as metamorphopsia (a visual distortion in which straight lines appear curved), micropsia (objects appear to be smaller than their actual size), and macropsia (objects appear to be larger than their actual size) can also occur, but are more common in children.[13–15] "Positive" symptoms such as photopsia (the sensation of unformed flashes of light before the eyes) or phosphenes (simple flashes) are sometimes followed by "negative" symptoms such as a scotoma (partial loss of sight).

The flickering or scintillating quality of aura elements is commonly reported and, according to one study, was described in approximately 70% of visual auras. To measure the perceived rate of flicker (temporal frequency) during visual auras, Crotogino et al asked migraine with aura subjects to match the flickering of their observed auras with the flickering generated by portable devices that contained adjustable light-emitting diodes.[16] To record the rate of aura flicker, subjects were instructed to look directly at the light-emitting diode and to adjust the dial until the temporal frequency of the light-emitting diode matched the flickering in their aura. The mean rate of flicker across individuals was approximately 17 Hz, although considerable interindividual variability was found.

A recent, detailed reappraisal of visual aura in 122 migraine patients across two international centers revealed that aura symptoms may be colored or black and white, have no consistent relationship to the side of head pain, and often simply consist of a visual "shimmering." In addition, the auras are often evolutive, heterogeneous, and pleomorphic.[17]

Pathophysiology

There is growing evidence that cortical spreading depression (CSD) underlies most forms of migraine aura.[18] CSD, originally described by Leao, is an intense depolarization of neuronal and glial membranes accompanied by a massive disruption of ionic gradients, and loss of membrane resistance.[19] It is characterized by cessation of spontaneous or evoked synaptic activity, and massive glutamate and potassium release, causing extracellular potassium concentrations to rise. The marked decrease in membrane resistance also results in an increase in intracellular sodium and calcium. Elevated potassium concentration is a strong depolarizing stimulus that promotes the contiguous spread of a depolarization wave across neural tissue. Large unregulated release of excitatory amino acids like glutamate and direct intercellular transfer of ions and small molecules through gap junctions facilitate the spread.[20] This intense neuroglial depolarization facilitates the access of hydrophilic molecules to approximate and discharge nociceptive meningeal trigeminovascular afferents.

How CSD is triggered in the human cortex during a migraine attack is uncertain, but it seems clear that CSD can subsequently activate central trigeminovascular neurons.[21,22] Once triggered, CSD slowly propagates (2–5 mm/minute) to adjacent tissues without regard to functional cortical divisions or arterial territories. CSD is associated with characteristic blood flow fluctuations in the cerebral cortex: an initial, small, brief, species-dependent reduction in cerebral blood flow is followed by a profound hyperemia and then by a long-lasting oligemia, which usually lasts up to an hour.[18] In 1958, Milner pointed out the similarity between the velocity of CSD propagation and the march visual aura reported by Lashley.[23,24] The velocity of spread is approximately 3 mm/minute, consistent with the speed of CSD in the human cortex. Recently, functional magnetic resonance imaging detected focal increase in occipital blood flow spreading at a rate of 3.5 mm/minute, retinotopically congruent with a patient's visual aura.[25]

Autonomic symptoms

The signature neuro-ophthalmic feature of the TACs is the association with prominent ipsilateral cranial autonomic features (Table 2). The TACs include CH, paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).[26] Lacrimation and conjunctival injection are the most common cranial autonomic symptoms followed by nasal congestion or rhinorrhea. Ptosis and myosis are also commonly reported. These autonomic features are typically transient, lasting only for the duration of the attack, with the exception of an interictal partial postganglionic Horner syndrome seen occasionally in patients with CH.

In migraine, patients may commonly possess attack-related cranial autonomic features as well. However, as opposed to the TACs, the autonomic symptoms are more likely to be bilateral, unrestricted to the side of the pain, of a lesser intensity, and occur on a less consistent basis with attacks.[27]

Table 2 Clinical features of the trigeminal autonomic cephalalgias and hemicrania continua

	Cluster headache	Paroxysmal hemicrania	SUNCT	Hemicrania continua
Sex F:M	1:2.5–7.2	1.6–2.4:1	1:1.5	1.8:1
Pain type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp	Throbbing, sharp, pressure
Pain severity	Severe	Severe	Severe	Baseline: mild, moderate, or severe Exacerbations: severe
Pain site	Orbit, temple	Orbit, temple	Periorbital	Orbit, temple, hemicranial
Attack frequency	1/alternate day–8/day	1–40/day (>5/day for more than half the time)	3–200/day	Daily and continuous
Duration of attack	15–180 minutes	2–30 minutes	5–240 seconds	Continuous
Autonomic features	Yes	Yes	Yes	Yes
Migrainous-associated features*	Yes	Yes	One-third	Yes
Alcohol trigger	Yes	One-fifth	No	Yes
Cutaneous triggers	No	No	Yes	No
Indomethacin effect	Variable but usually ineffective	Absolute response	Variable but usually ineffective	Absolute response
Abortive treatment	Sumatriptan injection Sumatriptan intranasal Zolmitriptan intranasal Oxygen	None**	None**	Indomethacin
First-line prophylactic therapy	Verapamil	Indomethacin	Lamotrigine	Indomethacin
Associated functional neuroimaging findings	Ipsilateral posterior hypothalamic gray matter fMRI activation during attacks[101,102]	Contralateral posterior hypothalamic gray matter fMRI activation[103]	Ipsilateral posterior hypothalamic gray matter fMRI activation[104,105]	Contralateral posterior hypothalamic gray matter, ipsilateral dorsal rostral pontine, ventrolateral midbrain, and pontomedullary junction PET activation[106]

Notes: *Photophobia, phonophobia, nausea, vomiting; **attacks too short to treat acutely in paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Abbreviations: F, female; fMRI, functional magnetic resonance imaging; M, male; PET, positron emission tomography; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Pathophysiology

The ipsilateral autonomic features in the TACs suggest cranial parasympathetic activation (lacrimation, eyelid edema, rhinorrhea, and nasal congestion) and sympathetic hypofunction (ptosis and myosis). There is considerable experimental animal literature to document that stimulation of trigeminal afferents can result in cranial autonomic outflow, the trigeminal-autonomic reflex.[28] Goadsby and Lipton have suggested that the pathophysiology of the TACs may be related to a central disinhibition of the trigeminal-autonomic reflex.[26]

Diplopia

Diplopia is an extraordinarily uncommon feature of primary headache disorders, and its presence mandates aggressive exclusion of secondary causes through cerebrovascular imaging and cerebrospinal fluid analysis. When diplopia accompanies symptoms of migraine, it is occasionally diagnosed as "ophthalmoplegic migraine." Ophthalmoplegic migraine is actually a rare form of neuralgia as opposed to a migraine subtype and, despite its name, is appropriately not listed as a migraine subtype in the ICHD-2. The condition has been recently reclassified as a demyelinating neuropathy of the ocular cranial nerves. In this condition, which may predominate in childhood, diplopia is often associated with migraine-like headache and periorbital pain.[29] The oculomotor nerve is most commonly involved followed by the abducens nerve and rarely the trochlear nerve. Ophthalmoplegia may last from days to months, usually with spontaneous remission. Magnetic resonance imaging findings include reversible enhancement of the cisternal segment of the oculomotor nerve and focal thickening at the exit of the nerve in the interpeduncular cistern.[30] Single photon emission computed tomography studies during attacks of ophthalmoplegia and migraine have demonstrated reversible reductions in regional cerebral blood flow in the thalamus ipsilateral to the site of ophthalmoplegia.[31] These findings suggest reversible ischemia in the territories of perforating branches of the posterior cerebral artery may accompany ophthalmoplegic migraine and possibly bear some relationship to the clinical features.

Diplopia has also been reported in several patients with CH, and may be related to compression of the oculomotor or abducens nerves by inflammatory and vasodilatory changes that occur within the cavernous sinus during CH attacks.[32] However, in the TACs, the presence of diplopia is the rare exception rather than the rule.

Palinopsia

Visual hallucinations are found in several neurological conditions and migraine is well recognized as a cause of simple visual hallucinations. The experience of retaining a visual image of objects remaining in the field of view after the patient has looked away or returning after a short delay is known as palinopsia (Greek: palin, again and opsis, vision). To investigate the frequency of palinopsia (visual perseveration) in patients with migraine with and without aura, Belcastro et al conducted structured interviews in 118 migraine patients matched with control subjects.[33] Palinopsia occurred in approximately 10% of migraine patients, and was seen more frequently in migraine with aura than in migraine without aura. Visual perseveration consisted of real objects or patterns that were located in the peripheral visual field after looking away, and these were unlikely to be associated with the onset of migraine attacks or an aura.

The mechanisms of palinopsia remain uncertain. A range of symptoms collectively termed palinopsia has been linked to dysfunction within parietal-lobe coordinate systems. Functional magnetic resonance imaging data has shown that the onset of palinopsia is associated with activation of the occipitotemporal region of the nondominant hemisphere. The most likely pathogenetic possibilities are partial seizures, cerebral hyperperfusion adjacent to areas of cortical damage, or hallucination in cases of visual loss.

Migraine

Epidemiology

Migraine is by far the most common primary headache disorder, affecting approximately 28 million people in the United States.[34] In 2004, the largest epidemiologic study of migraine to date – the American Migraine Prevalence and Prevention Study – sampled 120,000 United States' households. Migraine prevalence was approximately 17% among women and 6% among men, a finding which has remained consistent among previous epidemiologic studies. The average female-to-male migraine prevalence ratio is around 2.8, with a peak of 3.3 between age 40–45 years.[35,36] In addition, studies have consistently demonstrated that migraine prevalence is inversely related to household income. As income or education increases, migraine prevalence declines.[35–37]

Diagnostic criteria

Migraine is characterized by recurrent attacks of headache, autonomic nervous system dysfunction, and in a significant minority of patients, by aura.[38] The diagnostic criteria for migraine without aura (section 1.1) in ICHD-2 require at least five lifetime attacks lasting 4–72 hours each, with at least two of four pain features, and at least one of two sets of associated symptoms (Table 3). In children, attacks may be shorter (1–72 hours), and in young children, photophobia and phonophobia may be inferred from behavior. The diagnostic criteria for migraine with aura (section 1.2) require only two lifetime attacks of fully-reversible aura symptoms which are closely followed by headache (Table 4).

The migraine attack itself can be divided into four phases: the premonitory phase or prodrome occurring hours or days before the headache; the aura, neurologic symptoms that usually immediately precede the headache; the headache phase, comprised of headache and associated symptoms; and the postdrome. No single phase is necessary to make a diagnosis of migraine and most patients do not have all four phases.

Neuro-ophthalmologic manifestations

As described, in addition to photophobia, the classic neuro-ophthalmologic manifestation of migraine is visual aura. Migraine aura is defined as a focal neurological disturbance manifest as visual, sensory, or motor symptoms and is seen in about 20%–30% of migraineurs.[3,39,40] Typical aura symptoms develop gradually and last no more than 60 minutes, and visual aura is overwhelmingly the most common.[41] Ninety-nine percent of aura patients experience visual phenomenon in at least some attacks.[42] Headache follows aura 80% of

Table 3 Second edition International Classification of Headache Disorders diagnostic criteria for migraine without aura (section 1.1)

A. At least five attacks fulfilling criteria B–D
B. Headache attacks last 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)
D. During the headache attack, at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Symptoms not attributed to another disorder

Table 4 Second edition International Classification of Headache Disorders diagnostic criteria for typical aura with migraine headache (section 1.2.1)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
1. Fully reversible visual symptoms including positive features (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
2. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. Each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for migraine without aura (section 1.1) begins during the aura or follows the aura within 60 minutes
E. Symptoms not attributed to another disorder

Table 5 Second edition International Classification of Headache Disorders diagnostic criteria for basilar-type migraine (section 1.2.6)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
1. Dysarthria
2. Vertigo
3. Tinnitus
4. Hypacusia
5. Diplopia
6. Visual symptoms simultaneously in both temporal and nasal fields of both eyes
7. Ataxia
8. Decreased level of consciousness
9. Simultaneously bilateral paresthesia
C. At least one of the following:
1. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
2. Each aura symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for migraine without aura (section 1.1) begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

the time and usually begins within 60 minutes of the end of the aura.[41]

Migraine variants with prominent neuro-ophthalmologic symptoms

Aura without headache

Migraine aura without headache, previously referred to as acephalgic migraine or migrainous late-life accompaniments, may be encountered in both older patients with a remote history of migraine as well as patients who also have aura with their migraine attacks as well.[3,43] Ziegler and Hassanein reported that 44% of their patients who had headache with aura experienced aura without headache at some time.[44] Differentiating this benign disorder from transient ischemic attack and occipital lobe seizures may require investigation, especially when it first occurs after age 40 years, when negative features (eg, hemianopia) are predominant or when the aura is of atypical duration.[43]

Basilar-type migraine (BTM)

First described by Bickerstaff, BTM is a migraine subtype in which headache is accompanied by neurological symptoms referable to the brainstem, including dizziness, dysarthria, ataxia, tinnitus, hearing loss, bilateral paresthesia, altered consciousness, and syncope (Table 5).[45] Otherwise typical visual aura, but occurring in both temporal and nasal hemifields, as well as diplopia may be neuro-ophthalmologic features of BTM. The condition is more common in adolescent girls and young women. The historical concern of this representing basilar artery spasm has never been demonstrated, and BTM may be a variant of migraine with aura with CSD occurring in the brainstem.[46] BTM should be differentiated from demyelinating, inflammatory, vascular, or neoplastic conditions affecting the brainstem, and is ultimately a diagnosis of exclusion.

Retinal migraine

Retinal migraine is a rare migraine variant characterized by attacks of fully reversible monocular visual loss, scintillations, scotomata, or blindness associated with migraine headache.[47] It is most common in women in the second to third decade of life, typically in patients with a history of migraine with aura. Other causes of monocular visual loss including transient ischemic attack, optic neuropathy, mass lesions, retinal detachment, and intermittent angle-closure glaucoma must be ruled out by appropriate investigation. The pathophysiology may relate to CSD occurring in the retina, which has been demonstrated in an animal model.[48] Work by Hanke and de Lima has shown that retinal spreading depression spreads at a rate of 4 mm/minute and its duration in vitro is about 15 minutes.[49] Prophylactic aspirin, antiepileptic drugs, and tricyclic antidepressants have been reported to reduce the frequency of episodes of migraine with and without monocular visual defects.[47] Careful follow-up in retinal migraine patients is paramount because patients may manifest irreversible visual loss with their attacks, akin to migrainous infarction of the retina.[47]

Migraine with unilateral mydriasis

Migraine associated with persistent ipsilateral mydriasis has recently been described in a series of patients.[50] While the

precise mechanism of persistent mydriasis in these patients is unclear, it is thought to be benign and related to migraine-related ciliary ganglion dysfunction. This phenomenon could represent a complicated migraine; a new migraine category; an ophthalmoplegic migraine with selective parasympathy-coparesis; an episodic ciliary ganglionitis with migrainous features; or an association of Adie's pupil and migraine.[50]

Persistent visual aura

Persistent visual aura without infarction is a rare but well-documented condition. According to the ICHD-2 criteria, this disturbance is defined by the persistence of a migraine aura for more than 1 week without radiographic evidence of infarction.[3] This migraine-related complication seems to be more common in women. The pathophysiology of prolonged visual aura is not understood, but several mechanisms are probably involved, including sustained reverberating waves of CSD.[51] There is no radiographic evidence of infarction, but functional neuroimaging studies have demonstrated cortical hypoperfusion in certain cerebral areas.[52] Medications reported as effective include divalproex sodium, intravenous furosemide, lamotrigine, and nimodipine.[51–55]

Visual snow

Visual snow is an increasingly recognized phenomenon that occurs not uncommonly among patients with migraine. Visual snow, a type of positive persistent visual disturbance, is a disorder with continuous visual symptoms consisting of white and black dots in the entire visual field that can persist for years. Schankin et al recently presented results of a retrospective survey of 120 patients who reported visual snow phenomenon.[56] A female-to-male ratio of 1:2.2 was reported and 92% of patients had no response to medication. It appears to be a unique disease entity presenting clinically distinct from visual aura, and is often associated with other visual symptoms including floaters, palinopsia, halos, photophobia, and phosphenes. However, its onset seems to coincide with headache onset, and has a high prevalence among patients who have migraine without and with visual aura. The etiology is unknown.

Migraine with binocular blindness

Binocular blindness with migraine headaches is a very rare occurrence. While BTM can be associated with binocular vision changes including blindness, rarely do migraine patients complain of losing vision in both eyes during an attack of headache. To further characterize migraine-related binocular blindness, Rozen asked 383 migraineurs if they had ever experienced an episode of complete bilateral blindness with their headaches.[57] A total of six patients (1.6%) reported episodes of binocular blindness with their headaches. All affected patients were female and did not have a history of aura. Interestingly, all showed some abnormality in clotting testing – five of the six reported patients had polymorphisms in MTHFR C677T. The MTHFR 677TT genotype has been shown to be associated with an increased risk for the development of migraine with aura. Migraine with binocular blindness appears to be a female-predominant event occurring mostly in migraine patients without a history of aura. This rare migraine-related event may reflect an underlying clotting disorder or be a manifestation of retinal spreading depression. Alternatively, it may reflect activation of the retinal–thalamic–visual cortex pathway.

Treatment

A comprehensive migraine treatment plan includes (1) education and reassurance; (2) identification and avoidance of triggers to prevent attacks; (3) nonpharmacologic treatments such as behavioral interventions, biofeedback, and relaxation exercises; (4) acute medication to abort attacks (used a maximum of 2–3 days a week to avoid medication-overuse headache); and (5) long-term preventive medication to reduce the frequency and severity of anticipated attacks.[58]

Acute therapy

In cases where there is no substantial disability, most people obtain headache relief with nonspecific acute treatments, including simple analgesics such as acetaminophen.[59,60] The nonsteroidal antiinflammatory drugs – namely aspirin, ibuprofen, and naproxen sodium – block neurogenic inflammation by a direct effect on dural blood vessels and have direct antinociceptive effects on neurons.[61]

Patients with more severe migraine and those with lack of responsiveness to nonspecific analgesics should be treated with migraine specific medications, namely triptans, 5-hydroxytryptamine-1B/1D receptor agonists, or ergotamine compounds. Both classes relieve head pain, nausea, photophobia, and phonophobia, and restore the patient's ability to function normally during an acute attack.[62] The effectiveness of triptans is in part due to agonism of 5-hydroxytryptamine-1 inhibitory heteroreceptors on the trigeminal nerve blocking neurogenic inflammation and pain transmission and their direct inhibitory effects on pain transmission in the trigeminal nucleus caudalis.[63–65]

The precise timing of triptan administration in relation to the aura phase of migraine remains controversial.

Several studies have shown that triptan therapy administered during the aura phase of migraine is ineffective in preventing the onset of headache or shortening its duration.[66,67] However, researchers recently demonstrated that treating migraine with triptans within the first 15 minutes of the aura phase proved extremely effective in preempting the onset of migraine headache.[68]

There are seven triptans available in various formulations including oral tablets, orally disintegrating tablets, nasal sprays, and injectable formulations. The most common side effects of triptans include malaise/fatigue, dizziness/vertigo, and nausea. Contraindications to the use of triptans include ischemic heart disease, cerebrovascular disease, or uncontrolled hypertension.[69]

Ergotamine compounds are also appropriate treatment choices but are associated with higher rates of side effects than triptans and may be inferior in efficacy.[70] Dihydroergotamine is an ergotamine derivative that is available in nasal spray and injectable formulations. Because of their inability to tolerate or take oral medications, patients with nausea and vomiting may benefit from dihydroergotamine nasal spray for acute attacks. Contraindications to their use include renal or hepatic failure, pregnancy, hypertension, and coronary, cerebral, and peripheral vascular disease.

Preventive therapy

The major medication groups for preventive migraine treatment include β-adrenoceptor blockers, antidepressants, anticonvulsants, calcium channel antagonists, onabotulinumtoxin A, and medicinal herbs, vitamins, and minerals. Table 6 details the medication classes, individual agents, potential mechanisms of action, and adverse effects.

Trigeminal autonomic cephalalgias (TACs)

Cluster Headache (CH)

CH is characterized by short attacks of strictly unilateral head pain that occurs in association with ipsilateral cranial autonomic features. It is a relatively rare disorder and is more common in adult males, with a reported male-to-female gender ratio of 4.3:1.[71–73] In contrast to the pulsating pain of migraine, the pain of CH is described as sharp, boring, drilling, knife-like, piercing, or stabbing.[74] The pain is so severe it has been described as worse than childbirth and renal colic. Many patients contemplate suicide during attacks – the reason it is sometimes referred to as the "suicide headache." The pain is almost strictly unilateral and typically located over the retroorbital, supraorbital, or temporal regions.[71,72] Interestingly, cluster attacks occur more frequently on the right than the left.[74–76] Pain usually peaks in 10–15 minutes but remains excruciatingly intense for an average of 1 hour within a duration range of 15–180 minutes.[76] During an attack, patients find it difficult to lie still, exhibiting often marked agitation and restlessness.[72]

CH sufferers exhibit cluster attacks, periods, and remissions. A cluster attack is an individual episode of pain that can last from several minutes to a few hours. A cluster period refers to the duration during which recurrent cluster attacks are occurring; it usually lasts from a few weeks to months. In episodic CH, the frequency of attacks ranges from one every other day to eight daily, though 75%–88% of patients have one to two attacks daily.[77] The attacks tend to be less frequent at the beginning and end of a cluster bout. In chronic CH, patients either experience attack-free remissions for less than 1 month annually or no remissions at all.

Another hallmark of CH is its marked circadian and circannual periodicity. Most patients report predictability of attack onset nocturnally, awakening them from sleep, and less so during the day.[75] Ekbom reported that cluster bouts have a seasonal predilection, being more frequent in spring and autumn.[75] Kudrow studied this periodicity in a large series of patients and reported that the frequency of cluster bouts increases with a gradual increase or decrease in daylight hours during the year, with two significant peaks starting 7–10 days after the longest day and the shortest day.[78]

Neuro-ophthalmologic manifestations

The signature neuro-ophthalmic feature of CH is the association with often prominent ipsilateral cranial autonomic features. Lacrimation and conjunctival injection are the most common symptoms followed by nasal congestion or rhinorrhea. Approximately one-third of the patients report ptosis and myosis, though these symptoms are present in two-thirds of patients observed by clinicians during an attack.[76,77] These cranial autonomic features are transient, lasting only for the duration of the attack, with the exception of a partial postganglionic Horner syndrome.

Studies now have indicated that upwards of 20% of patients with CH may have visual, sensory, or language/speech aura – the same percentage of migraine sufferers who have aura.[79] There is no definitive explanation for the aura in cluster patients, but its presence suggests CSD as it occurs

Table 6 Classes of migraine prophylactic agents

Class	Commonly used medications	Mechanism	Side effects	Other
Beta-adrenoceptor blockers	Propranolol, timolol, metoprolol	Inhibition of noradrenaline synthesis and release, blocking 5-HT2_C and 5-HT2_B receptors[107,108]	Reduced exercise tolerance, bradycardia, hypotension, gastrointestinal complaints	
Calcium channel antagonists	Verapamil, flunarizine	Block 5-HT release, interfere with neurovascular inflammation, and interfere with cortical spreading depression[109]	Constipation, dizziness, ankle swelling, bradycardia, hypotension, nausea, fatigue. Flunarizine can also cause galactorrhea and Parkinsonism	May be particularly helpful for migraine with aura
Antidepressants	Amitriptyline, nortriptyline, venlafaxine	Inhibition of serotonin and norepinephrine reuptake, antagonize 5-HT$_2$ receptors[110]	Sedation, dry mouth, constipation, urinary retention	Amitriptyline is the only antidepressant with fairly consistent support for efficacy in migraine prevention[111,112]
Anticonvulsants	Topiramate	Increases GABAergic tone, blocks sodium and calcium channels, inhibits AMPA/ kainate receptors, carbonic anhydrase inhibition[113]	Sedation, paresthesia, weight loss, cognitive slowing, angle-closure glaucoma, nephrolithiasis	
	Valproate	Increases GABAergic tone, inhibits NMDA depolarization	Sedation, dizziness, tremor, weight gain, alopecia, hepatitis, thrombocytopenia	
	Gabapentin	Increases GABAergic tone, blocks voltage-gated calcium channels, increases 5-HT concentration	Sedation, dizziness, edema	
Neurotoxins	Onabotulinumtoxin A	Inhibition of pronociceptive, calcium-dependent neurotransmitter (CGRP, acetylcholine) release[114]	Headache, muscle stiffness, weakness, dysphagia, dysarthria, ptosis	Approved for prophylaxis in chronic migraine, not episodic migraine
Medicinal herbs, vitamins, and minerals	Butterbur, Feverfew, magnesium, riboflavin, coenzyme Q10	Varies by compound	Varies by compound	

Abbreviations: 5-HT, 5-hydroxytryptamine; AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid; CGRP, calcitonin gene-related peptide; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate.

in migraine aura.[80] Further study is required to elucidate the pathophysiology of aura and its association with CH.

Treatment

Acute therapy for CH includes non-oral triptans, such as subcutaneous or intranasal sumatriptan, and intranasal zolmitriptan. In addition, inhalation of 100% oxygen at 12–15 L/minute is rapidly effective in relieving pain in the majority of sufferers.[81] Oxygen does not seem to act directly on trigeminovascular afferent fibers, but may affect parasympathetic projections to the trigeminal system that may be particularly activated during CH attacks.[82]

The preventive treatments that are commonly used for CH include verapamil, lithium, methysergide, ergotamine, corticosteroids, and valproic acid. Verapamil is the preventive drug of choice in both episodic and chronic CH.[83,84] The dose is increased until the cluster attacks are suppressed or side effects intervene, including subclinical electrocardiogram abnormalities such as heart block.[85]

Paroxysmal hemicrania (PH)

PH is an indomethacin-responsive TAC characterized by strictly unilateral, brief, severe attacks of head pain that recur several times per day, typically with prominent ipsilateral cranial autonomic symptoms. The pain in PH is recurrent, short-lasting, and intermittent, generally occurring in brief episodes lasting 2–30 minutes at least five times a day.[26,86,87] The maximum pain is most often centered on the ocular, temporal, maxillary, and frontal regions, and is typically characterized as excruciating in severity, claw-like, throbbing, aching, or boring in quality. PH responds in an absolute fashion to indomethacin, a brain-penetrant nonsteroidal

antiinflammatory drug. This effect is so pathognomonic that indomethacin responsiveness is included in the diagnostic criteria for the disorder.

Neuro-ophthalmologic manifestations

As with the other TACs, ipsilateral cranial autonomic symptoms characteristically accompany attacks, and are typically more prominent than in CH. Lacrimation, conjunctival injection, nasal congestion, or rhinorrhea frequently accompany the headache. Eyelid edema, ptosis, myosis, and facial sweating are less frequently reported. Bilateral autonomic symptoms can occur in a minority of patients. Photophobia and nausea may accompany some attacks, though vomiting and phonophobia are rare.[86]

Aura is not unique to migraine but has also been described in various TACs, including PH. Matharu and Goadsby published a case of posttraumatic chronic PH with sensory and motor aura, and Seidel and Wober published a case of a 17-year old boy presenting with recurrent episodes of isolated visual aura followed infrequently by indomethacin-responsive headache attacks resembling PH.[88,89] Interestingly, in this case a lower dose of indomethacin lead to the abolition of head pain but persistence of both visual aura and autonomic symptoms; however, after titration of indomethacin to a higher dose, the aura and autonomic symptoms also ceased. This observation could suggest a differential dose-response relationship for indomethacin and head pain, aura, and autonomic symptoms. Migrainous aura may be seen with TACs and may represent the expression of an aura-susceptibility gene rather than typical migraine headache biology.

Treatment

PH and HC, by definition, require a therapeutic response to indomethacin. Complete resolution of the headache is prompt, usually occurring within 1–2 days of initiating the effective dose of indomethacin. The most common serious side effect of indomethacin is the development of peptic ulcers. Indomethacin suppositories are occasionally helpful if gastric intolerance is a major problem.[62]

SUNCT/SUNA

SUNCT is a very rare primary headache disorder. The diagnostic criteria require at least 20 high-frequency attacks (3–200 a day) of unilateral orbital, supraorbital, or temporal stabbing or pulsating pain, lasting 5–240 seconds, and accompanied by ipsilateral conjunctival injection and lacrimation.[3] The pain in SUNCT has a neuralgic character, being usually described as stabbing, sharp, burning, pricking, piercing, shooting, lancinating, or electric-like. The attacks are characteristically dramatic, with moderately severe pain peaking in intensity within 3 seconds and prominent tearing.[90,91] Attacks may be as infrequent as once a day or less to more than 60 per hour.[92] Attacks may be triggered by touching certain trigger zones within trigeminal innervated distribution and, occasionally, even from an extratrigeminal territory, mastication, wind blowing on the face, washing the face, brushing teeth, and movements.[93]

SUNA, a close relative of SUNCT and occurring in both episodic and chronic forms, requires at least 20 high-frequency attacks of unilateral orbital, supraorbital, or temporal stabbing pain lasting from 2 seconds to 10 minutes that are accompanied by either ipsilateral conjunctival injection and lacrimation, nasal congestion and rhinorrhea, or eyelid edema.[3]

Neuro-ophthalmologic manifestations

By definition, SUNCT/SUNA patients usually have extremely prominent ipsilateral conjunctival injection and lacrimation associated with their attacks. Pareja et al studied video records of SUNCT attacks and found dramatic conjunctival injection involving mostly vessels of the palpebral territory stemming from superior and inferior palpebral vessels that supply the tarsal conjunctiva and most of the ocular conjunctiva.[94] Ptosis, eyelid edema, rhinorrhea, nasal congestion, and sweating are less commonly reported. It is the prominence of the autonomic symptoms that helps distinguish SUNCT/SUNA from trigeminal neuralgia of the ophthalmic nerve, where autonomic symptoms are entirely absent.

Treatment

The treatment of SUNCT/SUNA is entirely prophylactic, as attacks are generally too short for any abortive treatment to be effective. Lamotrigine has been reported to be highly efficacious in treating the disorder, although randomized, controlled studies are lacking.[95]

Hemicrania continua (HC)

HC is an indomethacin-responsive primary headache disorder characterized by daily and continuous strictly unilateral headache with ipsilateral cranial autonomic features.[96] While technically not considered a TAC, being classified under other primary headaches (section 4) in the ICHD-2, one might argue for its inclusion in this category based on clinical similarities and overlapping patterns of activation with the TACs on functional imaging studies.[97] As is the case with PH, there is by definition an absolute and exquisite response to therapeutic

doses of indomethacin. The pain in HC is continuous, moderate to severe, and unilateral, varying in intensity – waxing and waning without disappearing completely.

Neuro-ophthalmologic manifestations

Ipsilateral cranial autonomic symptoms including ptosis, myosis, tearing, and sweating characteristically accompany attacks in HC.[96] Patients with HC have also described symptoms of ocular discomfort, at times premonitory. Some patients report an "ocular foreign body" sensation, described as a feeling of "sand in the eye," which may be specific for HC.[98] Peres et al published four cases of typical visual aura accompanying or preceding HC attacks. Indomethacin provided complete relief for both the headaches and the visual symptoms, suggesting that the auras might be pathophysiologically related to the headaches in HC.[99]

Treatment

Like PH, HC by definition requires a therapeutic response to indomethacin, and a therapeutic trial of oral indomethacin is undertaken in a similar fashion. In patients who cannot tolerate indomethacin, other prophylactic agents including conventional migraine prophylactic medications like topiramate and even melatonin may be effective.[100]

Summary

Primary headache disorders as a whole are common, and commonly feature prominent neuro-ophthalmologic symptoms. Migraine, TACs, and HC are the main primary headache syndromes associated with neuro-ophthalmologic manifestations including orbital pain, photophobia, visual aura, and autonomic features. The key to effective management of these disorders is a differential diagnosis through a thorough headache and medical history, a general physical, neurological, and ophthalmologic examination. Specific neuroimaging studies are indicated when the presentation is atypical, to exclude other underlying etiologies for the headache and ocular symptoms. Pharmacologic management is highly individualized and specific to the primary headache disorder diagnosed, and may include abortive and prophylactic medications.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL ARTICLE

Relationship Between Habitual Refractive Errors and Headache Complaints in Schoolchildren

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ABSTRACT

Purpose. Refractive error (RE) is considered to be a possible cause for headaches. We aimed to gain insight into the relation between habitual RE (sphere and astigmatism) and headache complaints.

Methods. In a cross-sectional study the habitual refractive state of 487 children, aged between 11 and 13 years, was measured using an autorefractometer (Topcon, RM-8000B). Headache complaints were measured using a questionnaire. Data were analyzed using Pearson correlation coefficients, bivariate analysis, and multiple logistic regression analysis.

Results. For right eyes we found 15% habitual myopia <-0.50 D and 12% habitual hyperopia $>+0.50$ D; habitual astigmatism >0.25 D was found in 33% of children. Pearson R between right and left eyes was 0.76 for the spherical component and 0.42 for the cylindrical. In the total group of children 70% reported the occurrence of headache in the last year. These headaches were reported as "often or frequent" by 37% of children, "severe" by 15%, "with long duration" by 45%, and "with severe burden" by 27%. In the total sample we found various associations between gender, sphere/cylinder components of habitual RE, and headache complaints. Headache was reported more in girls than in boys. Of the total variance of headache complaints in girls, the sphere component of habitual RE explained 4% of frequency, 6% of intensity, 2% of duration, and 2% of amount of burden. Of the total variance of headache complaints in boys the cylinder component of habitual RE explained 3% of frequency, and 4% in amount of burden.

Conclusion. Habitual RE and headache complaints are relatively common conditions in schoolchildren aged between 11 and 13 years. Headache complaints showed a small but statistically significant association with the sphere component of habitual RE in girls and the cylinder component of habitual RE in boys. The associations found between habitual RE and headache complaints indicate that habitual RE might be a risk factor for headache in children.

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Key Words: refractive error, astigmatism, headache, gender, schoolchildren

Headache is an important cause of health complaints and disability worldwide. Epidemiological studies in the general population of developed countries have shown an occurrence of sporadic headache in 40% and of chronic primary headaches in 15% (migraine, and tension-type headache).[1] Every day, a million people in European countries have a migraine attack, and an estimated 100 million workdays or schooldays per year are lost because of migraine.[2] Episodic tension-type-headache—"normal" or "ordinary" headache—is less disabling but more prevalent than migraine.[3] Headache can impair job productivity and reduce quality of life. Due to lost workdays, headache has serious socio-economic impact.[4] Many affected people are reluctant to seek medical treatment. Most people with tension-type headache manage themselves.[5] A recent study found that 60% of people reporting severe headaches used only over-the-counter medication.[6]

The proportion of refractive errors (RE) in the general population ranges from 13 to 80% in various studies. In different geographic areas and different age groups prevalence rates vary substantially.[7–10]

Although not based on firm evidence, uncorrected RE (especially hyperopia) is considered to be a possible cause for headache.[11–13] The criteria for the classification of headache of the International Headache Society (IHS) include an entity Headache Associated with Re-

fractive Errors (HARE), but it is indicated that its importance is widely overestimated.[14] In 2002 Gil-Gouveia and Martins[12] reported an association between hyperopia and HARE in healthy subjects with uncorrected or miscorrected RE compared with a control group. Although in the literature several possible ophthalmic causes for headache are mentioned, it remains unclear how to explain a possible causal relation. In 1966, Gordon et al.[15] claimed that minor RE often caused more headache and symptoms of eyestrain than major RE. Ciliary muscle strain has also been suggested as possible source of headache.[16] Another proposed mechanism is "brow furrowing," implying that prolonged contraction of the brow, scalp, and neck muscles in an attempt to maintain a clear image results in headache.[17]

Normally in prevalence studies RE is measured using subjective or objective methods, with and/or without the use of cycloplegia. In relation to complaints like headache it is not the absolute RE, rather than the RE that remains with or without correction, which might be of importance. This is defined as habitual RE.

Because headache is a serious burden and as the role of habitual RE in the occurrence of headache is still unclear, the objective of the present study was to gain insight into the relation between habitual RE (sphere and astigmatism) and self-reported headache complaints in children aged between 11 and 13 years.

MATERIALS AND METHODS

Design, Research Model, and Study Population

The present study has a cross-sectional design. We investigated whether reported headache complaints are associated with habitual RE (sphere and cylinder components), and whether these possible associations were modified by gender.

Twenty-one primary schools in the southern part of the Netherlands were approached. The children in their last year of primary school (aged between 11 and 13 years) were asked to participate in this study. The teachers of the schools distributed the study information to the children and their parents. The research followed the tenets of the Declaration of Helsinki, and informed consent was obtained from the parents after explanation of the nature and possible consequences of the study. Participation comprised a measurement of the RE of the eyes of the children with an autorefractometer in May 2003. Questionnaires asking for details of headaches were completed by the children. To facilitate participation the measurements took place during school time.

Survey Measures

Habitual Refractive Errors (Habitual RE). Habitual RE of both eyes were measured using an autorefractometer (Topcon RM-8000B). Spherical and astigmatic deviations were measured to the nearest 0.25 D. Astigmatic axes were measured to the nearest five degrees, negative cylinders being used for all measurements. Because the measurements involved the habitual RE the use of a cycloplegium was not indicated. Children normally wearing an optical correction were measured with their glasses or contact lenses (habitual RE). The autorefractor as used in the data collection has an automatic analysis system for image quality. If (e.g., by reflection from spectacle lenses) the image quality is too low, the instrument will display this measurement as an error.

Each eye was measured three times, of which the average was taken. All examinations were carried out by the same observer, who did not know the results of the headache questionnaire of each child. Right eyes were always measured before left eyes.

In most optometric studies the degree of ametropia is defined rather arbitrarily. For optical reasons low degrees of ametropia are relatively unimportant. In our case low degrees of ametropia were included since especially these might be of importance in relation to headaches.[15] Using the spherical part of the refraction, the children were placed in three categories: myopia <-0.50 D, emmetropia (-0.50 to $+0.50$ D), and hyperopia $>+0.50$ D. Astigmatism was categorized in two groups: children without astigmatism (0.00 to 0.25 D) and with astigmatism >0.25 D.

Headache Questionnaire. Headache characteristics were assessed using an adapted version of Waters' Headache Questionnaire (WHQ).[18–20] Headache intensity was measured using a Visual Analogue Scale (VAS) of the Pediatric Pain Assessment Tool (PPAT).[21–23] A so called VAS[24] is a psychometric single-item measurement scale represented on a continuous line ranging from 0 to 100 mm. The children were asked to mark the level of their headache intensity ("usual headache" and "worst headache") on this line. Headache burden was measured using a 5-points Likert scale, ranging from "I am only aware of it when I pay attention to it" to "headache: such that I can't do anything."[25]

If a child reported in the questionnaire to have suffered from the mentioned headache, she or he was counted as a case for this item. Children were assessed, according to Bentzen's modified definition of a health problem: "any concern in relation to health of a person determined by the person."[26] Key items were frequency, intensity, duration, and amount of burden due to these headache episodes.

For use in logistic regression analysis the scores on the headache scales were dichotomized. A higher category means a higher degree of complaints. The high frequency headache group (often) consisted of children with headache frequency of once a week or more often, the high intensity group (severe) had a usual headache intensity of at least 50 mm on the VAS, and in the long average duration group (long) headache duration usually lasted more than an hour. Children scoring 4 or 5 on a 5-points Likert scale were categorized within the severe burden group (severe).

Data Analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS) version 10.0. Pearson correlation coefficient was used to analyze correlations between right and left eye measurements.

Differences in the prevalence of headache complaints and habitual RE (sphere and cylinder) between the genders and optical correction subgroups were analyzed by Pearson χ^2 tests, supplied by Cramer's V association measures. Cramer's V ranges from 0 (no association) to 1 (perfect association).

To assess the influence of five independent variables (age, gender, wearing of glasses, sphere, and cylinder) simultaneously on headache complaints as dependent variable, we used multiple logistic regression analysis (stepwise criteria probability-to-enter ≤ 0.05, and probability-to-remove ≥ 0.10). Odds ratios were calculated to quantify the association between children's habitual RE and reported headache complaints. Because of multicollinearity,

right and left eye information was used separately. To estimate the proportion of variance in the dependent variable which is explained by the predictor (independent) variables we used the Nagelkerke R-squared. This test is an adjusted version of the Cox and Snell R-squared.[27]

RESULTS

Study Population

Nineteen of the 21 primary schools approached in the southern part of the Netherlands agreed to participate. Of the 588 children in the participating schools, 487 children (83%) actually participated in the present study. Nonparticipation was due to absence/illness (37 children; 6%), no permission of the parents (29 children; 5%), questionnaires not (correctly) filled out (35 children; 6%). In this group of schoolchildren (n = 487, aged 11 to 13 years), more girls took part in the study than boys (252 girls; 52%, and 235 boys; 48%). Of the 487 children, 74 (15%) were optically corrected. Boys were slightly less often optically corrected when compared with girls (14 vs. 17%).

Refractive Examination

Prevalence of habitual RE is presented in Table 1. A quarter of the children proved to have habitual spherical RE $> \pm 0.50$ D. One third of the children showed habitual cylindrical RE > 0.25 D.

Pearson correlation coefficients between right and left eyes for all children were 0.76 ($p < 0.01$) for the sphere component and 0.42 ($p < 0.01$) for the cylinder component.

In boys with glasses sphere and cylinder components of habitual RE were significantly more prevalent ($p < 0.01$), than in boys without glasses. For the sphere and cylinder components of habitual RE, Cramer's V was shown to be 0.31 and 0.20, respectively.

In girls with glasses cylinder components of habitual RE were significantly ($p = 0.01$) more prevalent than in girls without glasses (Cramer's V = 0.16).

The only significant difference in prevalence of habitual RE between girls and boys was found in the sphere component for left eyes of children with glasses ($p = 0.03$; Cramer's V = 0.31). Compared with girls with glasses, boys with glasses proved to have in left eyes more often myopia (41 vs. 19%) and more hyperopia (16 vs. 7%).

Reported Headaches and Gender and Wearing of Glasses

Seventy percent of all children reported headache complaints in the last year. Table 2 shows that 37% of children reported the frequency as often (once a week or more often). The intensity of the headache was scored as severe (at least 50 mm on the VAS) in 15% of cases. The average duration of headaches lasted longer than an hour in 45% of cases. Most children (73%) reported their headaches as a minor burden (scoring 1, 2, or 3 on a 5-point Likert scale).

Logistic Regression

Table 3 presents the multiple logistic analyses indicating the importance of habitual RE in relation to headache complaints.

In the total sample only gender, sphere, and cylinder remained significant variables. Headache was reported more in girls than in boys regarding frequency [Odds ratio (OR) 1.76; 95% confidence interval (CI) 1.21–2.57] and duration (OR 1.42; 95% CI 1.07–1.88). Sphere component of habitual RE was associated with frequency (OR 1.60; 95% CI 1.17–2.19), intensity (OR 1.64; 95% CI 1.11–2.42), duration (OR 1.50; 95% CI 1.05–2.16) and amount of burden (OR 1.51; 95% CI 1.09–2.09). Cylinder component of habitual RE was associ-

TABLE 1.
Prevalence of habitual refractive error of right and left eyes related to gender and optical correction (N = 487)

	Prevalence of refractive error				
	Total group of children (N = 487)	Boys with glasses (n = 32)	Boys without glasses (n = 203)	Girls with glasses (n = 42)	Girls without glasses (n = 210)
Right eye sphere component					
M	72 (15)	12 (37)	21 (10)	10 (24)	29 (14)
E	358 (73)	14 (44)	164 (81)	26 (62)	154 (73)
H	57 (12)	6 (19)	18 (9)	6 (14)	27 (13)
Left eye sphere component					
M	71 (15)	13 (41)	23 (11)	8 (19)	27 (13)
E	373 (76)	14 (43)	165 (81)	31 (74)	163 (77)
H	43 (9)	5 (16)	15 (8)	3 (7)	20 (10)
Right eye cylinder component					
Y	159 (33)	18 (56)	57 (28)	21 (50)	63 (30)
N	328 (67)	14 (44)	146 (72)	21 (50)	147 (70)
Left eye cylinder component					
Y	173 (36)	19 (59)	63 (31)	23 (55)	68 (32)
N	314 (64)	13 (41)	140 (69)	19 (45)	142 (68)

Values in parentheses indicate percentage values.
M, myopia; E, emmetropia; H, hyperopia; Y, astigmatism; N, no stigmatism; with glasses, children normally wearing glasses.

TABLE 2.
Numbers and percentages of reported headache complaints by schoolchildren and Pearson χ^2 tests for comparing differences in prevalence between subgroups for gender and wearing of an optical correction (N = 487)

	Prevalence of headache complaints				
Reported headache (last year)	Total group of children (N = 487)	Boys with glasses (n = 32)	Boys without glasses (n = 203)	Girls with glasses (n = 42)	Girls without glasses (n = 210)
Frequency (often)	182 (37)	8 (25)	64 (32)[a]	18 (43)	92 (44)[a]
Intensity (severe)	71 (15)	5 (16)	25 (12)	9 (21)	32 (15)
Average duration (long)	219 (45)	22 (51)[b]	77 (38)	24 (57)[b]	96 (46)
Average burden (severe)	131 (27)	7 (22)	54 (27)	11 (26)	59 (28)

Values in parentheses indicate percentage values.
[a]Difference in prevalence of headache between boys without glasses and girls without glasses p = 0.01 (Cramer's V = 0.13).
[b]Difference in prevalence of headache between boys with glasses and girls with glasses p = 0.05 (Cramer's V = 0.23).

ated with frequency (OR 2.01; 95% CI 1.07–3.78), and amount of burden (OR 2.71; 95% CI 1.25–5.89).

In boys the cylinder component of habitual RE of right eyes is associated with frequency (OR 2.96; 95% CI 0.97–9.02) and amount of burden (OR 4.14; 95% CI 1.18–14.55). The cylinder component of RE in boys explained 3 to 4% of the total variance in the relation to headache complaints (Nagelkerke R-squared).

In girls the spherical component of habitual RE of right eyes was associated with frequency (OR 1.63; 95% CI 1.09–2.42), intensity (OR 2.04; 95% CI 1.20–3.46), duration (OR 1.47; 95% CI 1.01–2.14) and amount of burden (OR 1.45; 95% CI 0.97–2.16). Of the total variance in the relation to headache complaints (Nagelkerke R-squared), the sphere component of habitual RE in girls explained 2 to 6%.

DISCUSSION

Habitual RE was present in 27% of schoolchildren aged between 11 and 13 years (15% myopia and 12% hyperopia). In this study we found in girls an association between the spherical component of habitual RE (especially hyperopia) and headache complaints. In boys the cylinder component of habitual RE of right eyes was associated with frequency of headache occurrence and the amount of burden.

The contribution of right eye habitual RE to headache complaints proved to be different than left eye habitual RE. We have no explanation for this finding. Dominance of right eyes might play a role. In our study the differences found between boys and girls is also remarkable. We have no explanation for the gender differences found in this study. Until now these differences have not been reported in the literature.

In a population with high prevalences of headache and RE one would expect, on chance grounds, many individuals to have both headaches and a RE, but these would not necessarily be etiologically related.[11] Our results seem to be in accordance with the statement of the Headache Classification Committee of the International Headache Society[14] that RE contributes significantly to headache complaints, but its contribution is limited, given the low explained variance of RE.

Generally, with a cross-sectional designed study causal relations cannot be proven. Normally it is not easy to distinguish whether a variable is cause or effect of the relation found in a study. However, with our subject of investigation it is unlikely that headache complaints cause ametropia or astigmatism. Findings also might be biased because of the mutual interaction of an unknown variable on the variables investigated. Gender and age both are related to RE and headache complaints but we took these factors into account. Other common etiological factors related to both RE and headache complaints were not found in literature. Therefore, in our opinion, it is plausible that the associations we found between ametropia or astigmatism and headache complaints might have a causal significance.

Our study population consisted of Dutch schoolchildren who had reached the last year of study of normal primary school education. The response rate was high. We consider it unlikely that reasons for participation were related to either RE or headache complaints; therefore, we have no reason to assume that selection bias has played a role.

Traditionally hyperopia or ciliary muscle strain is referred to as the cause of headache, since accommodation might arouse visual stress. In our study we also found a substantially higher score of headache in hyperopic girls. A role of habitual RE and ciliary muscle strain in the relation with headache complaints, as mentioned in the Introduction, cannot be excluded.[15]

Autorefractors give quick and accurate readings of RE, without examiner bias and without the involvement of highly trained clinical personnel.[28] Accommodation reduces the validity and reliability of the instrument,[29–34] because noncycloplegic measurements tend to underestimate the hyperopic status. Because we evaluated the children under conditions as close as possible to those under which they usually function (habitual RE), the use of a cycloplegium was not indicated. Information gained from cycloplegia (to detect latent hyperopia or pseudomyopia) would not in itself lead to different outcomes because we were interested in categorizing the children according to their habitual refractive state rather than in the absolute levels of their refraction deviations.

The questionnaire asked about headaches over the last year. One could argue that within this period of time RE might change, and this might in turn have impact on the results of the study. Indeed small changes in habitual RE can occur within this age group. These changes might influence the distribution of children among the categories as used. On the other hand although we asked about headaches over the last year, it is reasonable to assume that headaches over the last weeks are recalled more easily than headaches

TABLE 3.
Relation between gender, habitual refractive error (sphere and cylinder component), and headache complaints[a]

	Total group			Boys			Girls		
	Independent variables	OR (95% CI)	Nagelkerke R square	Independent variables	OR (95% CI)	Nagelkerke R square	Independent variables	OR (95% CI)	Nagelkerke R square
Right eye									
Frequency	Gender Sphere Cylinder	1.76 (1.21–2.57) 1.60 (1.17–2.19) 2.01 (1.07–3.78)	0.06	Cylinder	2.96 (0.97–9.02)	0.03	Sphere	1.63 (1.09–2.42)	0.04
Intensity	Sphere	1.64 (1.11–2.42)	0.02	—	—	—	Sphere	2.04 (1.20–3.46)	0.06
Duration	Gender Sphere	1.42 (1.07–1.88) 1.50 (1.05–2.16)	0.03	—	—	—	Sphere	1.47 (1.01–2.14)	0.02
Burden	Sphere Cylinder	1.51 (1.09–2.09) 2.71 (1.25–5.89)	0.04	Cylinder	4.14 (1.18–14.55)	0.04	Sphere	1.45 (0.97–2.16)	0.02
Left eye									
Frequency	Gender Sphere	1.76 (1.21–2.56) 1.42 (1.05–1.92)	0.04	—	—	—	Sphere	1.55 (1.00–2.39)	0.02
Intensity	—	—	—	—	—	—	—	—	—
Duration	Gender Sphere	1.52 (1.06–2.18) 1.31 (0.98–1.74)	0.02	—	—	—	—	—	—
Burden	Sphere	1.36 (0.99–1.88)	0.01	—	—	—	—	—	—

[a] Logistic regression analysis and Nagelkerke R-squared. Each separate cell of the table shows a reduced model for the relationship between the dependent and the presented independent variables. Odds ratios (and 95% confidence intervals) are presented for the association between children's refractive error and reported headache complaints.

from a year ago. We think the possible influences of these effects on the study results are minor.

We realize that the prevalence of RE varies enormously in different geographic areas and in ethnic populations.[35–38] Given that our findings can be generalized to different populations, a substantial number of headache complaints could be avoided.

CONCLUSION

In this study, the aim was to gain insight into the relation between habitual RE (sphere and astigmatism) and headache complaints.

The prevalences of habitual RE and headache complaints in children were relatively high. In girls the sphere component of habitual RE and in boys the cylinder component of habitual RE was statistically associated with headache complaints, but a very small amount of the variance of headache complaints was explained by the habitual RE.

We recommend incorporating measures of RE in the diagnostic process in children with headache complaints.

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RELATIONSHIP BETWEEN MIGRAINE HEADACHE AND REFRACTIVE ERRORS

Ophthalmology

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ABSTRACT

Headache is a public health problem. This study is to evaluate refractive errors among subjects with migraine headache and to compare it with healthy subjects. This is a prospective cross-sectional study of 188 subjects with migraine headache, aged between 20 and 40 years and 180 subjects without headache of same age group as control group. Retinoscopy and subjective refraction was done to find out anisometropia and type of refractive errors; myopia, hypermetropia and astigmatism. Forty-nine (26.06%) subjects with migraine headache had refractive errors, out of which 29(59.18%) had astigmatism, 15(30.62%) had hypermetropia and 05(10.20%) had myopia. Out of 26(14.44%) cases in control group with refractive errors, 16(61.54%) had myopia, 07(26.92%) had astigmatism and 03(11.54%) had hypermetropia. Anisometropia was found in 14(7.45%) patients with migraine headache and in 07(3.89%) healthy subjects. In this study, we observed that refractive error is a risk factor for migraine headache in comparison to control group.

KEYWORDS

Migraine Headache, Refractive Errors, Myopia, Hypermetropia, Astigmatism.

Introduction

Headache is known as the pain located above orbitomeatal line [1]. It is an universal experience and lifetime prevalence [2]. Most of the patients of headache are underdiagnosed. Headaches are associated with significant drop in the quality of life [3]. Due to high prevalence and negative impact on life, headaches are currently considered as a public health problem [4]. The management of headache in a patient is challenging. An accurate assessment is essential for its diagnosis and treatment.

Headache can be divided into primary and secondary type. Primary headaches are further divided into migraine and tension–type headache. Secondary headaches include conditions of other etiologies. The patients with primary headaches don't have any structural, metabolic or other lesion of the body whereas secondary headaches have some exogenous disorders.

The migraine headache has been ranked as third most prevalent disorder and placed seventh among the top ten causes of disability worldwide in the Global Burden of Disease Survey 2010 (GBD2010). According to third edition of International Classification of Headache Disorders (ICHD-3) [1] the migraine headaches are of two subtypes–

A. Migraine without aura, a clinical syndrome characterized by headache with specific features and associated symptoms
B. Migraine with aura characterized by transient focal neurological symptoms which precede or sometimes accompany the headache.

The prevalence of primary headache varies 9-11% in India, and uncorrected refractive errors among population vary from 2.63 % to 25.0% [3,5,6]. Refractive error is considered to be a possible cause for headache in some previous reports [7,8,9]. The uncorrected refractive errors are often associated with frontal and /or occipital headache [10,11].

Headache and refractive errors are common health related complaints to seek medical consultations by the patients of all age. Uncorrected refractive errors have a considerable impact on one's physical and mental development. So, corrective measures have to be taken at the earliest. Proper refractive correction can improve headache with refractive error in over 70% cases [12]. Thomas et al [13] observed that 21% of patients with headache consult ophthalmologist and Whittington et al [14] reported that 45% patients who were attending refraction clinics had complaint of headache. Gordon et al [15] had observed that minor refractive errors often cause more headache and symptoms of eye strain than major errors.

On review of literature, association between migraine headache and refractive errors have been found to be of equivocal results [16]. Chronicle and Mulleners had documented an inconclusive evidence on the involvement of refractive error in the etiology of migraine headache in their studies [17]. But Harle et al [18] in his study concluded that there is strong association between higher degrees of astigmatism in the patients with migraine headache.

Therefore, considering migraine headache, a serious burden to a clinician, this study was aimed to determine the relationship between refractive errors and migraine headache among subjects referred to the ophthalmology outpatient department (OPD) in a tertiary care hospital.

Material and Methods

This is a cross-sectional study of 188 patients diagnosed to have migraine headache between 20 and 40 years in the medicine department.Age, gender matched 180 healthy subjects without headache from ophthalmology department were included in the study as control group. The study was conducted from January 2015 to December 2017 in the ophthalmology outpatient department (OPD). We included consecutive patients referred from the medical OPD with diagnosis of migraine headache. This research protocol was approved by the Institutional ethics committee. All the investigations were done according to Helsinki declaration. The full informed consent was taken from all participants after explanation of the study procedures and participants were allowed to abstain or withdraw from the research at any point without having to give any reason. The identity of the study group and those excluded from the study were masked so that all the tests can be performed with equal emphasis to every patient.

The study group and control group were interviewed with structured questionnaires about demographic data. Those having other types of headache were excluded from the study. The participants in the study group were then asked about any aggravating factors, family history and history of trauma, medical history, dental caries, and features of raised intracranial pressure, menstrual disturbances, previous ocular surgeries and use of medicines. The study groups with systemic diseases, pregnancy, sinusitis, and intake of medicines, dental caries that cause headache or ocular conditions like amblyopia, squint, acute glaucoma, uveitis optic neuritis were excluded from the study.

Visual acuity was measured in each eye at 6 meter distance with illuminated Snellen's chart and near vision was recorded at 33 cm with Jagger's chart under good illumination.

Refractive error was measured by subjective and objective refraction. Retinoscopy was done with steak retinoscope at the working distance of 50 cm. Subjective refraction was done with appropriate corrective lenses after three days to eliminate cycloplegic effect completely. The spherical and astigmatic deviations were measured. The axes of astigmatism were measured to the nearest five degrees. They were classified into three groups according to spherical equivalent refractive error (SERE) +0.50 diopter sphere (Dsp) or more was considered as

hypermetropia and SERE -0.50 Dsp or less was considered as myopia. Astigmatism was considered when cylindrical component of the refractive error was 0.50 diopter cylindrical (Dcyl) or more in any axis. Myopia was categorized into mild (upto -3.0 Dsp), moderate (upto -6.0 Dsp) and severe (more than -6.0 Dsp) subgroups. Hypermetropia was categorized into mild (upto +3.0 Dsp), moderate (upto +6.0 Dsp) and severe (more than +6.0 Dsp) subgroups. The children with bilateral myopia or hypermetropia were classified into subgroups according to the more myopic or hypermetropia eye respectively. The astigmatism was categorized into three groups according to the axis of corneal astigmatism as with the rule, against the rule and oblique type.

Slit lamp biomicroscopy and fundus examination were done to rule out any anterior or posterior segment ocular pathology. Ocular motor functions were evaluated in six cardinal gazes. Intraocular pressure was measured with Goldman tonometer.

Statistical analysis of headache and control groups were done by calculating t-test to compare means of two groups, chi-square test for non parametric data, odds ratio (OR) and 95% confidence intervals (CI) were calculated to compare the relative risk of the groups for categorical variables Statistical software SPSS version 20.0 was used to analyze the data of the study.

Observations

A total of 188 subjects with diagnosis of migraine headache and 180 without headache as control normal group participated in the study. It included 113(60.1%) females and 75(39.9%) males in migraine headache group, 98(54.44%) females and 82(45.56%) males in control group (Table-1).

Table-1: Age, sex and previous examination in migraine headache (n=188) and control (n=180) group

Study groups	Mean age (years)	Sex (%)		Previous examination (%)	
		Male	Female	Yes	No
Migraine headache	28.86± 7.18	75(39.9)	113(60.1)	132(70.2)	56(29.8)
Control	27.18±7.14	82(45.56)	98(54.44)	41(22.8)	139(77.2)

Minimum age of subjects with diagnosis of migraine headache was 20 years and maximum age was 40 years. Mean age of the participants was 28.86±7.18 years in headache group and 27.18±7.14 years in group without migraine headache. Two study groups were age matched with two-tailed P value 0.4486, 95% confidence interval (CI) -6.041 to 2.677 and two groups passed normality test.

All the subjects were tested with retinoscope for the refractive errors and appropriate corrections were prescribed. Most of the subjects with migraine headache had near normal visual acuity though 49 (26.06%) of them had refractive errors in comparison to 26(14.44%) in control group. Twenty nine (59.18%) patients diagnosed to have astigmatism, 15(30.62%) had hypermetropia, 05(10.20%) had myopia in the group with migraine headache. Out of 26(14.44%) subjects with refractive errors in control group, 16(61.54%) had myopia, 07(26.92%) had astigmatism and 03 (11.54%) had hypermetropia (Table-2).

Table-2: Frequency of ocular morbidity in migraine headache and control groups

Ocular morbidity	Frequency (%) in migraine headache group	Frequency (%) in control group
Refractive error	49(26,06)	26(14.44)
Myopia	05(10.20)	16(61.54)
Hypermetropia	15(30.62)	03(11.54)
Astigmatism	29(59.18)	07(26.92)
Anisometropia	14(7.45)	07(3.89)

To quantify the association between refractive errors in two groups, we had calculated OR with 95% CI as 2.088(1.23 to 3.54).The prevalence of refractive errors were higher in subjects with migraine headache group than in controls and difference was statistically significant ($p<0.05$).

Astigmatism in 29 (59.18%) subjects was significantly more prevalent in migraine headache group compared to the control group of 07(26.92%). The prevalence of myopia in migraine headache group 05 (10.20%) was less than in the control group 16(61.54%). Hypermetropia was significantly more prevalent in migraine headache group 15(30.62%) than the control group 03 (11.54%). The relative risk of these two refractive errors was significant between the two groups. The relative risk of astigmatism and myopia between two groups are statistically significant. Prevalence of different types of refractive errors in migraine headache and control groups with p value, OR are summarized in Table -3. Pearson Chi square test also showed significant association between refractive errors with migraine headache.

Table-3: Comparison of the prevalence of refractive errors between migraine headache and control groups

Refractive errors	subjects		p-value	Odds ratio
	Migraine headache group (n=188)	Control group (n=180)		
Astigmatism	29	07	0.0002	4.508
Hypermetropia	15	03	0.0064	5.116
Myopia	05	16	0.0127	0.2831

Discussion

Headache is of multifactorial origin. The subjects referred with diagnosis of migraine headache are challenging to manage because due to recurrence of the headache most of them are not satisfied with the medical treatment. Our hospital covers about five million rural population of low socio-economic status who don't have access to the well facilitated health care services.

In the present study mean age of the participants were 28.86±7.18 years in migraine headache group and 27.18±7.14 years in control group. In both the groups, number of females was more than the males. Because of psychological stress and emotional factor, 132 (70.2%) patients of migraine headache had previous eye examination within last six months than 41(22.8%) in control group.

In this study, the prevalence of refractive errors was higher in 49(26.06%) patients with migraine headache compared to 26(14.44%) patients of control group. The difference between two groups was significant and it corroborates with the previous reports. The prevalence of refractive errors in the subjects with migraine headache in our study was similar to the study of Cameron et al and Jain at al [19] .

Jain S et al [19] had reported 36% ocular etiology for headache complaints cases, of which 65% were due to refractive errors and out of which 41%, 22%, 12% was due to astigmatism, hypermetropia and myopia respectively. In our study, we also found 26.06% subjects had refractive errors with complaints of migraine headache out of which 59.18%, 30.62%, 10.20% was due to astigmatism, hypermetropia and myopia respectively. Gunes A et al 20 had also reported that migraine patients had higher degrees of astigmatic refractive error.

In our study, 05 (10.20%) subjects with migraine headache and 16 (61.54%) subjects of control group had myopia. The number of subjects with myopia in migraine headache group was lower comparing the subjects with hypermetropia and astigmatism in that group. Therefore, myopic subjects had lower headache complaints in comparison with hypermetropia and astigmatism type of refractive errors.

The prevalence of hypermetropia was more in the migraine headache group 15(30.62%) compared to control group 03(11.54%) and the difference was statistically significant.

In this study, subjects were recruited from hospital OPD. A small sample size and inadequate masking is the probability of high prevalence of refractive errors among the patients with migraine headache complaints than control group in our study. Therefore further investigations are needed to establish a definite correlation of refractive errors and migraine headache.

Summary

An ophthalmologist can play a vital role in the control of headache complaints in patients with migraine. The association between refractive error and headache found in this study indicate that refractive error might be a risk factor for migraine headache. This study enhances our understanding of the relationship of migraine headache and refractive errors to improve opportunities for its treatment and prevention. So, it can be concluded that the different types of refractive errors and migraine headache link very closely.

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REVIEW

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Retinal migraine

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Abstract

Retinal migraine is usually defined by transitory attacks of fully reversible monocular visual loss, mostly with aura. An accurate diagnostic can be completed based upon the International Classification of Headache Disorders-2 (ICHD-2) criteria. In view of this, we summarized some clinical features, treatment principles, complications, prognosis and prophylaxis.

Keywords: migraine, retinal blood vessels, eye vascular network, monocular visual loss

Introduction

Retinal migraine is an ophthalmo-pathological condition described as a transient monocular scotoma or vision loss, being accompanied or followed by a headache. The timing, the intensity and the aura (if present or preceded), may differ from person to person. Among other causes, apparently, the major one stays the ischemia or vascular spasm in, or behind the affected eye. A distinction should be noted, when a confusion between the terms "retinal migraine" and "visual migraine" arises. Visual migraine results from the cortical spreading depression and is denominated as scintillation scotoma. Retinal migraine is a rare retinal disorder. The symptoms are usually transient, but the pathophysiological mechanisms still remain not completely elucidated [**1,2**].

Pathophysiological effectors and mechanisms

Substance P, nitrous oxide, calcitonin generated peptides have been suspected as chemical effectors in the possible pathophysiological mechanisms of retinal migraine, by exercising a non-desired effect leading to the plasma extravasation, neurogenic inflammation, vasodilatation. Other neuro-ophthalmological structures involved are: periaqueductal gray (PAG), locus coeruleus (LC), dorsal Raphe nucleus (DRC), retinal vasculature, and activation of the retinal-thalamic-visual pathway [**3**].

On the contrary, photophobia in migraine may start in cone-driven retinal pathways, exerting a hypersensitive-excitation effect on light-sensitive thalamic neurons. Photophobia is aggravated by the light-intensity dependence, when the eyes of the patients are exposed to

different wavelengths of visible light. Fundoscopy (**Fig. 1**) and fluorescence angiogram expose a delayed tilling or occlusion of the central retinal artery and its branches, (**Fig. 2**) with, either normal ciliary circulation or irregular/ discontinuous choroidal defects and capillary leakage flux [**4**]. The vascular theory still remains doubtful due to the complexity of retinal vascular supply. Retina has a binary circulation: central retinal artery supplies, inner retinal layers. Those microstructures lack adrenergic innervation, maintain sensory-nerves and are auto-regulated [**5**].

Symptomatology

When aura is present: flashing, sparkling, twinkling lights (scintillations). Non-aura: blind spot, a partial loss of vision, temporary blindness, scotoma. A retinal migraine attack begins with monocular visual symptoms, afterwards when relaxation time of the blood vessels is manifested, blood flow resumes and sight returns.

Diagnostic tools and laboratory tests

They should be directed and based on the patient's medical history and physical exam. Some laboratory blood markers, such as platelet count, coagulogram, homocysteine and protein S (optional), can be precious adjuvants as diagnostic tools. Tourniquet or capillary-fragility test (Rumpel-Leede test/ Hess test) can sometimes be a good option too. Optical coherence tomography, retinal oximetry, scanning laser ophthalmoscopic angiography, Doppler studies in order to investigate fundoscopy, visual field examination during the attack are also useful options.

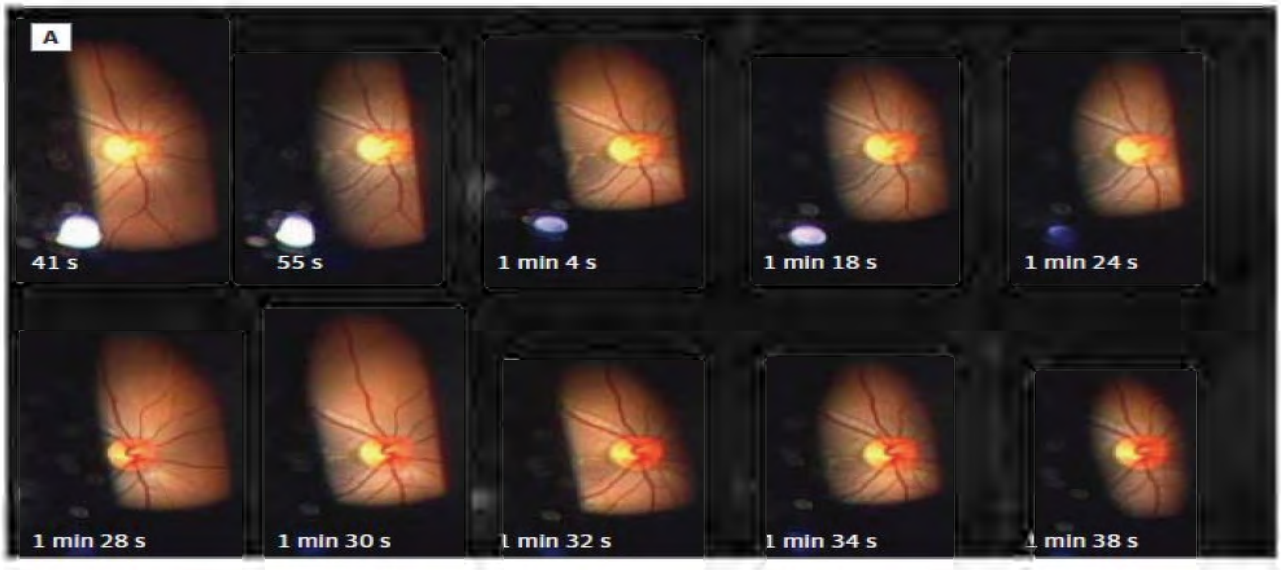
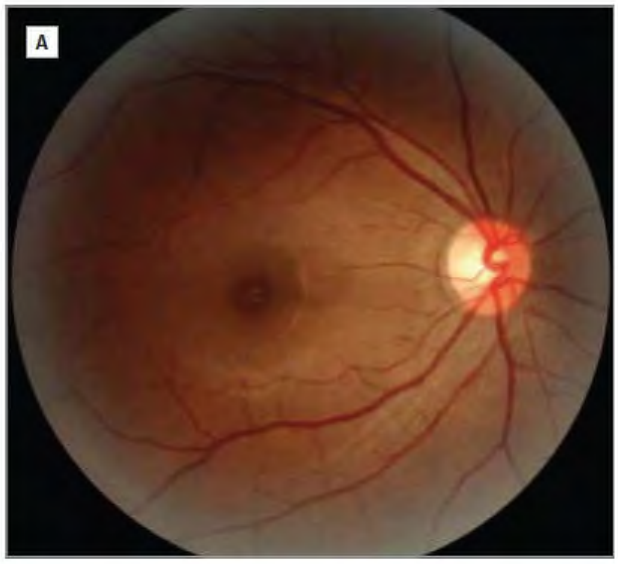


Fig. 1 Video-assisted fundoscopy recorded for 1 min. 48 sec during the migraine attack. Dynamic changes in the retinal artery and veins can be detected.
Source: *Ota I, Kuroshima K, Nagaoka T. Research Letter. Fundus video of retinal Migraine. JAMA Ophthalmology. November 2013; 131(11): 1481-1482* ***[6]***



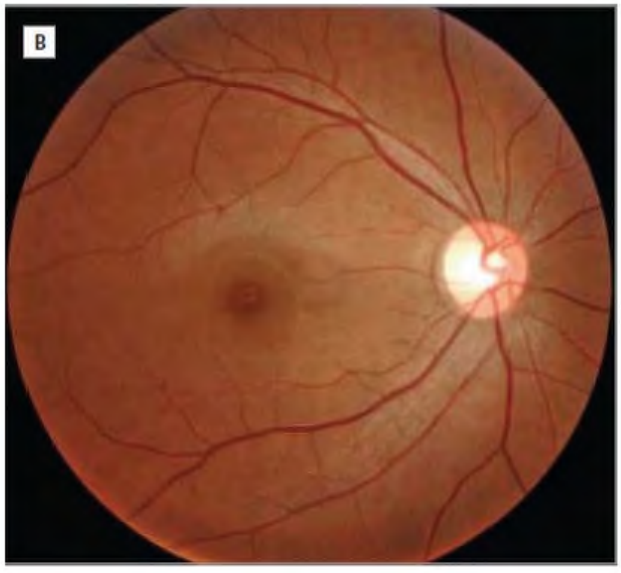


Fig. 2 Fundoscopy of the eye, immediately after the attack onset (A), and at one-month distance after the attack (B).
Source: *Ota I, Kuroshima K, Nagaoka T. Research Letter. Fundus video of retinal Migraine. JAMA Ophthalmology. November 2013; 131(11): 1481-1482 [**6**]*

Reported complications

- reversible and irreversible central retinal artery occlusion
- retinal infarction
- branch retinal artery occlusion
- retinal hemorrhages and disc edema
- ischemic optic neuropathy
- choroidal ischemia
- dilatation of retinal veins
- vitreous hemorrhage
- retinal pigmentary changes
- stroke

Treatment

Analgesics and nonsteroidal anti-inflammatory drugs, caffeine, treatment with triptans, ergotamine compounds, may be a favorable option. Triptans and ergotamines, both exert an effect by stimulating the serotonergic receptors in the cerebral and cardiac vasculature. They should be instituted as therapy within 24h of each other [**7**].

Prevention

It is well documented that visual disturbances caused by retinal migraine attack disappear without treatment within one hour or less. People performing activities that require clear vision, when a retinal migraine occurs, need to stop the activity and relax until the vision returns to normal, preferably in a dark or a semi obscure good freshly aerated room. If driving, they should park on the side of the road and wait for the vision disturbances to pass completely. They should also avoid common migraine triggers and stress, and they should get a regulated sleep and a healthy nutrition.

Conclusions

Retinal migraine is a challenge and sometimes a pitfall before being diagnosed. Aura, is the most essential characteristic, but most cases labeled as “retinal migraine”, are not migraines. Sometimes, a vasculo-allergic migraine can be underdiagnosed or overdiagnosed as a retinal migraine. On the other hand, monocular visual phenomena typically originate in the retina, choroid and optical nerve. It is believed that retinal vasospasm initiates transient monocular visual loss, being the most plausible explanation. Optic nerve infarction and retinal infarction can occur due to the retinal vascular changes and the particularities during the migraine attack. Taking into account that vasospasm is the most common

cause of the symptoms and the use of aspirin has its own risk and has been reported not very effective, the adequate use of verapamil and nifedipine, should constitute a good treatment option. No drug trial has been reported in retinal migraine, this being the reason why the treatment should be prescribed and orientated according to each patient's needs. An inter-disciplinary consult of a neurologist and an ophthalmologist is a wise prerequisite.

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Spatial contrast sensitivity of migraine patients without aura

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Cephalalgia

Benedek K, Tajti J, Janáky M, Vécsei L & Benedek G. Spatial contrast sensitivity of migraine patients without aura. Cephalalgia 2002; 22:142–145. London. ISSN 0333-1024

Visual disturbances are frequent symptoms in migraine. Since there is a possibility of separate damage in the magno- or parvo-cellular visual pathway in migraine patients, we performed a study including the measurement of static and dynamic spatial contrast sensitivity on 15 patients suffering from migraine without aura under photopic and scotopic conditions. Fifteen healthy volunteers without primary headache served as controls. The results revealed a marked decrease in contrast sensitivity at low spatial frequencies in the migraine patients. Spatial contrast sensitivity demonstrated some lateralization, as the sensitivity to low spatial frequencies obtained through separate eyes showed significantly larger side-differences in migraine patients than in control subjects. These findings suggest that the mechanisms responsible for vision at low spatial frequencies are impaired in migraine patients. This might indicate impaired function of the magnocellular pathways in this condition. □ *vision*, *headache*, *migraine*, *contrast sensitivity*, *visual pathways*

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Introduction

Visual symptoms are common in migraine. The most striking ones appear in the aura, frequently involving transitionally blurred vision, homonymous hemianopsy, scotomas or photophobia (for reviews, see 1, 2). These phenomena obviously signal the involvement of visual retino-cortical mechanisms in the pathophysiology of migraine. The major question remains, however, of whether the parallel parvo- and magno-cellular visual pathways are equally affected in this condition or there is a preponderance of magnocellular malfunctions in migraine-associated visual phenomena (3, 4). The answer to this question is greatly hindered by the difficulty in distinguishing between magnocellular and parvocellular dysfunctions in human clinical investigations (5, 6). Nevertheless, it is generally held that the parvocellular pathway dominates the information transfer at high spatial frequency (SF) and low temporal frequency (TF), while the magnocellular pathway conveys information at low SF and high TF (7, 8). This warrants the application of contrast sensitivity measurements in migraineurs.

The use of scotopic stimulating conditions was indicated by animal experiments in which visual stimulation at low SFs and under scotopic conditions excited predominantly magnocellular ganglion cells in the retina (9, 10). Scotopic tests have been employed in several human studies in the search for pathological alterations in human magnocellular functions (11, 12). With regard to these facts, we set out to compare photopic and scotopic spatial contrast sensitivity functions in migraine patients without aura. To increase the sensitivity of these examinations, both static and dynamic contrast sensitivity functions were tested.

Subjects and methods

The patients enrolled in the study were 15 women with migraine without aura. The visual acuity was 1.0 in all cases. The age-range was 18–53 years, with a median age of 31 years. The duration of the complaints ranged between 1 and 25 year, with a median value of 10 years. The frequency of their headache was in the interval between monthly occurrence and three attacks per year. The patients were diagnosed according to the criteria of the International Headache Society (13). All subjects underwent detailed neuro-ophthalmological examinations, including physical examination, CAT scan, blood chemistry, ophthalmoscopy and visual perimetry. Only patients with no other neurological or ophthalmological

diseases were included in the study. Intraocular pressure level was routinely measured in all patients. It was below 16 mmHg in all cases. In two cases the sinusoidally reversing grating caused acute headache, as described by Shepherd et al. (14). These patients were excluded from the study. Similarly, patients who had migraine attacks without aura two weeks before or after the study were also excluded.

The control group comprised 15 age-matched female volunteers with good vision and without neurological symptoms or primary headache.

Monocular static and dynamic contrast sensitivity was measured at nine spatial frequencies (SFs) (0.5, 1.2, 1.9, 2.9, 3.6, 4.8, 5.7, 7.2 and 14.3 cycle/degree) with a computerized test (Venus, NeuroScientific Corporation, USA). The stimuli were luminance contrast horizontal gratings with a sinusoidal luminance profile. For the dynamic test, the pattern was reversed at a temporal frequency of 4 Hz. The display subtended a visual angle of 13°×13° and was viewed from a distance of 1 m. The luminance of the screen was 17 and 0.17 cd/m^2 under photopic and scotopic conditions, respectively. The maximum contrast was 70.7%. Both eyes were tested under photopic conditions, while only the right eye was tested under the scotopic one. For the measurement of contrast thresholds, the contrast was initially set at 15 dB above the mean normal value. The participants were all able to detect this submaximal contrast level. The contrast level was then decreased by 3 dB every 5 s until they failed to detect the stimulus any longer (descending method). Patients gave a verbal indication of changes in contrast detection. In both the static and the dynamic test the contrast was then set at 15 dB below the threshold measured with the descending method and it was increased by 3 dB every 5 s without interstimulus interval until subjects detected the stimulus (ascending method). The whole procedure was repeated five times in order to obtain a mean contrast threshold at a given SF. The contrast sensitivity was defined as the reciprocal of the contrast threshold (14). The sequences of the descending and ascending methods, the SFs tested and the static vs. dynamic tests were counterbalanced across the subjects. Not all the patients completed all the tests. In some rare cases the testing was prematurely concluded. This is indicated by the differing degree of freedom values.

Statistical evaluation was carried out by means of ANOVA and posthoc analysis (with multiple comparison, Newman-Keuls test) with the STATISTICA program.

Results

Spatial contrast sensitivity functions revealed significant impairments in migraine patients (Fig. 1). The decrease in contrast sensitivities was most marked at low SFs and specially in measurements under scotopic conditions. Significant differences in contrast sensitivity under photopic static condition were observed by diagnosis ($F[3, 40] = 25.01$, $P < 0.001$), by frequency ($F[8, 320] = 138.1$, $P < 0.001$) and for the interactions ($F[24, 320] = 10.4$, $P < 0.001$) (Fig. 1a). Significant differences in contrast sensitivity under photopic dynamic condition were also observed by diagnosis ($F[3, 42] = 8.85$, $P < 0.001$), by frequency ($F[8, 336] = 102.7$, $P < 0.001$) and for the interactions ($F[24, 336] = 6.84$, $P < 0.001$) (Fig. 1b). The post hoc comparison showed significant differences between the migraine and control values for both eyes at the five lowest spatial frequencies in the photopic static situation and in the three lowest frequency band in dynamic situation.

As regards the ANOVA analysis of static contrast sensitivities under scotopic conditions, we found significant differences by diagnosis ($F[1, 23] = 87.2$, $P < 0.001$), by frequency ($F[8, 184] = 149.3$, $P < 0.001$) and for the interactions ($F[8, 184] = 20.2$, $P < 0.001$) (Fig. 1c). At last, significant differences in contrast sensitivities under scotopic dynamic condition were also observed by diagnosis ($F[1, 23] = 92.3$, $P < 0.001$), by frequency ($F[8, 184] = 160.4$, $P < 0.001$) and for the interactions ($F[8, 184] = 45.6$, $P < 0.001$) (Fig. 1d). The *post hoc* analysis of the dynamic scotopic contrast sensitivity values showed significant differences between the control and migraine patients at the five lowest spatial frequencies. In contrast, the static scotopic contrast sensitivity showed significant differences at all spatial frequencies.

Interocular contrast sensitivity difference values were calculated in measurements performed under photopic circumstances at the four lowest frequency band. As regards the ANOVA analysis of static contrast sensitivities, we found significant differences by diagnosis ($F[1, 20] = 21.0$, $P < 0.001$), but not by frequency and not for the interactions. Significant differences in contrast sensitivities under dynamic conditions were observed by diagnosis ($F[1, 21] = 9.37$, $P < 0.001$), by frequency ($F[3, 63] = 3.2$, $P < 0.05$) but not for the interactions.

Discussion

Our results showed significant changes of spatial contrast sensitivity in patients with migraine without aura. A particularly noteworthy reduction was found in the low SF range of spatial contrast sensitivity. Our finding therefore seems to support the notion that there could be an asymmetric disturbance in the function of the parallel visual pathways of migraine patients without aura. Quite recently, McKendrick et al. (15) reported a similar dysfunction in migraine with aura.

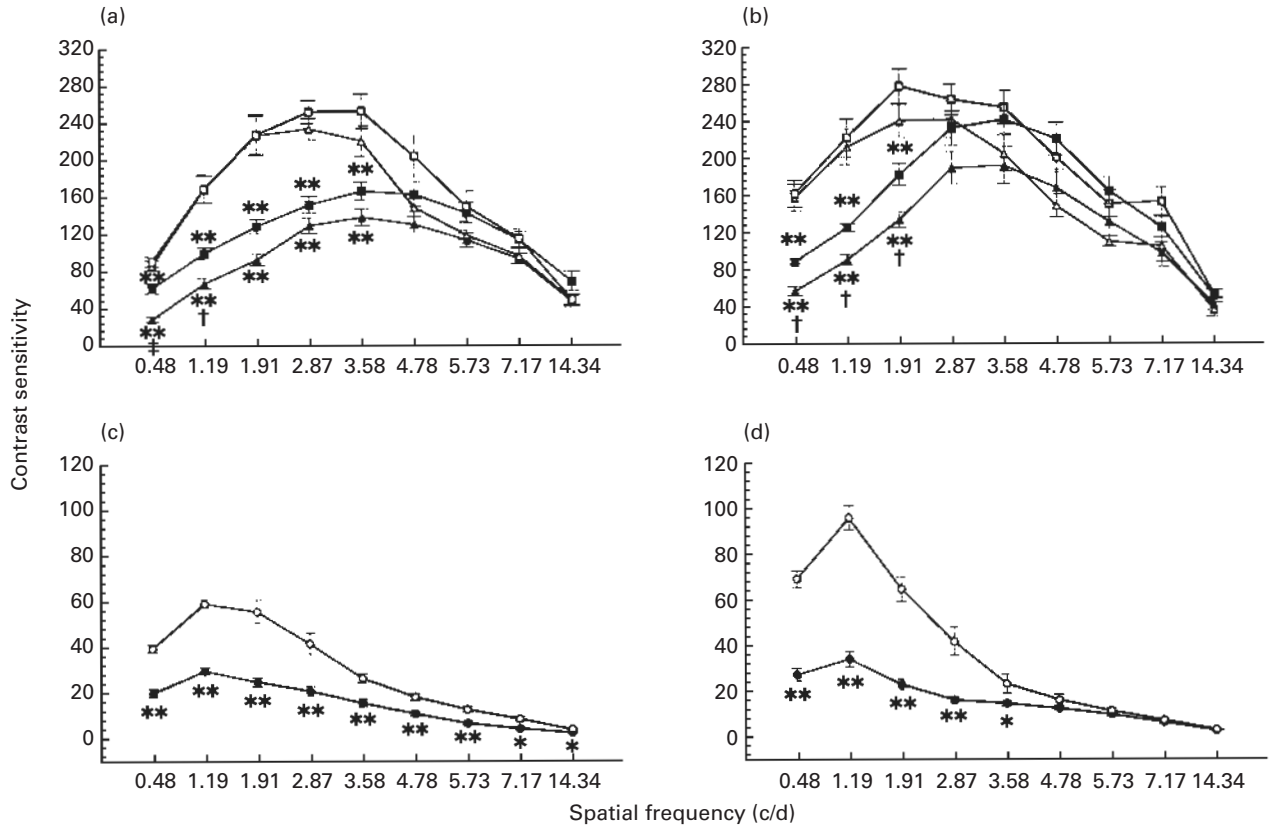

Figure 1 Spatial contrast sensitivity functions of migraine patients and control subjects. (a) photopic contrast sensitivity estimated by static stimulation and (b) photopic contrast sensitivity functions estimated by dynamic method. Control subjects, open symbols; migraine patients, filled symbols; ■,□ through the more sensitive eye, ▲,△ through the less sensitive eye. (c) scotopic spatial contrast sensitivity estimated by static stimulation and (d) scotopic spatial contrast sensitivity estimated by dynamic stimulation. Control subjects ○, migraine patients ●. * and ** mark significant differences to the corresponding eyes of control subjects on the 0.05 and 0.001 probability levels, respectively. † and ‡ denote significant interocular contrast sensitivity differences on the 0.05 and 0.001 probability levels, respectively. Values are shown as mean ± S.E.M.

In this type of migraine patients a definite reduction was found in temporal contrast sensitivity (4) that is also in concert with our conclusions.

In view of the well-known dominance of the magnocellular pathway in the transmission of visual information in the low SF range (7, 8), our finding may suggest impaired magnocellular visual functions in migraine patients. Further, the magnocellular ganglion cells in the retina (16) and in the dorsal lateral geniculate nucleus (17, 18), and the cells in layer 4C (19) display a similar contrast sensitivity function to that observed in humans under scotopic circumstances (20). There is also clinical evidence that the scotopic vision is impaired after magnocellular damage (12, 21). Therefore, finding that the decrease in the contrast sensitivity in the migraine patients was especially marked under scotopic circumstances further substantiates the notion of magnocellular damage in this condition.

It remains to be settled whether the weaker contrast sensitivity at low SF represents a cortical or precortical mechanism. Cortical neuronal changes have been extensively investigated during the last years. A definite visual cortical hyperexcitability was reported in migraine patients (22). Cortical site of action is warranted by studies investigating sensory habituation processes, too (2, 23, 24). These results are in line with the interhemispheric differences that has been reported concerning a series of parameters measured interictally or ictally in migraine patients (25). The visual evoked potential studies by Tagliati et al. (26) and Shibata et al. (27) demonstrated significant hemispheric side differences in hemianopic migraine aura. Positron emission tomography, however, failed to indicate any side difference during the visual aura of classic migraine, although there was a 40% overall decrease in the regional cerebral blood flow (28). A precortical site of action in the pathophysiology of migraine has been raised earlier (3). Interictally persisting dysfunctions of the precortical visual processing have been substantiated by the evoked potential

studies of Oelkers et al. (29). The eye to eye side difference in the interictal measurements of contrast sensitivity in our migraine patients could indicate an additional evidence for some precortical sites of pathophysiological actions in migraine. It is possible that the interocular and interhemispheric differences represent two separate pathophysiological processes. Although, cortical afflictions in migraine patients have already been widely investigated, studies on retinal or optic tract abnormalities are, however, rather rare. Our findings lead us to suggest that a thorough investigation of the pathophysiological phenomena in the whole visual pathway of migraine patients might promote our knowledge concerning the pathomechanism of this painful condition.

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REVIEW

Symptoms related to the visual system in migraine [version 1; peer review: 2 approved]

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Abstract

Migraine is a common headache disorder characterized by often-severe headaches that may be preceded or accompanied by a variety of visual symptoms. Although a typical migraine aura is not difficult to diagnose, patients with migraine may report several other visual symptoms, such as prolonged or otherwise atypical auras, “visual blurring”, “retinal migraine”, “ophthalmoplegic migraine”, photophobia, palinopsia, and “visual snow”. Here, we provide a short overview of these symptoms and what is known about the relationship with migraine pathophysiology. For some symptoms, the association with migraine is still debated; for other symptoms, recent studies indicate that migraine mechanisms play a role.

Keywords

migraine aura, prolonged aura, persistent aura, retinal migraine, ophthalmoplegic migraine, photophobia, palinopsia, visual snow

Open Peer Review

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	1	**2**
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Introduction

Symptoms related to the visual system are common in migraine, a neurovascular brain disorder characterized by episodes of often-severe headache lasting between 4 hours and 3 days[1]. In almost one third of patients with migraine, the headache is preceded by a visual aura[2] but there are several other visual symptoms related to migraine. The purpose of this narrative review is to provide a brief overview of these visual symptoms. Because migraine prevalence is high—lifetime prevalences are 33% in women and 13% in men[2]—many physicians, especially general practitioners, neurologists, and ophthalmologists, will see patients with migraine. First, as background, the typical migraine aura is discussed, followed by the differential diagnosis of atypical auras. Next, visual symptoms other than migraine aura are reviewed: photophobia, palinopsia, and visual snow.

Typical visual migraine aura

In its most typical form, a visual aura begins with a "scintillating scotoma", a small blind spot with a flickering, brightly colored, and typically jagged front—the so-called fortification spectrum—that generally expands in a C-shape to one side of the visual field (Figure 1)[1,3]. The expansion is gradual and lasts between 5 and 60 minutes[1]. These visual symptoms are fully reversible and should not be accounted for by another disorder, according to the third edition of the International Classification of Headache Disorders[1]. The positive symptoms often take shapes other than a classic fortification spectrum. Patients commonly report that the aura starts with light flashes or balls of light that gradually expand across the visual field[4,5]. Furthermore, positive symptoms do not have to occur; patients can also report that the scotoma (that is, the blind spot or the hole in the visual field) has no colors or jagged lines. When patients close their eyes, the positive features of an aura remain visible. Besides having visual symptoms, patients may experience sensory symptoms, speech problems, and sometimes motor symptoms during their auras[1]. If a person has had two attacks fulfilling criteria for migraine with aura, he or she is classified as a migraine with aura patient[1]. If a person has only attacks without aura, he or she is classified as migraine-without-aura. Migraine with aura patients can still have attacks without aura. In a general-population study, median attack frequency was 12 attacks per year and 25% of patients with migraine had at least two attacks per month[2].

Figure 1. Example of a migraine aura. This picture illustrates the typical gradual expansion of a migraine aura along with the characteristic fortification spectrum.

Gradual expansion is considered the most typical feature of a migraine aura[1]. This corresponds with the suspected underlying pathophysiological mechanism called "cortical spreading depolarization" (CSD): a wave of intense neuronal and glial depolarization that is followed by neuronal depression. Preclinical and clinical studies suggest that the velocity of CSD through the occipital cortex is in line with the velocity of the visual spread observed by patients[6–8]. Patients can report a classic cascade in aura symptoms: the aura starts with visual symptoms and is followed by sensory symptoms, aphasia, and sometimes motor problems[9]. It is believed that in these cases the CSD expands from the occipital cortex to the motor cortex[10]. However, a prospective diary study showed that in 34% of patients the aura symptoms start simultaneously, suggesting that CSD may also start in a non-symptomatic brain area and reach two cortical areas at about the same time[5,11]. Sometimes patients report complex visual phenomena during their auras, such as distortions of observed body parts (for example, disproportionately large ears, sometimes referred to as the Alice in Wonderland syndrome) or visual splitting (one half of the observed face shifts upwards or downwards)[3,12,13]. This suggests that more complex processes of visual perception, involving orientation and size, can also be altered during migraine attacks. Additionally, patients often report that during migraine auras their vision is "blurred" or "foggy" or that they see "heat waves". In the diary study, this was registered in 33% of auras[5]. However, information on gradual expansion was not collected. Furthermore, these symptoms have not been prospectively studied in migraine without aura patients. Therefore, there is still discussion about whether these symptoms are part of the aura spectrum.

In most patients, the aura is followed by a migraine headache. Typically, the headache starts after the aura has ended, although the headache can also start during or—in rare cases—before the aura[5,9,14]. In a minority of attacks, the aura is not followed by headache[4,9] and this classically occurs in elderly patients and is often referred to as "late-life migraine accompaniments"[15].

Current acute migraine medication is able to treat the headache only and has no effect on the auras. Preventive drugs such as beta-blockers, candesartan, topiramate, valproate, and amitriptyline and nortriptyline are generally considered when patients have an average of more than two attacks per month. When successful, the auras can also be prevented. For patients with frequent auras, lamotrigine can also be tried[16].

Atypical visual migraine auras

Atypical auras are important to identify because of the differential diagnosis with other diseases. First, migraine auras can mimic stroke because of the homonymous visual field defects or additional focal symptoms[17]. However, in migraine aura, symptoms gradually develop whereas in stroke they are often maximal from the start. Furthermore, classic aura features (colors and zig-zag lines) are generally not present in stroke[18]. Nonetheless, it can be hard to discriminate between the two diagnoses and other clinical factors such as age and cardiovascular risk factors should be taken into account. When the aforementioned "late-life migraine accompaniments" in an elderly patient are considered, secondary causes such as cerebral amyloid angiopathy should also be excluded. Amyloid spells (that is, transient focal neurological episodes caused by superficial cortical siderosis) can mimic migraine auras[19].

Second, occipital epilepsy can also present with visual symptoms followed by headache but without the characteristic motor seizures. Classically, patients describe these symptoms as colored phosphenes[3], although phosphenes can also be reported as aura symptoms by patients with migraine[20]. However, visual symptoms in epilepsy generally last shorter than 5 minutes and often start in the periphery of one temporal visual field whereas in migraine the auras generally start more to the center and expand to the periphery[20]. These criteria are not specific and sometimes electro-encephalography recordings could help in diagnosing occipital seizures. The following entities have been described as variants of migraine aura, although the actual relationship with migraine has been criticized for some of them.

Prolonged and persistent aura

In migraine, visual auras can last longer than the classic 60 minutes that is defined by the International Classification of Headache Disorders[21,22]. In one diary study, 26.4% of patients had a visual aura, a sensory aura, or speech problems that lasted longer than 60 minutes[22]. This is often referred to as "prolonged aura". However, visual auras lasting longer than 2 hours are considered rare and require additional investigation since they can be associated with cerebral infarction. If the aura is typical of previous auras (except in its duration) and there are imaging signs of ischemic infarction in the relevant brain area the term "migrainous infarction" is used to classify the infarct, but only if other causes of stroke are ruled out. Most cases of migrainous infarction are of cortical origin, suggesting that CSD could play a role; however, this could be confounding by indication since cortical infarcts are more likely to be classified as migrainous whereas subcortical infarcts may be attributed to a different cause[23–25]. There is still debate on whether increased prevalence of patent foramen ovale in patients with migraine could play a role as well[23,26].

If infarction and other causes of binocular visual disturbances are excluded and aura symptoms last longer than 1 week, the term "persistent aura without infarction" is used[1]. This is very rare. Symptoms can last months to years. Evidence on treatment is limited, lamotrigine is recommended on the basis of case series[27], and in one randomized controlled trial intranasal use of ketamine in patients with prolonged auras limited the aura severity but not the duration[28].

Migraine aura status

Some patients with migraine with aura may experience a sudden and large increase in the frequency of their auras, typically without headache. If at least three auras occur over a period of 3 days, the term "migraine aura status" is used[1]. However, this diagnosis requires that secondary causes, including occipital infarction, arterial dissection, reversible cerebral vasoconstriction syndrome, and posterior reversible encephalopathy syndrome, be excluded[1,29]. Retrospective studies indicate that a migraine aura status is rare[30,31]. Aura frequency can spontaneously normalize within a few weeks, but acetazolamide[32] or valproate[31] could aid in this process and prevent new episodes, although evidence is limited to case reports.

Retinal migraine

The relevance of "retinal migraine" is still debated and unfortunately the term has been misused to describe visual auras, although these are binocular and homonymous and therefore of cortical origin. The term "retinal migraine" is reserved for monocular, fully reversible visual symptoms with at least two of the following criteria: the visual symptoms spread gradually during at least 5 minutes, last between 5 and 60 minutes, and are accompanied or followed within 60 minutes by headache[1]. Importantly, secondary causes of monocular visual disturbances should be excluded. Critics of retinal migraine argue that symptoms are not monocular in patients with this diagnosis but binocular and that patients were not properly instructed to discriminate between monocular and binocular symptoms[33]. Nonetheless, cases have been reported of recurrent, transient monocular visual disturbances followed by migraine headache in patients who were clearly instructed[33]. Proponents additionally argue that CSD can occur in the retina, although these studies are still limited to *in vitro* models[34].

Ophthalmoplegic migraine

Some patients with migraine—in particular, children with migraine—reported transient double vision after a migraine attack. This ophthalmoplegia involved mostly the third cranial nerve. Therefore, the term "ophthalmoplegic migraine" was introduced. A prerequisite is that the ophthalmoplegia is preceded by a "migraine-like" headache in the prior four days. However, a literature review of published cases showed that one third of cases did not have a headache fulfilling migraine criteria[35]. Furthermore, the time between the headache and the ophthalmoplegia could be as long as 14 days and there was

often focal enhancement of the third cranial nerve on magnetic resonance imaging. It was therefore re-classified as "recurrent painful ophthalmoplegic neuropathy", and demyelization was suggested to play a role[1,35].

Photophobia

One of the main discriminating symptoms between migraine headache and other headache disorders is photophobia accompanying the headache, often occurring simultaneously with phonophobia[1]. Patients often report that the migraine headache is worsened by the presence of light and that they have to lie in the dark.

Therefore, photophobia is classically viewed as an ictal symptom. However, studies focusing on the premonitory phase—most often defined as the 48 hours before the migraine attack starts—found that up to 49% of patients already experienced photophobia before the headache developed[36,37]. Furthermore, patients report that they have light aversion on days not preceding or following a migraine attack[38]. There is increasing evidence for this hypersensitivity to light. Interictally, patients with migraine have a lower light discomfort threshold than controls[39]. Additionally, many of them find patterns with high contrast more discomforting to look at[38,39]. This is supported by visual hyperexcitability studies using visual adaptation techniques[40], visual evoked potentials[41], and positron emission tomography (PET) brain imaging[42] in patients with interictal migraine. Interestingly, migraine with aura patients reported more discomfort than migraine without aura patients, suggesting that visual hyperexcitability could play a more prominent role in the former[39]. This is in line with the hypothesis that migraine with aura patients have a lower threshold to experience a CSD. Although light stimulates nociceptive trigeminal neurons[43], it is thought that central processes involving thalamus and visual cortex have a more important role[44]. There is also recent evidence from longitudinal studies that visual sensitivity already increases in the days preceding a migraine attack[45,46]. Although these discoveries are promising, they have not led to therapeutic options for photophobia.

Palinopsia

Palinopsia is derived from the Greek words *palin* (again) and *opsis* (vision) and is used to describe perseveration of visual images. This can be experienced as seeing an afterimage of an object (after staring at an object and looking away) or as a series of images when an object is moving (Figure 2)[47]. Especially the former can be a normal physiological phenomenon when the stimulus was bright or there was a high contrast, and it results mostly in a negative afterimage: the afterimage is in complementary color. A positive afterimage, which has colors similar to those of the original image, is generally not considered physiological, although there is no strict cutoff in terms of frequency, duration, or other characteristics[47]. There is evidence that patients with migraine are more prone to palinopsia, although the number of studies is limited and methods differ[45,48,49], complicating estimates on the prevalence of this symptom. In palinopsia, as in photophobia, it is thought that a central origin in the lateral geniculate nucleus of the posterior thalamus or visual cortex plays a role. Possibly altered sensory processing leading to palinopsia occurs primarily in the days preceding a migraine attack[45].

Visual snow

Visual snow is characterized by the continuous presence of countless small dots in the entire visual field (Figure 3)[50]. Patients often describe it as "TV static from a detuned analogue television" since the dots are flickering on and off[50]. Although the severity of the snow can vary during the day, symptoms are never fully absent. Visual snow was not considered a separate entity until 2014[50]. Earlier reports often referred to the snow as a form of "persistent migraine aura", possibly because many patients have a history of migraine with aura[27,51–55]. However, in visual snow, the classic migraine features such as scintillating scotomas and fortification spectra are absent[1,50,54]. Furthermore, persistent migraine auras often start unilaterally and expand whereas patients with visual snow generally report that it started in the entire visual field and there was no spatial expansion[50].

Figure 2. Example of palinopsia. An example of a moving object (the hand is moving from left to right) with perseverance of multiple images is shown.

Figure 3. Example of visual snow. Patients with visual snow observe tiny dots in the entire visual field. The dots often resemble the "static" from a detuned analogue television because the dots "flicker on and off". Classically, the dots are black/gray on a white background and white on a black background, but colors may vary.

Little is known about the epidemiology of visual snow[50,56]. Age of onset is often in the early twenties. In visual snow, in contrast to migraine, current data do not show an increased prevalence in females. Visual snow seems to be related to migraine: two case series found that between 47 and 59% had a history of migraine and that the prevalence of migraine with aura was relatively high compared with that of migraine without aura[50,56]. Furthermore, patients with migraine sometimes also report seeing visual snow, albeit transient and not continuous. In a prospective diary study, 8% of patients with migraine reported visual snow during their visual aura but not outside the aura[5].

A diagnosis of visual snow is made after exclusion of secondary causes of pan-field visual disturbances, such as lesions in the visual pathways and retina. Nevertheless, ophthalmic and neurological examinations in patients with visual snow are generally normal[50]. Most patients report additional visual symptoms: palinopsia, enhanced entopic phenomena (excessive floaters or blue field entoptic phenomena and spontaneous photopsia), photophobia, and nyctalopia. Therefore, it was proposed that visual snow is part of a clinical syndrome[50]. The syndrome criteria were proposed for research purposes and have no current clinical consequence for diagnosis or prognosis. Visual snow has also been reported as a persistent visual effect after intake of illicit hallucinogenic drugs such as LSD and ecstasy[57]. However, since there are patients with visual snow who never used hallucinogenic drugs[50] and since visual snow is also reported in children[58], it seems that hallucinogenic drug use is not the only potential risk factor.

It is hypothesized that cortical hyperexcitability plays a role in visual snow as well. Theoretically, the visual disturbances can also be localized to bilateral retinal pathology; however, this seems unlikely since ophthalmological examinations and electro-retinograms are generally normal in patients with visual snow[50]. Therefore, visual snow is generally considered a cortical problem. Indeed, there is some evidence that cortical excitability parameters are increased in patients with visual snow and without comorbid migraine. This has been tested by using visual tasks[59] and visual-evoked potentials[60], but findings still have to be replicated in larger studies. One study using [^{18}F]-2-fluoro-2-de-oxy-D-glucose PET showed hypermetabolism in the lingual gyrus, an area that modulates visual processing, in visual snow patients compared with healthy controls[61]. The same area was shown to be involved in previous migraine studies on photophobia[42,62]. However, because 14 out of 17 patients with visual snow also had comorbid migraine, it remains unknown whether this hypermetabolism is specific for visual snow[61]. Treatment of visual snow is limited to case reports and expert opinion. Lamotrigine may sometimes help[63,64].

Conclusions

The visual aura is the most typical form of visual disturbances in migraine but there are several other visual symptoms that people with migraine report. In this review, we have given a short clinical overview of these symptoms and what is known about the relationship with migraine pathophysiology. Although there are currently no specific therapeutic options focusing on visual symptoms, recent studies have begun to unravel some of the mechanisms that are involved.

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ORIGINAL ARTICLE

The Correlation Between Migraine Headache and Refractive Errors

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ABSTRACT

Purpose. A literature review reveals historical references to an association between migraine headache and refractive errors, but a lack of scientific evidence relating to these claims.

Methods. In a masked case–controlled study, we investigated the four aspects of refractive errors that have been implicated in the literature as correlated with migraine: spherical refractive error, astigmatic refractive error, anisometropia, and uncorrected ametropia. We also compared the calculated scalar value of refractive error, aided and unaided visual acuity, and spectacle use in migraine and control groups. We then investigated the relationship between refractive components and key migraine headache variables.

Results. Compared with the control group, the migraine group had higher degrees of astigmatic components of refractive error assessed both objectively (C, $p = 0.01$; C_0, $p = 0.01$; C_{45}, $p = 0.05$) and subjectively (C, $p = 0.03$; C_0, $p = 0.03$; C_{45}, $p = 0.05$), uncorrected astigmatic components of refractive error (C_0, $p = 0.02$; C_{45}, $p = 0.04$), and anisometropia ($p = 0.06$).

Conclusions. Perhaps the historical literature is indeed correct that low degrees of astigmatism and anisometropia are relevant in migraine. Our most significant finding was of higher degrees of astigmatism in the migraine group. This study does indicate that people who experience migraine headaches should attend their optometrist regularly to ensure that their refractive errors are appropriately corrected.

(Optom Vis Sci 2006;83:82–87)

Key Words: refractive error, migraine, spectacles, astigmatism, anisometropia

A recent review of the association between refractive errors and migraine shows the literature to be equivocal.[1] Early studies provide anecdotal evidence, but the few modern studies, which included control groups and masked experimenters, have found little evidence of an association. The early uncontrolled studies argued that migraine is associated with low refractive errors, notably astigmatism,[2,3] or latent errors, particularly low anisometropia.[4] A slightly later study found little difference in refractive error in people with migraine and control subjects.[5] Subsequent studies are difficult to interpret because of a lack of a control group or statistical analysis[6–11] or because they did not relate to migraine specifically but rather to headache generally.[12–14]

Chronicle and Mulleners[15] suggested that there was a lack of conclusive evidence concerning the involvement of refractive error in the etiology of migraine. In a more recent study,[16] no significant difference between a group of migraine and a group of control patients was found in the subjective refractive error or the proportion of participants who wore spectacles. Yet there is evidence that the public remains convinced that there is an association between their eyesight and headaches[17] with 21% of people with headache having consulted an eye care practitioner for advice, second only to a visit to a general medical practitioner (28%) and far more commonly than a visit to a pharmacist (8%).

The present article describes a masked case–controlled study of the optometric correlates of migraine, some of the results of which have been published elsewhere.[18,19] The migraine and control groups were compared with respect to the four aspects of refractive error historically suggested to be linked to migraine: spherical refractive error, astigmatic refractive error, anisometropia (the intereye difference in the spherical equivalent), and uncorrected ametropia (the difference in the mean spherical equivalent between the spectacle refractive correction and the final subjective refractive error found). Scalar calculations were performed to compare total refractive error and intereye difference in total refractive error together with the recorded aided and unaided visual acuity and habitual spectacle use. The correlations between the key migraine headache variables and the key refractive variables were then investigated.

METHOD

This study is part of a case–controlled study looking at the optometric correlates of migraine using a large battery of optometric tests. The recruitment of the people with migraine and age- and gender-matched control subjects has been described elsewhere.[18] Participants were recruited to the study as part of collaboration with local general medical practitioners (who referred consecutive patients with migraine) and with a London Hospital Neurology Unit specializing in Migraine Headache (who selected patients with migraine from a database). All patients had a formal medical diagnosis of migraine and this was confirmed with a headache questionnaire, which ensured the diagnosis of migraine met International Headache Society (IHS) criteria.[20] Participants for the migraine group were aged between 10 years and 50 years with a frequency of migraine headaches of at least one per month. Individuals with systemic health problems, pregnancy, or ocular disease were excluded from the study. The tenets of the Helsinki declaration were followed: full informed consent was obtained and participants were able to abstain or withdraw from the research at any time without having to give a reason. No participants withdrew after they had arrived at the clinic. The research and ethics committees of the Institute of Optometry (London) and City University (London) approved the study.

Before attending the research clinic, participants in the migraine group were asked to complete a 6-week headache diary, including data on the last migraine headache. On attending the research clinic, all participants were asked to complete a questionnaire[20] detailing their symptoms and history, including questions relating to headaches. The design of the questionnaire allowed for confirmation that the migraine group met the IHS criteria for migraine headache[21] and that the control group were truly migraine-free. Participants attended in pairs, one from the migraine group and one from the control group. We took several measures to ensure that the researcher was masked[18] as to the identity of the participant: the members of each pair were seen in random order, participants were asked not to reveal their identity, and the contents of the questionnaire were not revealed to the research optometrist until the end of the tests of both the migraine sufferer and the control participant. The masked nature of the study was successfully maintained for all migraine participants and all but three of the control participants. All participants were headache-free at the time of testing.

Participants own spectacles were analyzed using a Shin-Nippon -15C lensometer (focimeter) to establish their own habitual spectacle refractive error. Aided and unaided visual acuities were taken monocularly using a National Vision Research Institute of Australia Bailey-Lovie Chart[22] and were rated using the VAR score and counting per letter correctly identified.[23] To ensure full optical correction of all the participants, the subjects then underwent objective refractive assessment using a Keeler spot retinoscope with 6-m fixation[24] followed by subjective refractive assessment using standard optometric procedures that included assessment of spherical error,[24] crossed cylinder evaluation of astigmatism corrected with negative cylindrical lenses,[24] and a binocular balancing technique.[24]

Refractive errors were analyzed using both the raw data and the components of astigmatic decompensation calculations.[25] Humphrey's principle of astigmatic decompensation represents the cylindrical power C as a combination of two obliquely crossed cylinders, C_o at axis 0° and C_{45} at axis 45°, and has been suggested as a good method to statistically analyze ophthalmic prescriptions,[24] because all cylinders are put on a common basis.

A given prescription of sphere S, cylinder C, and axis ϑ can be used to calculate:

$$C_0 = C\cos 2\theta$$
$$C_{45} = C\sin 2\theta$$

and it follows that:

$$C = \sqrt{C_0^2 + C_{45}^2}$$

The spherical equivalent power m is the algebraic mean of the two principle powers S and (S + C) such that:

$$M = S + (C/2)$$

As such, for any given prescription, the total spherocylindrical power can be represented by a single scalar quantity[26,27] as:

$$u = \sqrt{C_0^2 + C_{45}^2 + M^2}$$

where u is given the same sign as M.

Distributions were tested for normality by inspecting frequency distributions and carrying out the Kolmogorov-Smirnov test of normality. It is well known that refractive error is not, strictly speaking, normally distributed with the distribution of spherical refractive error showing leptokurtosis.[28,29] However, refractive errors seem reasonably well-described by parametric descriptive statistics and, as is usual practice,[28–32] we described our variables in this way. When carrying out comparative statistics, we took a conservative approach and used the nonparametric Mann-Whitney U test. When group means are quoted, the 95% confidence limits are given in parentheses. Spearman correlations were carried out to compare spherical refractive error, astigmatic refractive error, anisometropia, and uncorrected errors with migraine variables of severity of worst headache, duration of worst headache, the number of headaches in the last 12 months, and the number of days since the last migraine headache.

The statistical analysis of multieye data in ophthalmic research is discussed in the literature.[33,34] The inclusion of data from each eye of each participant, especially when the data from each eye are highly correlated (like in the present data), is deprecated because it overestimates the statistical significance of the data. An acceptable solution is to average the data from right and left eyes for each participant,[33,34] and this was the approach that was followed here with the obvious exception of the data for anisometropia.

The key variables found to be statistically different in the migraine group were reanalyzed with outliers (values >3 interquartile ranges [IQRs]) from the upper or lower interquartile range) removed to determine the contribution of these few subjects compared with the entire sample.

RESULTS

Age, Gender, and Spectacle Use

There were 25 participants in each group. The mean age of the migraine group was 37.5 years (33.2–41.8 years), which did not differ significantly (t test, $p = 0.77$) from the mean age of the control group of 36.8 years (33.3–40.2 years). Each group had 21 female and four male participants. Similar numbers wore specta-

cles in each group (χ^2 test, p = 0.77). In the migraine group, 14 used spectacles and in the control group, 12 wore spectacles.

Visual Acuity

The mean VAR score for unaided visual acuity was 82.6 (73.1–92.0) for the migraine group and 79.8 (68.8–90.9) for the control group. The groups were not significantly different (Mann-Whitney U test, p = 0.96). The LogMAR (and Snellen) equivalents for the mean unaided visual acuities are 0.35 ($20/40^{-2}$) for the migraine group and 0.4 (20/50) for the control group. The mean VAR score for aided visual acuity was 101.3 (99.4–103.3) for the migraine group and 101.1 (99.5–102.7) for the control group. The two groups did not differ significantly. The LogMAR (and Snellen) equivalents for the mean aided visual acuities are −0.02 ($20/20^{+1}$) for the migraine group and −0.02 ($20/20^{+1}$) for the control group.

Total and Spherical Refractive Error

The mean of the spherical refractive error S, from the right and left eyes, were calculated and then compared in the two groups. The true (signed) rather than absolute values were taken so that bias toward myopia or hyperopia could be distinguished. This mean subjective spherical refractive error S_r, was −0.540 DS (−1.581–0.501) for the migraine group and −1.080 DS (−1.926–0.234) for the control group and the groups were not significantly different (Mann-Whitney U test, p = 0.10).

The mean scalar value u_s of the absolute value of u from the right and left eyes of the subjective refraction (a representation of the total spectacle prescription found) was 2.037 (1.143–2.931) for the migraine group and 1.482 (0.660–2.304) for the control group and the groups were not significantly different (Mann-Whitney U test, p = 0.11).

Astigmatic Refractive Error

The average of the absolute astigmatic refractive error C from the right and left eyes was calculated and then compared in the two groups. The mean objective (retinoscopy) astigmatic refractive error C_{ob} was also calculated in the same way to ascertain if these results held for both objective and subjective data. To establish if these astigmatic results were influenced by axis, the C_0 and the C_{45} components of the Humphrey decompensation were analyzed for both objective and subjective data. The average of the absolute value for C_0 and C_{45} from the right and left eyes were calculated and then analyzed between the groups. The astigmatic data are shown in Figures 1, 2, and 3. To compare the data, Mann-Whitney U tests were performed. Outliers (those data points further than 3 IQRs) were removed and the Mann-Whitney U tests reperformed on the amended dataset to establish the influence of the outliers on the group as a whole. These results are in Table 1.

Anisometropia

Anisometropia was considered as a continuous variable and was calculated as the absolute interocular difference in M, the spherical equivalent of each eye. The mean degree of anisometropia was

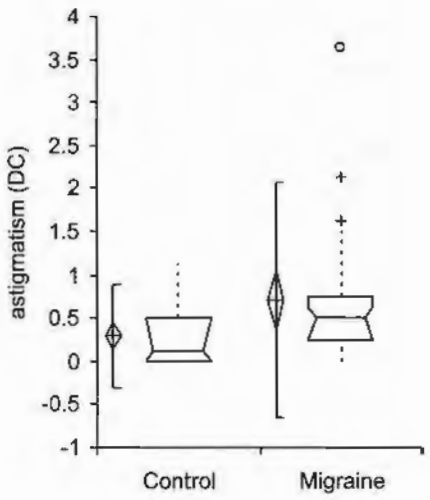

FIGURE 1.

A box plot showing the distribution of mean subjective astigmatic power C (y axis) for people with migraine and control subjects (x axis). The diamond and line shows parametric statistics. The center of the diamond shows the mean and the height of the diamond shows the 95% confidence interval. The notched box and whiskers show nonparametric statistics. The center line of the box is the median, the notch is the confidence interval of the median, whereas the overall size of the box is the interquartile range (IQR). The dotted line connects the nearest observations within 1.5 IQRs of the lower and upper quartiles. "+" markers indicate near outliers between 1.5 and 3.0 IQRs away, whereas "o" markers indicate outliers over 3.0 IQR away.

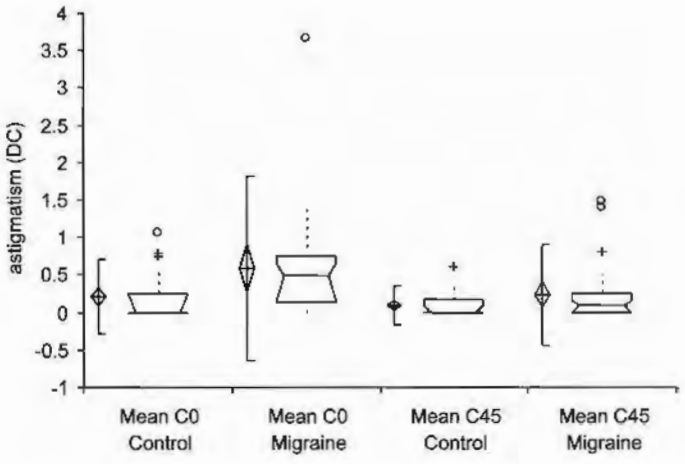

FIGURE 2.

A box plot showing the distribution of mean objective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and controls (x axis). For figure description, see Figure 1.

0.515 DS (0.297–0.733) for the migraine group and 0.295 DS (0.145–0.445 DS) for the control group. This difference approached significance (Mann-Whitney U test, p = 0.06). The intereye difference in u (a representation of total anisometropia) was 0.623 (0.356–0.890) in the migraine group and 0.332 (0.182–0.482) and this difference was not significant (Mann-Whitney U test, p = 0.09).

Uncorrected Ametropia

The spherical equivalents of the lensometry results of the participants' own spectacles M_s were calculated and then averaged for

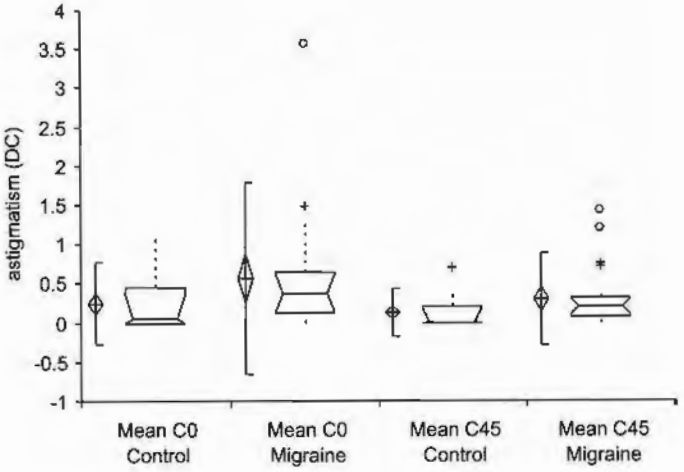

FIGURE 3.

A box plot showing the distribution of mean subjective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and control subjects (x axis). For figure description, see Figure 1.

the lenses of the two eyes. The absolute difference between this mean spectacle spherical equivalent M_s and the mean subjective refraction spherical equivalent M_r was calculated to give a value of uncorrected ametropia. The mean uncorrected ametropia in the migraine group was 0.339 D (0.214–0.463 D) and was 0.221 D (0.118–0.325 D) in the control group, and these results were not significantly different (Mann-Whitney U test, $p = 0.13$).

The u value lensometry results of the participants' own spectacles u_s was calculated and then averaged for the lenses of the two eyes. The difference between this mean u_s and the mean subjective refraction spherical equivalent u_r was calculated to give a value of uncorrected scalar u. The mean uncorrected u in the migraine group was 0.715 (0.123–1.306) and was 0.558 (−0.073–1.190) in the control group, and the difference between the two groups was not significant (Mann-Whitney U test, $p = 0.09$). To assess whether these results were influenced by the astigmatic component, we assessed the uncorrected decompensated astigmatic component, i.e., the absolute difference between the mean C_{0s}, C_{45s} of the participant's own spectacles and the C_{0r}, C_{45r} of the participants' subjective refraction was calculated. The mean uncorrected C_0 in the migraine group was 0.279 DC (0.144–0.413 DC) and was 0.126 DC (0.044–0.209 DC) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U test, $p = 0.02$). The mean uncorrected C_{45} in the migraine group was 0.116 DC (0.068–0.165 DC) and was 0.075 DC (0.025–0.125 DC) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U test, $p = 0.04$).

Correlations

The Spearman correlations between severity of worst headache ($r_s < 0.33$, $p > 0.11$), duration of worst headache ($r_s < 0.17$, $p > 0.42$) and the days since the last migraine headache ($r_s < 0.32$, $p > 0.18$) and each of the refractive variables of mean sphere, mean astigmatic power, anisometropia, and uncorrected error were all low and not significant. The number of headaches in the last 12 months did show a statistically significant correlation with anisometropia such that the fewer the headaches, the more the anisometropia ($r_s = -0.42$, $p = 0.04$). The number of headaches in the last 12 months was not significantly correlated with each refractive variable ($r_s < 0.27$, $p > 0.21$).

DISCUSSION

It is not uncommon for optometrists to encounter patients who believe that migraine has a visual trigger or that the headache might be ameliorated by an optometric intervention. However, the lack of evidence-based research led Gordon et al.[14] to conclude that the whole issue of headache and refractive error has been dominated "by clinical anecdote throughout the 20th century." They asked that future research in this area addressed (1) the scale of the problem; (2) whether people with migraine are optometrically unusual; (3) if they are optometrically unusual, what is the mechanism generating the headache; and (4) whether correction ameliorates the headache. Because the level of evidence in the literature for any association between migraine and refractive error is, by modern standards, weak, it is not surprising that the IHS classification system[21] classifies headache attributed to refractive errors quite separately from those of migraine.

Although only large epidemiologic studies can hope to address the scale of the problem, it is known that migraine is a very common condition with more than 2.5 million persons in North America having at least one day of migraine per week.[35] Our sample of people with migraine had a higher mean level of astigmatism than our control group. If only a small number of these people need refractive corrections then, in view of the prevalence of migraine, the number of these people who might benefit from optometric intervention is substantial.

The range of low degrees of refractive errors in both our groups was fairly typical of the age group in a U.K. population.[24] Our masked case–controlled study provides some evidence that astigmatic refractive error and possibly anisometropia are greater in people with migraine than control subjects, as suggested in the historical texts. For astigmatism, the difference was driven in part by a few people with migraine who were particularly optometrically unusual but still held for the group as a whole (when the outliers were removed) for C and C_0 components. Objective, subjective, and uncorrected astigmatic refractive components were all significant findings.

The differences between the two groups were not large and, as a result of the large number of statistical comparisons made, it is possible that some of the statistically significant findings resulted by chance. In any event, it seems unlikely that the degree of uncorrected astigmatism that we found is a direct cause of migraine, but a subtler path may exist. One hypothesis might be that astigmatic errors of refraction cause changes to visual perception that alter the hyperexcitability in the visual cortex of the brain of some migraine sufferers[36–38] perhaps because astigmatic blur may exacerbate the perception of striped patterns thought to be important in the visual triggers of migraine.[36,37] An alternative hypothesis could be that neurotic personality traits that are associated with migraine[39–41] result in a greater likelihood of people with migraine demanding small cylindrical corrections during a subjective refraction, particularly because more of the control subjects than the migraineurs had zero astigmatism. However, greater astigmatic

TABLE 1.
The astigmatic refractive components of total mean astigmatism (C) and the decompensated astigmatic components (C_0, C_{45}) for the migraine and the control group were compared for both subjective and objective refractive data[a]

	Subjective Refractive Results (DC)			Objective Refractive Results (DC)		
	Migraine	Control	p Value	Migraine	Control	p Value
C	0.705 (0.363–1.047)	0.295 (0.143–0.447)	0.03 [0.04]	0.710 (0.359–1.061)	0.245 (0.106–0.384)	0.01 [0.01]
C_0	0.565 (0.257–0.874)	0.247 (0.115–0.380)	0.03 [0.05]	0.588 (0.279–0.898)	0.205 (0.082–0.329)	0.01 [0.01]
C_{45}	0.295 (0.145–0.445)	0.131 (0.055–0.208)	0.05 [0.11]	0.235 (0.065–0.404)	0.088 (0.023–0.153)	0.05 [0.12]

[a]The mean results are shown with the 95% confidence limits in parentheses. Mann-Whitney U tests were performed to compare these results and the statistical significance of the differences found between the groups is shown as the p value in the table. Finally, outliers were removed from the data and the Mann-Whitney U tests comparisons repeated; these are shown in small font and in square brackets in the p value column.

power was found in the migraine group for both objective (retinoscopy) and subjective testing and so this would seem unlikely.

The higher levels of astigmatism in the migraine group reached statistical significance and an inspection of Figure 1 indicates that there were more cases in the migraine group than the control group in which the degree of astigmatism was of a level that would be considered by many practitioners to be clinically significant.[42] Uncorrected astigmatic refractive errors were significantly greater in people with migraine than control subjects. A theoretical causative effect is weakened by a lack of significant correlations between the headache characteristics and refractive error, although it is possible that refractive error could have an association with migraine headaches while having no impact on the severity or frequency of headaches. Whether correcting refractive errors does, or does not, have an impact on migraine severity or frequency is a matter for future research, but this study does suggest that people with migraine headaches should attend their optometrist regularly to ensure that their refractive errors are appropriately corrected.

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Review Article

The optometric correlates of migraine

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Abstract

Migraine is a common, chronic, multi-factorial, neuro-vascular disorder typically characterised by recurrent attacks of unilateral, pulsating headache and autonomic nervous system dysfunction. Migraine may additionally be associated with aura; those focal neurological symptoms that may precede or sometimes accompany the headache. This review describes the optometric aspects of migraine headache. There have been claims of a relationship between migraine headaches and errors of refraction, binocular vision anomalies, pupil anomalies, visual field changes and pattern glare. The quality of the evidence for a relationship between errors of refraction and binocular vision and migraine is poor. The quality of the evidence to suggest a relationship between migraine headache and pupil anomalies, visual field defects and pattern glare is stronger. In particular the link between migraine headache and pattern glare is striking. The therapeutic use of precision-tinted spectacles to reduce pattern glare (visual stress) and to help some migraine sufferers is described.

Keywords: migraine, orthoptics, pattern glare, pupils, refraction, tinted lenses, visual fields

Brief historical overview of explanations of migraine

From 3000 BC, vision has been linked to migraine headache (Alvarez, 1945; Pearce, 1986). Hippocrates himself alluded to the visual prodrome of migraine (Allory, 1859). Migraine has been described in other ancient writings, too numerous to review here. Particularly relevant to the present review, Celsus (AD 30, cited by Thomas, 1887) listed sunlight among the triggers of migraine. The severity of migraine, and its association with photophobia, was highlighted by Araetaeus (AD 81, translated by Adams, 1856):

> For they flee the light; the darkness soothes the disease; nor can they bear readily to look upon or hear anything pleasant… The patients are weary of life and wish to die.

Gowers (1886) referred to the two main theories of migraine, vascular and neural; an observation which is equally valid today. The 1920s saw allergic theories come and go, as did the psychosomatic theories of the 1950s (Pearce, 1986). Nowadays migraine headache can be considered to be a reaction or biological adaption determined by a primary disorder of brain threshold in combination with a variety of external precipitating factors. Together, these lower this threshold to a point when a migraine attack will occur.

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Pathophysiology of migraine

Goadsby *et al*. (2002) have reviewed migraine pathophysiology from a medical perspective, but in a broad sense, migraine can be thought of as a tendency to have headache that is characterised by certain associated symptoms. The basis of this predisposition has been attributed to a lack of stability in the control of pain, the control of sensory information coming from the pain producing intracranial structures and sensitivity to cyclic changes in the central nervous system (Lance and Goadsby, 1998).

The migraine brain has a reduced threshold to a variety of stimuli, and this has been described as cortical hyperexcitability. The factors that set this threshold are genetic (Ophoff *et al*., 1996; Ducros *et al*., 2001), and involve magnesium deficiency, excitory amino acids, sensitivity of the dopamine system and the hypothalamus, reduced habituation to visual and auditory stimuli, and vascular reactivity. Because of this reduced

threshold, migraines can be initiated by 'triggers'. Such triggers can be divided into internal and external. One example of an internal trigger might be hormonal factors, whilst external triggers could be flickering lights, certain patterns or strong smells. External triggers have the potential to cause, and therefore to prevent, migraine and will be outlined in more detail later.

Once triggered, a migraine has two main consequences: spreading depression (which may or not be perceived as aura) and pain. Leão (1944) described 'spreading depression' as a progressive shutdown of cortical function and suggested that it may be related to the fortification spectra of migraine. Waves of cortical inhibition, sometimes preceded by transient excitation, move slowly over the cortex (2–3 mm min^{-1}), suppressing normal activity, and take 5–60 min before recovery takes place.

Spreading depression is associated with vascular changes (Lauritzen *et al*., 1982; Piper *et al*., 1991; Goadsby, 1992). One such vascular change that has been suggested in patients with migraine with aura is a 'spreading oligaemia' (Olesen *et al*., 1981; Dreier *et al*., 2001). Dreier *et al*. (2002) have suggested that the link between the vascular oligaemia and the neurological spreading depression may be that endothelial irritation triggers cortical spreading depression. Hadjikhani *et al*. (2001) showed vasoconstriction and then vasodilation followed the cortical spreading depression using an imaging study. The oligaemic waves of reduced blood flow progress over the cortex at the same rate of 2–3 mm min^{-1} as cortical spreading depression. They start in the visual cortex and advance forward without respecting arteriolar territories. These vascular changes can last several hours and are followed by delayed hyperaemia (Andersen *et al*., 1988). As the spreading oligaemia reaches sensory motor areas of the brain, the patient experiences the focal neurological aura symptoms. The neurological changes during aura parallel what is seen if the brain is directly stimulated (Penfield and Perot, 1963; Brindley and Lewin, 1968) and are also remarkably similar to the changes that would be predicted if ocular dominance columns (Hubel and Weisel, 1968) in the cortex were serially activated.

Woods *et al*. (1994) demonstrated a spreading oligaemia directly with a positron emission tomography study. Interestingly, the patient in this study did not perceive aura in any traditional sense, suggesting that the oligaemia can traverse the whole cortex without the patient experiencing symptoms. Indeed, Lance and Anthony (1966) claimed that only 10% of migraine patients perceive the fortification spectra but 25% of patients perceive less specific symptoms of 'spots before the eyes' or 'shimmering vision' covering the entire visual field.

Other neuro-vascular interactions can occur with migraine. Kruit *et al*. (2004) found that some patients with migraine were at risk of subclinical lesions in certain brain areas and suggested that the cerebellar region of the posterior circulation territory was an area where migraine sufferers had a greater number of infarcts than controls. Lipton and Pan (2004) considered that this might be evidence that migraine is a progressive brain disease as this area had been previously implicated in persons with stroke and migraine (De Benedittis *et al*., 1995; Hoekstra-van Dalen *et al*., 1996).

There is some pathophysiological evidence linking the aura phase of migraine and the pain phase of migraine. Moskowitz (1984) considered that the spreading depression of the cortex might depolarise trigeminal nerve fibres and initiate pain. However, if this hypothesis were true then the headache would always develop on the side of the head responsible for the aura symptoms (e.g. a left sided headache would arise from a right field aura). Olesen *et al*. (1990) showed that in 38 patients with migraine with aura, three experienced headache on the 'wrong' side and Jensen *et al*. (1986) showed that aura symptoms were ipsilateral to the headache in 19 patients and contralateral in 18 patients. Thus, there must be some 'central link' which can trigger pain on either side of the head for one-sided aura symptoms. Bolay *et al*. (2002) have suggested that cortical spreading depression activates trigeminal vascular afferents to evoke meningeal and brainstem events that potentially lead to the development of headache.

An alternative explanation to the link between pain and aura was provided by May *et al*. (2001) who examined neural influences on the cranial circulation by studying healthy volunteers' responses to injection of the pain-producing compound 'capsaicin' using magnetic resonance angiographic techniques. They concluded that their data was consistent with the notion that pain drives changes in vessel calibre in migraine, not vice versa.

Migraine classification

Headache is an extremely common symptom presenting to primary health care professionals, and an accurate diagnosis is essential to ensure both the correct management of benign conditions and to ensure that when headache presents as a symptom of serious disease then it is dealt with appropriately. The International Headache Society (IHS) published the second edition of The International Classification of Headache Disorders recently (Headache Classification Sub-Committee of the International Headache Society, 2004). The IHS classification is lengthy and is briefly summarised in *Table 1*. The first edition has been summarised, from a clinical optometric viewpoint, by Patel *et al*. (2003).

Migraine is described in section 1 of the IHS classification. Section 11 of the classification describes

Table 1. A summary of the classification of migraine

Migraine without aura
Migraine with aura
Typical aura with migraine headache
Typical aura with non-migraine headache
Typical aura without headache
Family hemiplegic migraine
Sporadic hemiplegic migraine
Basilar-type migraine
Retinal migraine
Childhood periodic syndromes that are commonly precursors of migraine
Benign paroxysmal vertigo of childhood
Abdominal migraine
Cyclical vomiting
Complications of migraine
Chronic migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine-triggered seizure
Probable migraine
Probable migraine without aura
Probable migraine with aura
Probable chronic migraine

headache or facial pain associated with disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures. The 'eyes' section is further subdivided into acute glaucoma, refractive errors, heterophoria or heterotropia and ocular inflammatory disorder. Section 13 of the classification describes cranial neuralgias and central causes of facial pain: ophthalmoplegic migraine, optic neuritis and ocular diabetic neuropathy are included in this section. Since the present review is concerned only with migraine, these other types of eye headache will not be discussed. However, it should be noted that, to an optometrist, these sections of the IHS classification would appear weak.

Notwithstanding these comments, it must be recognised that the IHS classification is a useful framework for classifying headaches (Leone *et al*., 1994). However, others have suggested that the classification is more useful for research than for clinical practice (Cady and Dodick, 2002).

The visual disturbances of migraine

Visual aura

The cornerstone to visual aura in migraine are fortification spectra or 'teichopsia', although this may present in only 10% of migraine patients (Lance and Anthony, 1966). Originally described by Airy (1870), the term 'teichopsia' was coined from the Greek terms 'teckhos' meaning fortification and 'opsis' meaning seeing, alluding to the zig-zag design of early Italian military fortifications with which Airy was familiar. The symptoms of scintillating scotoma and a marching fortification figure that gradually expands and then breaks up is characteristic of migraine with aura. Wilkinson (2004) has reviewed migraine visual aura in the context of other visual hallucinations and suggested how these might relate to the neural mechanism of aura.

Queiroz *et al*. (1997) showed that visual aura accompanied the patient's first headache in 39% of patients but only 19% had visual aura with every attack. The free period between visual aura and head pain was <30 min in 75% of cases. The symptoms were described as 'small bright dots' (42%), 'flashes of light' (39%), 'blind spots' (32%) and 'foggy vision' (27%). Fortification spectra were reported by only 20%.

Usually migraine aura are binocular but rarely migraine can affect the anterior visual pathway and produce monocular symptoms. These retinal migraines produce monocular scotomas, and are caused if any of the circulation of the anterior visual pathway becomes involved in the angio-spastic disturbances of migraine. Often the visual loss is described as a black-out or grey-out which can last from seconds to hours, the vast majority lasting <30 min (Hupp *et al*., 1989).

Migraine aura can occur without headache. The Framingham Study (Wijman *et al*., 1998) demonstrated that these migrainous visual accompaniments occur in just over 1% of the population aged between 30 and 62 years. This study showed that the mean age of onset of these symptoms was 56 years and in 58% of subjects no headache was reported. Indeed, 42% had no headache history at all.

A variety of ophthalmic conditions may produce visual-aura-like symptoms and need to be differentially diagnosed. *Table 2* contrasts the signs and symptoms of these conditions.

Photophobia and glare

Most migraine sufferers avoid bright light during headache (Selby and Lance, 1960) and many migraine sufferers feel the need to use sunglasses even in between attacks (Drummond, 1986). Wolff (1963) argued that true photophobia is pain induced and exacerbated by bright light, for example in corneal disease or anterior uveitis, and is derived from stimulation of the trigeminal nerve. He argued that glare or dazzle, on the other hand, is uncomfortable but not painful. Glare can be caused by stray light scattering into the eye from ocular structures (such as cataract) or environmental factors (such as a poorly placed lamp). Glare might also be caused by a general excitability of the senses in migraine sufferers, and they have been shown to be more susceptible to glare than controls (Drummond, 1986).

Table 2. A variety of ophthalmic conditions may produce visual-aura-like symptoms and need to be differentially diagnosed. The characteristic signs and symptoms of these conditions are shown

Diagnosis	Monocular or binocular disturbances	Onset of symptoms	Usual duration of symptoms	Scotoma	Photopsiae	Build up of scotoma	Migration of scotoma
Migraine with aura	Binocular	Gradual	15–30 min	Yes	Yes	Yes	Yes
Retinal migraine	Monocular	Gradual	15–30 min	Yes	No	No	No
Amaurosis fugax	Monocular	Sudden	Minutes	Yes	No	No	No
Occipital transient ischaemic attack	Binocular	Sudden	Minutes	Yes	Yes	No	No
Posterior vitreous detachment	Monocular	Sudden	1 month	No	Yes	No	No
Retinal break or detachment	Monocular	Sudden	1 month to continuous	Yes	Yes	Yes	No

Stimulation of the trigeminal nerve during a migraine attack probably accounts for photophobia. Drummond and Woodhouse (1993) stimulated the trigeminal nerve with ice on the forehead and measured discomfort thresholds for migraine sufferers and controls. They showed that trigeminal discharge contributes to photophobia in migraine sufferers and that this trigeminal discharge continued during headache-free periods. However, Drummond (1997) has shown that it is glare, rather than true photophobia, that probably accounts for the light sensitivity experienced by migraine sufferers between attacks. This heightened sensitivity to light is consistent with the heightened sensitivity found to other visual stimuli in migraine sufferers, such as pattern glare, which is discussed later.

Visual migraine triggers

Migraine triggers are the internal or external factors that excite the migraine brain above its genetically reduced threshold and in so doing, precipitate the chain of neurovascular events that produce a migraine headache. It has been suggested that common triggers include certain foods, stress, smells, hormonal changes, irregular meals, changes in sleep pattern and environmental factors such as excessive heat, light or noise (Peatfield and Olesen, 1993). It should be noted that some authors suggest that migraines occur spontaneously and that the triggers that patients associate with their migraine headache are actually due to the fact that in the 'prodrome' phase of a migraine attack some migraine sufferers have a craving for certain foods or drinks (Dowson and Cady, 2002). These then may be blamed for the attack when in fact they are a consequence. Nevertheless, it is generally considered that by making lifestyle changes, the frequency and severity of migraine headache can be reduced.

Migraine patients are sensitive to light during and between headaches (Drummond, 1986). It has also been stated that migraine, as compared with other headaches, is worse during midnight-sun summer than during the polar night (Salvesen and Bekkelund, 2000). These visual stimuli do not have to be strong. Jacome (1998) described a patient who, on multiple occasions, could trigger his typical headache within 30 min just by rubbing his eyes gently and inducing bilateral photopsias. Liveing (1873) described falling snow as a migraine trigger. Debney (1984) produced a thorough review of the literature relating to visual stimuli as migraine trigger factors. She showed that visual stimuli were quoted by at least 10 other authors and ranked visual triggers as similarly important to other more obvious triggers such as stress and hormonal factors.

Debney (1984) reviewed the medical notes of 344 migraine patients and showed that 62% had 'glare' as a precipitating factor, 53% had 'flicker' as a precipitating factor and 1% had 'colour' as a precipitating factor. Debney analysed these findings further and sought to correlate other precipitating factors to those patients who claimed their migraines were induced by visual stimuli. She found significance only with two factors: 1, 'other sensory and environmental factors'; 2, 'dietary factors'. Debney (1984) suggested:

> …that it would be interesting if the aberrant biochemistry underlying dietary triggers of migraine also affected the sensitivity of the sufferer to visual triggers and to other sensory and environmental triggers.

Debney (1984) then analysed her data further and split them into two groups, one detailing visual tasks quoted to have induced migraine because of glare, and one detailing visual tasks quoted to have induced migraine because they involve flicker. In the glare group, she found that the following situations had all been implicated in precipitating migraine: sun reflections; rippling water or sea; at the beach; snow; paper; chrome trim on a car; microscopy; facing bright windows; fluorescent lighting. In the flicker group, she found that the following situations had all been implicated in precipitating migraine: television; cinema; faulty fluorescent lighting; lighting in vehicular tunnels;

flashlights; headlights; stroboscope; travelling past railings, telegraph poles and fences (by train).

Debney (1984) listed many visual stimuli reported to induce migraine. This list was lengthy but can be summarised by splitting visual triggers into four simple groups; glare, flicker, patterns and colours. Glare could be explained by the trigeminal nerve sensitivity demonstrated by migraine sufferers (Drummond, 1986) or, with flicker, patterns and colour, by cortical hypersensitivity theories (Wilkins, 1995). Both these aspects will be discussed later.

Traditional clinical advice is to avoid trigger factors. Interestingly however, Martin (2000) showed that in patients with visually triggered headaches, there is a desensitisation period such that the visual triggers become less likely to produce headache symptoms with continued exposure. This finding could conceivably alter the way headaches are managed, with exposure to triggers to produce desensitisation as a possible approach, rather than avoidance.

In conclusion, visual stimuli are common and potent migraine triggers. This is emphasised by the fact that some experimenters have used an alternating red and green checkerboard as a strong visual stimulus to cause migraine headache for experimental purposes (Cao *et al*., 1999).

Refractive errors and migraine

In the early 1900s, uncontrolled studies by Gould (1904) and Snell (1904) argued that low refractive errors, particularly astigmatism, are associated with migraine.

Turville (1934) claimed that uncorrected errors of refraction were a major cause, or at least an important precipitating factor, in cases of migraine. He also claimed that the conventional methods of the time used to provide correction for refractive errors were inadequate. In his opinion, the investigation of refractive errors must include both manifest and latent errors. He defined a latent error not just as latent hyperopia but also as heterophorias, accommodative anomalies 'and in fact any departure from normal visual activity, physiologically, optically, functionally, mentally and psychologically.'

Turville stated that even an inequality of refractive error of 0.25 dioptres was important in many cases and noted that the difference was rarely more than 0.75 dioptres. Turville's study lacked a control group and lacked any form of statistical analysis. It is unclear whether it was the correction of refractive errors, the correction of any decompensated phorias, or placebo effects that were relieving symptoms.

Wilmut (1956), although mostly concerned with the effect of binocular vision on migraine (described below), considered the refractive errors of 116 cases of migraine and compared them to a non-migraine group. He found a similar prevalence of refractive errors in migraine and a non-migraine control group.

Several other authors have argued that headaches or migraine are associated with uncorrected refractive errors, but these studies will not be described in detail because there were no control groups or statistical analyses (Gordon, 1966; Lanche, 1966; Vaithilingham and Khare, 1967; Cameron, 1976; Hedges, 1979; Worthen, 1980).

Waters (1970) identified by a questionnaire, in a random sample of a general population, groups of individuals with; headache, unilateral headache, migraine, and a fourth group who had not had a headache for a year. A masked assessment of the visual acuity and ocular-motor balance was then performed on each group. Visual acuity was measured unaided and aided if spectacles were worn. Waters found that there was no significant difference between the unaided vision, or visual acuity with spectacles if normally used, of either men or women in the four groups. In addition, he found no significant difference between groups in the number of individuals wearing spectacles for either distance or near vision. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. However, Waters did not assess refractive error at all and so doubt must be raised over his conclusions.

Vincent *et al.* (1989) determined the prevalence of visual symptoms and eyestrain factors in a group of chronic headache sufferers as compared with age- and sex-matched controls and found near visual tasks to be one of the many visual triggers to chronic headache. However, this questionnaire survey did not take account of whether the near visual tasks were carried out with corrected or uncorrected refractive errors. Nevertheless, it has been suggested (Gordon *et al*., 2001) that Vincent's data could suggest a relationship between headache, refractive error, accommodation and convergence.

Gordon *et al.* (2001) reviewed the experimental and clinical evidence on possible links between refractive errors and headaches and listed several issues that were still to be resolved. This review did not relate specifically to migraine, so will not be described in detail. Evans *et al.* (2002), in a study described in the next section, found no significant difference between a group of migraine and a group of control patients in the subjective refractive error or in the proportion of participants who wore spectacles.

To conclude, the association between uncorrected refractive errors and migraine seems to be equivocal. Early studies reported much anecdotal evidence but the few modern studies, which included masked control groups and statistical analyses, have found little

evidence. Often researchers have failed to classify headaches correctly and so data relating specifically to migraine is rare. In addition, little or no evidence appears to relate to any possible pathogenic link between refractive errors and migraine.

Binocular vision (orthoptic anomalies) and migraine

Snell (1904) argued that heterophoria is a cause of headache, especially esophoria when found in conjunction with myopia. Turville (1934) suggested that low convergent and divergent fusional reserves are correlates of migraine and that base in prisms are an effective treatment for many cases of severe classical migraine. Turville describes his first successful case of relief of migraine with base in prisms and it is interesting to note that this patient was esophoric rather than exophoric as might have been expected. The prism power was determined in an unconventional way: as one-third of the recovery point from the measurement of the *divergent* fusional reserves. He described a migraine sample of 123 cases, but there was no control group or placebo treatment. As recently as 2000, the use of base in prism to relieve migraine headache was still advocated (Bush, 2000).

Wilmut (1956), using a polarised version of the Turville Infinity Balance, found that 91% of patients with migraine had 'excessive exophoria' and had previous argued that 56% of his cases were cured with base in prism (Wilmut, 1951). Wilmut's (1956) study was of a clinical sample and may have suffered from referral bias, and does not appear to have been a randomised control trial. However the results were compared with an unspecified control group in which exophoria occurred in only 25%.

Waters' (1970) questionnaire regarding headache and migraine sufferers, discussed in the previous section, not only looked at visual acuity but also ocular-motor balance. The ocular-motor balance was assessed by the cover test and a Maddox hand frame with habitual spectacle correction, if worn. Thus, the total dissociated strabismus or phoria was assessed. Waters stated that there was no evidence that the proportion of subjects with esophoria or exophoria for either distance or near vision differed in the four groups in either sex. Unfortunately, the data for esophoria and exophoria were combined and so data on this aspect are not meaningful. The only statistically significant finding Waters made was that the migraine group had a higher proportion of individuals who had hyperphoria at near. Waters stressed however that this result was only meaningful when the male and female groups were analysed together and over 20 chi-squared tests had been completed. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. He also noted that the beneficial effect of any treatment, if applied in an uncontrolled manner, could not be considered as evidence relevant to the aetiology of headache.

Friedman (1977) claimed that 'fusional stress' could accompany 'dynamic binocular seeing' and that this could be a cause of migraine. He advocated a specific instrument for intensive visual training. Friedman presented no data to back up his claims, only case study reports.

Worthen (1980) studied the effects of stimulating extraocular muscles in patients on whom operations for strabismus were performed under local anaesthesia. The muscles were exposed under light anaesthesia and then stimulated in various ways. Pinching, pricking or cutting the recti muscles caused no sensations, but traction produced prompt exclamations of pain. The pain was always described as an aching sensation localised deep in the eye/orbit on the side of the stimulated muscle. Worthen went on to describe two case studies where the reproduction of extraocular muscle imbalances produced consistent results of headache and aesthenopic symptoms. Electromyographic recording of these patients suggested that the symptoms arose from increased tension in the muscles of the head and neck. Nevertheless, Worthen claimed that the headaches caused by muscle imbalance (heterophoria) could be eliminated by proper alignment of the visual axes and stated that prisms, orthoptic training, or even surgery may be necessary. He suggested that occlusion could be used to diagnose headaches associated with binocular anomalies. Although Worthen (1980) used an interesting approach, his small number of subjects limits the strength of his conclusions.

Sucher (1994) related the symptoms of headache to the 'monocular blur effect': a consistent blur of one eye when viewing the 6/18 letters on a letter chart during the Turville infinity balance test, whilst the patient raises and lowers their chin. Sucher found a statistical relationship between this monocular blur effect and patients who have three or more headaches a month. He also found that the monocular blur occurred on the same side as lateralized headaches in 94%, and then in 93%, of two cohorts of patients tested. Sucher speculated that the monocular blur effect could be corrected by prisms, and that this correction would then relieve tension on the ocular motor system and so remove a source of headache. However, Sucher's study did not look at the effect of treatment.

Evans *et al.* (2002) compared 21 migraine sufferers to 11 controls and found no difference between the groups in relation to strabismus or hyperphoria. The main purpose of this study was to investigate the effect of coloured filters (Wilkins *et al.*, 2002), so the migraine sufferers were selected as those who found a coloured

filter to be helpful. They therefore did not represent a 'normal' group of migraine sufferers. Evans *et al.* (2002) did find using one test method, that the migraine group tended to have a marginally decompensated exophoria at near; however, other test methods suggested that the migraine group were as able to compensate for their exophoria as the control group.

Decompensated heterophoria, the diagnosis of which is discussed by Evans (2002), has been linked to headaches by many authors (e.g. Jenkins *et al.*, 1989; Yekta *et al.*, 1989; Evans, 2002). However, these authors do not specifically discuss migraine.

The association between anomalies of binocular vision and migraine seems to be equivocal. Early studies have suggested anecdotal evidence but the few modern studies, which have been more statistically and methodologically robust, have either found little evidence, or have generally related to headache or aesthenopic symptoms, rather than specifically to migraine.

Visual fields and migraine

The visual system beyond the eye can be investigated in a number of ways. Psychophysical testing of visual processing can shed light on perceptual issues in migraine as discussed by Coleston *et al.* (1994), McKendrick *et al.* (1998) and others. These studies do not involve clinical optometric approaches and will not be discussed in detail here, but are reviewed by Chronicle and Mulleners (1996). Electrophysiology can directly measure cortical activation but is also not an optometric procedure and is extensively reviewed elsewhere (Aurora *et al.*, 1998; Áfra *et al.*, 1998, 2000; Cao *et al.*, 1999).

Several studies have assessed visual fields in migraine. McKendrick *et al.* (1998) showed deficits to tasks involving 16 Hz flicker using a Medmont 6000 perimeter auto flicker paradigm in a single migraine sufferer. Later, McKendrick *et al.* (2000) performed similar temporally modulated perimetry in 16 migraine sufferers and 16 controls and suggested that migraine sufferers have selective visual dysfunction for temporally modulated targets of a temporal frequency >9 Hz.

Other visual field anomalies have been found in migraine patients. McKendrick *et al.* (2002) performed short-wavelength automated perimetry (SWAP) and standard automated perimetry (SAP) using a Humphrey Visual Field Analyser. Although they did not find a significant difference in mean deviation and pattern standard deviation between migraine sufferers and controls using SAP, both these parameters were significantly worse in the migraine group using SWAP. The authors suggested that migraineurs should not be included in visual field normative databases.

Klein *et al.* (1993) reported results from the Beaver Dam Eye Study that showed no relationship between open-angle glaucoma and migraine headache. They used diagnostic criteria based on visual fields, intraocular pressure, cup/disc ratio and history. Usui *et al.* (1991) found no greater prevalence of migraine in a glaucoma population compared with a normal population and Pradalier *et al.* (1998) commented that migraine prevalence was not significantly different between normal and high tension glaucoma sufferers.

Alternatively, other authors have found that there is a relationship between normal tension glaucoma and migraine headache (Cursiefen *et al.*, 2000). In particular, migraine has been considered a risk factor for glaucomatous visual field progression (Drance *et al.*, 2001). Comoglu *et al.* (2003) found glaucomatous-like visual field defects in patients with migraine in the absence of raised intraocular pressures and suggested that there might be a relationship between the pathophysiology of normal tension glaucoma and migraine. McKendrick agreed with this viewpoint (McKendrick *et al.*, 2000, 2002) and concluded that the similarity of SWAP defects and temporally modulated perimetry defects in migraine sufferers and glaucoma sufferers might raise the possibility of a common pre-cortical vascular involvement in these two conditions.

We would suggest an alternative explanation that migraine headache might cause a magnocellular-specific dysfunction unrelated to glaucoma. Such an interpretation would account for the fact that some studies have suggested a link to normal tension glaucoma, as intraocular pressures would remain unaffected. We are currently comparing visual fields, ocular tensions, and optic nerve head analysis in migraine and control groups to investigate this hypothesis.

Interestingly, McKendrick and Badcock (2003) have shown that migraine sufferers with visual field loss to temporally modulated targets but not to SAP exhibit dysfunction of both the parvo-cellular and magnocellular pathways. How this might relate to the mechanism of visual field dysfunction in migraine is yet to be investigated. Coleston *et al.* (1994) also found evidence suggesting both magno- and parvo-cellular deficits in migraine. These authors suggested that the deficit was pre-cortical, and they noted that this could reflect either intrinsic abnormalities or a consequence of attacks. As considerably more nerve fibres run from the cortex back to the lateral geniculate nucleus than the ascending geniculostriate pathway, they hypothesised that recurrent migraine episodes might cause cortical damage which in turn causes pre-cortical deficits. Chronicle and Mulleners (1994) suggested that cerebral ischaemia occurs in migraine and that this results in long-term damage to GABA-ergic cells in the visual cortex, which are especially sensitive to hypoxia.

Pupil anomalies and migraine

Lance (1993) has suggested that migraine could be viewed as a derangement of autonomic monoaminergic function. If so, then pupil dysfunction should be a feature of the migraine headache. However, the issue is confused by Rubin *et al.* (1985) who found that any difference in pupil responses between migraine sufferers and controls can be attributed, at least in part, to differences in personality. They claim that the migraine personality is more neurotic and depressive, and so responds emotionally in a different way to non-migraine controls. This, they claim, can affect the pupil responses as emotional factors are related to the autonomic nervous system.

Whilst the pupil abnormalities associated with migraine headache are often subclinical, there is some good evidence that such pupil anomalies can be unmasked by experimental procedures. Often this has involved the use of pharmacological agents to elicit different responses in migraine and non-migraine sufferers and this research is reviewed below.

Sympathetic hypofunction

Fanciullacci *et al.* (1977) have shown greater pupil dilation from instillation of phenylephrine and a reduced pupil dilation from the instillation of fenfluramine in idiopathic headache, as compared with controls. They concluded that this showed a supersensitivity of iris adrenergic receptors in idiopathic headache. Herman (1983) has shown that anisocoria exists in both migraine and cluster headache sufferers but by only a mean of 0.8 mm. Gotoh *et al.* (1984) found sympathetic hypofunction in migraine sufferers during headache-free periods with a variety of neurological tests. Rubin *et al.* (1985) have shown that 70% of migraine sufferers in the inter-ictal phase have deficient sympathetic innervation of the dilator pupillae as compared with controls if challenged by a cold compress. Drummond (1987) compared the pupil diameter of the headache side and non-headache side in migraine sufferers, tension headache sufferers and non-headache controls. He showed that pupil diameter was smaller on the side of the headache both during headache and during headache-free periods in patients who habitually had headache on the same side of the head. Drummond (1990) has shown that facial temperature and pupil responses show a sympathetic deficit in migraine sufferers. The facial temperature was asymmetric and associated with the side of headache during a headache attack but not between attacks. In contrast, pupil diameter was smaller on the usual side of headache both during the headache and during the headache-free interval.

De Marinis (1994) stated that the evidence was so strong that pharmacological tests of the pupils could be used to differentially diagnose different forms of idiopathic headache. De Marinis *et al.* (1998) used pharmacological pupillary tests to investigate the oculosympathetic system in patients diagnosed as having migraine without aura. In contrast to the findings of Drummond (1987, 1990), De Marinis *et al.* claimed that the oculosympathetic hypofunction was not related to headache side and was temporally related to the migraine attack, being absent after 15 days. Battistella *et al.* (1989) showed that this sympathetic hypofunction existed in children with migraine but to a lesser extent which suggests a progression of the sympathetic hypofunction from childhood into adulthood.

Parasympathetic deficits

Purvin (1995) described a case of a 46-year-old woman who had suffered migraine headaches for the previous 20 years. Following one attack, she developed Adie's tonic pupil in one eye. He stated this could be caused by an unusually prolonged migrainous vasospasm leading to local ischaemia of the posterior lateral ciliary artery supplying the ciliary ganglion.

Overall considerations of the pupil and migraine

The evidence for a sympathetic hypofunction in migraine is strong although authors disagree on whether it persists in the headache-free period and if it is related to the side of the habitual headache.

The evidence of Adie's tonic pupil relates to one case study which although detailed is not good evidence and may represent a unique patient event rather than a general trend for all migraine sufferers.

Evans and Jacobson (2003) recently presented a case study of transient anisocoria in a migraineur and suggested that migraine headache can exaggerate physiological anisocoria and that in their case there were no sympathetic or parasympathetic deficits.

Pattern glare/visual stress and its relief with colour

Some people will report visual perceptual distortions (illusions), eyestrain, and headaches when viewing patterned stimuli. This has been termed 'patterned glare' (Wilkins and Nimmo-Smith, 1984) and more recently 'pattern glare' (Evans and Drasdo, 1991). *Table 3* summarises the feature of patterns that cause pattern glare. When the symptoms of pattern glare are present in everyday life then this is called visual discomfort or visual stress. The early literature included several references to the anomalous visual effects of such patterns (e.g. Purkinje, 1823; Brewster, 1832) and by

Table 3. A summary of the features which make geometric patterns most likely to produce an epileptic response

Feature	Reference
Contrast energy concentrated within one orientation	Wilkins *et al.* (1979)
The length of line is long	Wilkins *et al.* (1979)
High luminance, high contrast	Wilkins (1995, p. 17)
Square wave grating	Soso *et al.* (1980)
Increased size of pattern	Wilkins *et al.* (1979)
Spatial frequencies between two and four cycles per degree	Wilkins *et al.* (1979)
Pattern direction is reversed 10–20 times a second	Wilkins (1995, pp. 31–34)
Binocular rather than monocular viewing	Jeavons and Harding (1975), Wilkins *et al.* (1979, 1980).
Pattern presented in the visual hemi-field that corresponds to the side of the patients cortex that is most easily excited	Wilkins *et al.* (1980), Soso *et al.* (1980), Binnie *et al.* (1981)

the 1960s and 70s these effects were being used in the art world, in a movement called 'Op Art'.

Wade (1978) listed the visual phenomena exploited in op-art and included afterimages, Hermann grid effects, Gestalt grouping principles, blurring and movement due to astigmatic fluctuations in accommodation, scintillation and streaming (possibly due to eye movements) and visual persistence. Symptoms produced from such visual phenomena can range from 'unpleasantness' to producing epileptic fits in susceptible individuals.

Wilkins (1995) summarised the various effects that normal subjects perceive when viewing a striped pattern as follows: red, green, blue, yellow, blurring, bending of the lines, shadowy shapes amongst the lines, shimmering of the lines, flickering of the lines, nausea, dizziness and pain. Wilkins (1995) suggested that if a person suffered from two or more of these illusions when looking at a striped pattern then they were more sensitive than average, should avoid looking at such a pattern for a long time, and could be diagnosed with visual stress. Conlon *et al.* (2001) showed that her patients with visual stress reported most perceptual distortions with a grating of 4 cycles per degree but that patients with little or no visual stress still had perceptual distortion but at a much higher spatial frequency of 12 cycles per degree. A commercially available test is now available for pattern glare/visual stress, which takes advantage of this (IOO Sales Ltd, London, UK).

Mechanism of visual stress

Wade (1977) had earlier suggested three mechanisms that could explain some of these illusions: physiological fixation instability, accommodative changes and the chromatic aberrations of the eye. Zanker (2002) agreed from a computational viewpoint, and claimed that the illusions could have an almost trivial solution in terms of small involuntary eye movements leading to image shifts that are picked up by motion detectors in the early motion system. Wilkins (1995) suggested that these explanations were not adequate to explain the illusions and agreed with Georgeson (1976, 1980) that the illusions had a structure that could more readily be attributed to inhibitory connections in the visual cortex.

A detailed paper by Wilkins *et al.* (1984) was the seminal work in establishing a neurological basis for visual stress. These authors demonstrated in a number of experiments that the illusions were produced by pattern glare, showed that if the number of illusions was more than two then the patients was more likely to have visual stress, that the illusions produced were lateralized with other symptoms and that the same stimuli that produced pattern glare also produced epileptiform EEG activity in susceptible individuals. Unlike the epileptic response to patterns, the illusion response to patterns does not spread widely across a hemisphere probably because the processing is more focal. This focal (localised) response does not spread widely because the cortex is not sufficiently hyper-excitable (Wilkins, 1995).

It should be noted that this visual stress is conceptually different to the sensory visual deficits discussed earlier (e.g. Coleston *et al.*, 1994; McKendrick and Badcock, 2003). Visual stress seems to be a manifestation of cortical hyperexcitability resulting in a visual trigger for migraine (Wray *et al.*, 1995), eyestrain and visual perceptual distortions. It can be thought of as a visual component to the migraine brain's over-sensitivity to environmental triggers (Welch, 2003). In contrast, the sensory visual deficits seem more likely to be a consequence of neural damage caused by migraine over a number of years. In contrast with this view, Shepherd (2000) reported a correlation between pattern glare and contrast sensitivity and supra-threshold contrast scaling in migraine, but did not find any overall effects due to migraine duration or frequency of migraine attacks.

Pattern glare, visual stress and headache

Interestingly, this illusion response to patterns has a relationship to headache frequency. Wilkins *et al.* (1984) showed that there is a direct correlation between the number of headaches reported and the number of illusions seen whilst viewing a striped pattern of about 4 cycles per degree. Unfortunately, several of the experiments cited in this paper excluded migraine sufferers. However, experiment 7 in this paper did show that migraine sufferers perceive more illusions with a pattern glare stimulus than tension headache sufferers. The correlation between migraine headache and pattern glare only held when the pattern design was within the

epileptogenic range and did not hold when other symptoms such as back pain were discussed. For these reasons Wilkins and his team suggested that the finding could not be attributed to response bias.

People are more susceptible to illusions on days when they have headaches (Nulty *et al*., 1987). In addition, people show more aversion to striped patterns if they are headache sufferers particularly if the headaches are migraines. Marcus and Soso (1989) showed that when viewing epileptogenic striped patterns, 82% of migraine suffers demonstrated aversion whist only 18% of a control group did so. There was no difference between migraine with and without aura. If the illusions appear more pronounced on one side of a pattern then that patient is more likely than others to experience head-pain that is consistently lateralized (Wilkins *et al*., 1984).

Aurora *et al*. (1998, 1999) used transcranial magnetic stimulation to demonstrate that the visual cortex is indeed hyperexcitable in people who suffer from migraine. Huang *et al*. (2003) used functional MRI in patients who had migraine with aura to show that square-wave gratings that produced pattern glare did induce a hyperneuronal response in the visual cortex.

The relief of pattern glare and visual stress with colour

Colour preference can be related to psychology (red for danger and excitement or blue being a calming colour) or to ocular pathological conditions such as the brunescence of nuclear sclerotic cataract producing yellowing vision. Some individuals may wear tinted lenses due to neuroses (Howard and Valori, 1989). Other people with certain neurological disorders, such as dyslexia, migraine or epilepsy can be helped by using individually prescribed coloured filters (Lightstone, 2000), most likely through their effect on pattern glare/visual stress (Wilkins, 2003). Griffiths (2001) stated that measuring colour preference should be part of a routine optometric examination and produced a six-colour system to do this. However, the randomised controlled trials of Wilkins *et al*. (1994, 2002) and Robinson and Foreman (1999) suggest that a greater degree of precision is required and this is supported by recent data alluded to by Wilkins *et al*. (2004). The Intuitive Colorimeter (Wilkins and Sihra, 2000) is commonly used for this purpose in the UK.

The use of individually prescribed coloured filters for children with reading difficulties has been described as Meares-Irlen syndrome, which is likely to be a manifestation of visual stress. This subject has recently been reviewed by Evans (2001) and Wilkins (2003). The benefit from coloured filters is not solely attributable to placebo effects (Wilkins *et al*., 1994; Robinson and Foreman, 1999); conventional optometric or orthoptic anomalies (Evans *et al*., 1995, 1996b; Scott *et al*., 2002); spatio-temporal contrast sensitivity functions (Simmers *et al*., 2001); or a magnocellular deficit (Evans *et al*., 1995, 1996a; Simmers *et al*., 2001). Instead, the benefit from coloured filters is most likely attributable to pattern glare (Evans *et al*., 1995, 1996a) which can be caused by lines of text (Wilkins and Nimmo-Smith, 1984). Deficits of visual attention in some people with reading difficulties might make them particularly sensitive to pattern glare (Evans, 2001). As people with migraine are particularly sensitive to pattern glare, it is not surprising that migraine-like headaches are prevalent in children with reading difficulties who benefit from precision-tinted lenses (Evans *et al*., 1996b).

It is argued that coloured filters change the distribution of the firing pattern within the visual cortex and, since cortical hyperexcitability may vary locally within the visual cortex, individually prescribed coloured filters are an effective treatment (Wilkins, 1995; Wilkins *et al*., 2004). This hypothesis has been supported by recent work showing that the representation of colour in the visual cortex follows topographic maps (Xiao *et al*., 2003).

Chronicle and Wilkins (1991) have found that the visual stress of migraineurs is determined by the colour of the illuminating light, tending to avoid red illumination. In contrast, Good *et al*. (1991) showed that migraine frequency was reduced in children who wore rose tinted spectacles compared with a blue tint. If the tint is prescribed precisely and individually, then the reduction in symptoms with colour is not due to alterations in binocular function or refraction (Evans *et al*., 1996a,b, 2002).

Wilkins *et al*. (2002), in a double-masked randomised controlled study, compared the effectiveness of precision-tinted ophthalmic lenses in the prevention of headache in migraine sufferers. They showed with headache diaries that headache frequency was significantly lower when a precise optimal tint was worn when compared with a suboptimal tint used as a control. The group was a selected group of migraine sufferers that found colour helpful and their optometric characteristics were described by Evans *et al*. (2002). Evans *et al*. (2002) showed that pattern glare symptoms of visual stress were reduced with a precisely selected colour of tinted spectacles. However, this reduction in visual stress was not significantly different from that produced by only a slightly different tint that was used as a control.

To conclude, certain visual stimuli produce visual stress. Migraine sufferers are particularly susceptible to visual stress and it can be reduced with precision-tinted spectacles. By reducing visual stress in migraine sufferers, migraine frequency can be reduced.

Table 4. Summary of visual correlates of migraine. The visual correlates have been divided into sensory and motor correlates. Levels of evidence based on the Centre for Evidence Based Medicine (Oxford, UK) (1999) recommendations have been assigned (where 1 is high evidence and 5 is low evidence) by the present authors

Factor	Assessment (clinical or research)	Evidence (levels 1–5)	Relevance (correlate, cause, treatable?)
Visual sensory factors			
Pupil (sympathetic hypofunction)	Research tests Routine clinical tests	Level 1b	Correlate
Pupil (parasympathetic hyperfunction)	Research tests	Level 4	Correlate
Flicker	Routine clinical tests	Level 2b	Correlate
Visual stress/pattern glare	Routine clinical tests	Level 1b	Correlate Cause? Treatable
Visual motor factors and refractive error			
Exophoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Hyperphoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Refractive error	Routine clinical tests	Level 4	Correlate Cause? Treatable

Summary

Headache is a common symptom reported by patients who consult optometrists (Barnard and Edgar, 1996). As migraine accounts for as many as 54% of all headaches (Leone *et al*., 1994) this suggests that optometrists are likely to encounter patients with migraine very commonly.

Some authors have argued that optometric anomalies are a trigger for migraine (Snell, 1904; Turville, 1934; Wilmut, 1956; Waters, 1970; Griffin, 1996; McKendrick *et al*., 1998). In contrast, the medical literature is sceptical about the role of visual factors in headaches and migraine (Lyle, 1968; Headache Classification Sub-Committee of the International Headache Society, 2004).

In the current climate of clinical governance, there is a need for evidence-based research to guide optometrists as to the role they can play, if any, in managing some cases of migraine. This review has critically examined the evidence that correlates migraine headache and optometric factors. Each optometric correlate of migraine can be segregated into either a visual sensory or visual motor factor, and *Table 4* summarises the evidence. With the exception of the sensory visual factor of visual stress/pattern glare, and sympathetic hypofunction, the evidence correlating optometric factors with migraine is generally poor.

Thus, it appears that there is acceptable evidence in the literature to suggest that both cortical hyperexcitability (as demonstrated by pattern glare) and peripheral neurological defects (as demonstrated by the sympathetic hypofunction with pupil responses in migraine sufferers) are associated with migraine headache. The cortical and peripheral theories are not incompatible. It could be suggested that cortical hyperexcitability is an interictal status that leads to pattern glare and that this sensory visual factor is a trigger for migraine. This is consistent with many other authors who have found that migraine can be triggered by certain visual stimuli. It seems that precision-tinted lenses might be one method of minimising the impact of visual triggers for migraine headache sufferers. Additionally, pre-cortical changes to the visual system (such as the pupil changes and some of the visual field anomalies found) may be a long-term consequence of the neuro-vascular interactions of migraine headache.

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The Relation Between Migraine, Typical Migraine Aura and "Visual Snow"

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Objective.—To assess the relationship between the phenotype of the "visual snow" syndrome, comorbid migraine, and typical migraine aura on a clinical basis and using functional brain imaging.

Background.—Patients with "visual snow" suffer from continuous TV-static-like tiny flickering dots in the entire visual field. Most patients describe a syndrome with additional visual symptoms of the following categories: palinopsia ("afterimages" and "trailing"), entopic phenomena arising from the optic apparatus itself (floaters, blue field entoptic phenomenon, photopsia, self-light of the eye), photophobia, nyctalopia (impaired night vision), as well as the non-visual symptom tinnitus. The high prevalence of migraine and typical migraine aura in this population has led to the assumption that "visual snow" is caused by persistent migraine aura. Due to the lack of objective measures, alternative diagnoses are malingering or a psychogenic disorder.

Methods.—(1) The prevalence of additional visual symptoms, tinnitus, and comorbid migraine as well as typical migraine aura was assessed in a prospective semi-structured telephone interview of patients with "visual snow." Correlations were calculated using standard statistics with $P < .05$ being considered statistically significant. (2) Areas with increased brain metabolism in a group of "visual snow" patients in comparison to healthy controls were identified using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography and statistical parametric mapping (SPM8 with whole brain analysis; statistical significance was defined by $P < .001$ uncorrected for multiple comparisons).

Results.—(1) Of 120 patients with "visual snow," 70 patients also had migraine and 37 had typical migraine aura. Having comorbid migraine was associated with an increased likelihood of having palinopsia (odds ratio [OR] 2.8; $P = .04$ for "afterimages" and OR 2.6; $P = .01$ for "trailing"), spontaneous photopsia (OR 2.9; $P = .004$), photophobia (OR 3.2; $P = .005$), nyctalopia (OR 2.7; $P = .01$), and tinnitus (OR 2.9; $P = .006$). Typical migraine aura was associated with an increased likelihood of spontaneous photopsia (OR 2.4; $P = .04$). (2) After adjusting for typical migraine aura, comparison of 17 "visual snow" patients with 17 age and gender matched controls showed brain hypermetabolism in the right lingual gyrus (Montreal Neurological Institute coordinates 16-78-5; $k_E = 101$; $Z_E = 3.41$; $P < .001$) and the left cerebellar anterior lobe adjacent to the left lingual gyrus (Montreal Neurological Institute coordinates -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$).

Conclusions.—Comorbid migraine aggravates the clinical phenotype of the "visual snow" syndrome by worsening some of the additional visual symptoms and tinnitus. This might bias studies on "visual snow" by migraineurs offering study participation more likely than non-migraineurs due to a more severe clinical presentation. The independence of entoptic phenomena from comorbid migraine indicates "visual snow" is the main determinant. The hypermetabolic lingual gyrus confirms a brain

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dysfunction in patients with "visual snow." The metabolic pattern differs from interictal migraine with some similarities to migrainous photophobia. The findings support the view that "visual snow," migraine, and typical migraine aura are distinct syndromes with shared pathophysiological mechanisms that need to be addressed in order to develop rational treatment strategies for this disabling condition.

Key words: visual snow, migraine, aura, [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

Abbreviations: OR odds ratio, VS visual snow, [18F]-FDG PET [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography

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Patients with "visual snow" (VS) describe a visual disturbance that consists of tiny dynamically flickering dots in the entire visual field resembling the "static" or "snow" of a badly tuned analogue television. The symptoms are continuous and can persist over years. Persistent visual disturbance is mentioned sporadically in the literature without larger systematic studies.[1-3] Patients are often diagnosed as having persistent migraine aura, malingering, or psychogenic disorder because objective measures for the condition are not available to date. A recent study of a substantial cohort of subjects with VS confirmed that the visual disturbance is often associated with migraine and migraine aura. However, not every patient with VS has a history of migraine. Further, VS starts only rarely with migraine aura, and the phenotypical description as well as the clinical course of VS by no means resembles typical migraine aura, which is in general homonymous, often presents with moving zigzag lines, and typically lasts less than 60 minutes. This suggests that VS is a unique condition different from migraine aura.[4-6] Importantly, VS should be seen as a syndrome since it is almost always associated with additional visual complaints including palinopsia, entoptic phenomena that arise from the optic apparatus itself (ie, floaters, blue field entoptic phenomenon, self-light of the eye and photopsia),[7] poor night vision (nyctalopia), and photophobia. A large proportion of VS patients has bilateral continuous tinnitus.[5]

To investigate the role of migraine and typical migraine aura mechanisms underlying VS, we sought to assess whether the presence of migraine or aura is associated with different phenotype of the *VS syndrome*. We prospectively recorded accompanying visual and auditory symptoms in a large cohort of

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patients with VS and correlated these symptoms with comorbid migraine and typical migraine aura. To assess potential pathophysiological correlates, we further studied brain metabolism in patients with the hypothesis that VS is associated with regional hypermetabolism distinct from previous findings in migraine.[8,9]

Clinical data of a subgroup of the study population have been previously presented in a report on the detailed phenotype[5] and in preliminary form.[10,11]

SUBJECTS AND METHODS

The study was approved by the Institutional Review Board (# 11-07270 and # 11-07431) and the radiation safety committee (58605-RU-04-URH) of the University of California, San Francisco. Patients were recruited via advertisements in social media with the support of a self-help group on VS (Eye on Vision Foundation; http://www.eyeonvision.org/). After being contacted by the patient, eligibility was assessed during telephone interviews.

Clinical Data.—*Telephone Interview*.—After being approached by the patient, verbal consent was obtained and subjects with self-suspected VS underwent a semi-structured telephone interview. The following items were covered during the interview:

1. Demographics (age, gender) and handedness.
2. Patients were asked to describe their current visual symptoms in their own words. Based on that information and additional open questions, a diagnosis of VS was made and associated visual symptoms were recorded as described recently.[10] In brief, VS was defined as dynamic, continuous, tiny dots in the entire visual field (similar to "TV static" or "TV snow") lasting longer than 3 months (criterion A).[5] Other symptoms were palinopsia ("afterimages" and "trailing" of moving objects), entopic phenomena (phenomena arising from the structure of the visual system itself including (1) excessive floaters in both eyes; (2) excessive blue field entoptic phenomenon, ie, uncountable little gray/white/black dots or rings shooting over the visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky; (3) self-light of the eye, ie, colored waves or clouds when closing the eyes in the dark; and (4) spontaneous photopsia, ie, bright flashes of light),[7] photophobia, and nyctalopia (impaired night vision). Due to its high prevalence in subjects with VS,[5] the presence or history of tinnitus was also covered during the interview despite being a non-visual symptom.
3. Headache history was assessed according to the International Classification of Headache Disorders – 2nd edition.[6] Migraine aura was only diagnosed when typical features were present, which are unilaterality (homonymous), development over 5 minutes, duration for less than 60 minutes, reversibility, zigzag lines, and scotoma.[4,6]

Data Analysis.—SPSS (v20, IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the clinical data. Standard descriptive statistics were applied. If appropriate, data are presented as mean ± standard deviation. Nominal data were compared using chi-square or Fisher's exact test, ratio data using *t*-test. Statistical significance was defined as $P < .05$.

Functional Brain Imaging.—All subjects participating in the positron emission tomography (PET) study gave written informed consent. Inclusion criterion was VS with at least 2 additional visual symptoms as defined previously.[5] Control subjects did not have VS, associated visual symptoms, tinnitus, a history of frequent migraine attacks (more than 1 every 2 months), or of migraine aura. Exclusion criteria for both groups were ophthalmological pathology other than refraction anomalies, any lifetime history of intake of hallucinogenic drugs, and pregnancy in women. Each subject underwent a detailed personal interview with a focus on visual symptoms, migraine history including typical aura and general past medical history. On the scanning day, each subject had a fasting period of at least 6 hours prior to the acquisition of a high-resolution T1-weighted anatomical MR image (MPRAGE sequence) on a General Electric Signa HDxT 3.0 Tesla scanner (GE Healthcare, Fairfield, CT, USA). Afterwards, a [^{18}F]-2-fluoro-2-deoxy-D-glucose PET ([^{18}F]-FDG PET) scan was acquired using standard parameters, with injection of 10 mCi via an antecubital vein and 45 minutes distribution period in a dark room with eyes closed, on a

GE Discovery VCT PET/CT scanner (GE Healthcare) in three-dimensional (3D) mode with septa retracted. Images were reconstructed by 3D iterative reconstruction into 47 image planes (separation 3.27 mm) and into a 128 by 128 image matrix (pixel size: 2.1×2.1 mm^2). The structural magnetic resonance imaging (MRI) was coregistered to the PET using SPM8 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm). The coregistered MRI was automatically segmented into gray matter, white matter, and cerebrospinal fluid and normalized into standard stereotaxic space. The spatial normalization parameters from this step were applied to spatially normalize the PET image. Final voxel size was $2 \times 2 \times 2$ mm^3. PET images were then smoothed with a Gaussian Kernel of 12 mm full-width at half maximum. The group of VS patients was compared with controls using a 2-sample *t*-test with masking of non-brain tissue (whole brain explicit mask generated with WFU PickAtlas from Advanced Neuroscience Imaging Research Laboratory, Department of Radiology of Wake Forest University School of Medicine, http://fmri.wfubmc.edu/), and using proportional scaling. Due to the high prevalence of typical migraine aura in patients with VS,[11] the presence of migraine aura was used as a covariate of no interest. According to the clinical manifestation of VS, we suspected hypermetabolism in VS patients. We therefore assessed brain areas with *increased* metabolism in VS patients compared with controls in a voxel-wise fashion. In line with previous studies on migraine,[12,13] we considered voxels reaching a significance threshold of $P < .001$ uncorrected for multiple comparisons to be significant.

RESULTS

Clinical Data.—Of the 142 patients who contacted the Headache Center at the University of California, San Francisco, 120 subjects (mean age 31 ± 12 years; 62 female) met criterion A for "visual snow,"[5] ie, presence of dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.

Additional Visual Symptoms.—Palinopsia with "afterimages" from stationary scenes was present in 84%, and with "trailing" in 58%. Excessive floaters were the most common entoptic phenomenon with a prevalence of 83%. Second most common was the blue field entoptic phenomenon (76%). Spontaneous photopsia and consistent self-light of the eye occurred in half of patients. About two thirds of patients had photophobia and nyctalopia. In addition to these visual symptoms, 64% of patients noted continuous bilateral and mainly high-pitched tinnitus (Table 1).

Table 1.—Additional Symptoms in Patients With "Visual Snow"

	All Visual Snow Patients N = 120	
Palinopsia ("afterimages")	101	84%
Palinopsia ("trailing")	69	58%
Floaters	99	83%
Blue field entoptic phenomenon	91	76%
Self-light of the eye	64	53%
Spontaneous photopsia	64	53%
Photophobia	86	72%
Nyctalopia	76	63%
Tinnitus	77	64%

Association of Additional Symptoms With Migraine and Typical Migraine Aura.—The presence of migraine was associated with an increased prevalence of the additional symptoms palinopsia (odds ratio [OR] 2.8 for "afterimages" and OR 2.6 for "trailing"), spontaneous photopsia (OR 2.9), photophobia (OR 3.2), nyctalopia (OR 2.7), and tinnitus (OR 2.9). Spontaneous photopsia was more prevalent in patients with typical migraine aura (OR 2.4, Table 2).

Functional Brain Imaging.—Seventeen patients (10 female, mean age ± standard deviation 31 ± 7 years) with VS and at least 2 additional visual symptoms were recruited for the imaging study. Seven had VS as long as they could remember. Mean age of onset in the remaining was 25 ± 8 years. Fourteen (82%) had a history of migraine. Five of those had migraine with typical aura, and 1 had typical migraine aura without history of migraine.[6] All 3 patients without history of migraine had a positive family history of migraine. Besides headache, past medical history included depression, Graves' disease, hypothyroidism, acne, and attention deficit hyperactivity syndrome, each present only in 1 subject. The current regular medication as well as the past medication

Table 2.—Correlations Between Additional Symptoms in Patients With "Visual Snow" and Comorbid Migraine and Typical Migraine Aura (Statistics: Chi-Square Test)

	Patients With "Visual Snow" N = 120							
	Migraine				Typical Migraine Aura			
	Yes n = 70	No n = 50	*P*	OR (95% CI)	Yes n = 37	No n = 83	*P*	OR (95% CI)
Palinopsia ("afterimages")	63	38	.04	2.8 (1.0; 7.8)	34	67	.12	—
Palinopsia ("trailing")	47	22	.01	2.6 (1.2; 5.5)	25	44	.14	—
Floaters	60	39	.27	—	30	69	.79	—
Blue field entoptic phenomenon	53	38	.97	—	28	63	.98	—
Self-light of the eye	38	26	.81	—	20	44	.92	—
Spontaneous photopsia	45	19	.004	2.9 (1.4; 6.2)	25	39	.04	2.4 (1.0; 5.3)
Photophobia	57	29	.005	3.2 (1.4; 7.2)	30	56	.13	—
Nyctalopia	51	25	.01	2.7 (1.2; 5.8)	26	50	.29	—
Tinnitus	52	25	.006	2.9 (1.3; 6.2)	27	50	.18	—

—, NA.

trials for VS are shown in Table 3. All subjects stated having normal ophthalmological exams except for some refraction anomalies. The 17 controls had the same age and gender distribution (10 female, 31 ± 7 years). Since history of migraine and typical migraine aura were exclusion criteria for controls, they differed significantly from VS patients in respect of history of migraine ($P < .001$, Fisher's exact test) and history of typical migraine aura ($P = .02$, Fisher's exact test).

The voxel-wise [^{18}F]-FDG PET group comparison evidenced hypermetabolism of the right lingual gyrus (Montreal Neurological Institute coordinates: 16-78-5; cluster size $k_E = 101$; $Z_E = 3.41$; $P < .001$) and a trend for the anterior lobe of the left cerebellum (Montreal Neurological Institute: -12-62-9; $k_E = 152$; $Z_E = 3.28$; $P = .001$) (Figure) in patients with VS when compared with healthy controls after adjusting for the presence of typical migraine aura.

DISCUSSION

"Visual snow" (VS) is a disabling disorder with patients complaining about TV-snow-like tiny flickering dots in the entire visual field. The symptoms can be continuous and might persist over years. In a recent study, almost all patients with VS had additional visual symptoms, such as palinopsia, entoptic phenomena (floaters, blue field entoptic phenomenon, and others), nyctalopia (impaired night vision), photophobia, and tinnitus suggesting that VS is likely a clinical syndrome.[5] In our study population, the majority of patients with VS had comorbid migraine (58%), and 31% had typical migraine aura. This high comorbidity, when compared with the general population,[14] has led to the assumption that VS might represent persistent migraine aura as often discussed in the initial case series,[1-3] although the clinical presentation is clearly different from typical migraine aura.[5]

Here, we sought to understand whether the VS syndrome manifests differently in patients with migraine or typical aura. For that, a cohort of VS patients was carefully phenotyped in respect to the clinical presentation and comorbidities. We found that VS patients, who also have migraine according to International Classification of Headache Disorders – 2nd edition[6] had a significantly higher likelihood of having palinopsia, photophobia, nyctalopia, and tinnitus. Of the entoptic phenomena, ie, visual perceptions arising from the optic apparatus itself,[7] only spontaneous photopsia was more prevalent in VS patients with migraine history, while floaters, blue

Table 3.—Current Regular Medication and Past Treatment Trials for "Visual Snow" in 17 VS Patients Who Took Part in the [18F]-FDG PET Study

	Current Medication	Medication for "Visual Snow"		
		Generic Name	Duration	Effect
1	—	—	—	—
2	—	Sertraline, fluoxetine	6 months	None
3	—	—	—	—
4	Dexlansoprazole, bupropion, zolpidem, topiramate, dicyclomine	—	—	None
5	Methimazole	Fluoxetine, verapamil, lamotrigine	—	None
	—	Sertraline	—	Worsening
6	—	Amitriptyline, propranolol	2 months	None
7	—	—	—	—
8	—	Naproxen	—	Improvement
	—	Sertraline, clonazepam	—	None
9	Throid (porcine), vitamin D, fexofenadine	—	—	None
10	—	—	—	—
11	—	—	—	—
12	—	—	—	—
13	Minocycline	—	—	None
14	—	—	—	—
15	—	—	—	—
16	—	—	—	—
17	—	—	—	—

—, no current medication and/or no medication tried for "visual snow" in the past.

field entoptic phenomenon, and self-light of the eye were equally distributed. Three major conclusions might be drawn from this: First, the presence of migraine might aggravate the manifestation of the VS syndrome by worsening some, but not all additional visual symptoms. Second, our study population was recruited via a self-help group, and it is possible that patients with a more severe clinical manifestation are more eager to participate in a research study. Therefore, a more severe manifestation of the VS syndrome in migraineurs indicates that the high prevalence of migraine in our VS study population might be subject to a selection bias suggesting that the relevance of migraine for VS pathophysiology might be overrated as well. In contrast, the presence of typical migraine aura, ie, the putative correlate of cortical spreading depression[15] that presents with a homonymous, centrifugally moving scintillating scotoma shaped in zigzag lines,[16,17] does not substantially alter the distribution of the additional visual symptoms in the VS syndrome. Typical migraine aura may thus not influence the VS phenotype suggesting that the high prevalence of aura is less subject to selection bias than migraine. Although VS is clearly not persistent migraine aura,[5] typical migraine aura might share some pathophysiological background with the VS syndrome. Third, the impressive entoptic phenomena floaters, blue field entoptic phenomenon, and self-light of the eye are present in VS patients independently of a history of migraine, suggesting that these symptoms are probably not mediated or facilitated by a migrainous mechanism. In contrast, they might depend solely on the presence of VS.

Some of the additional visual symptoms in patients with VS can also be found in migraineurs. This might, at least in part, explain how a migrainous, but not typical migraine aura, comorbidity might potentiate these symptoms in VS patients. For migraineurs without VS, the higher prevalence of palinopsia when compared with healthy controls seems to be of minor relevance since it affects only 14.2% of the group and occurs only episodically.[18]

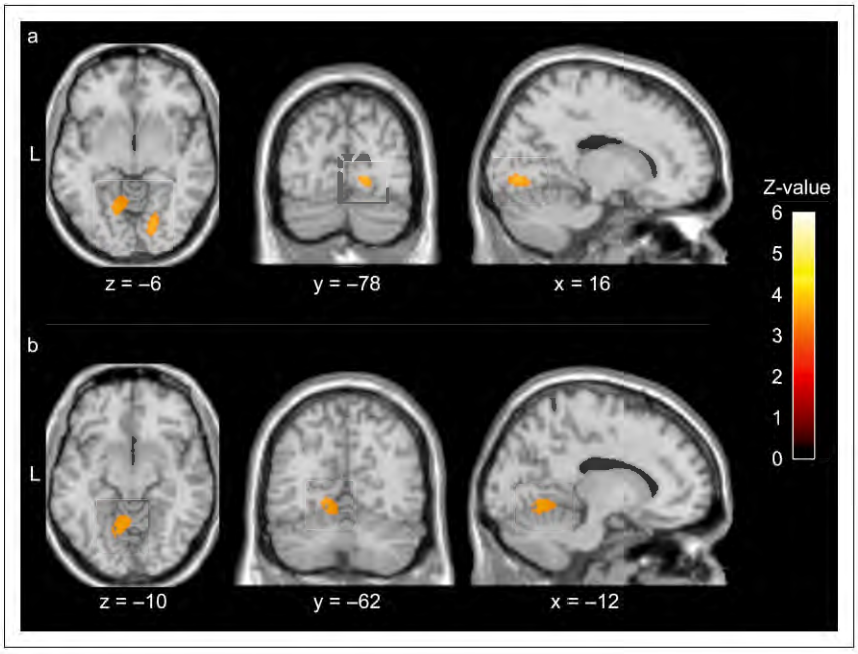

Figure.—When comparing the brain metabolism of patients with "visual snow" to healthy controls in [^{18}F]-FDG PET using a paired *t*-test in SPM8, the right lingual gyrus (in [a]; Montreal Neurological Institute 16-78-5; $k_E = 101$; $Z_E = 3.41$; $P < .001$) and the anterior lobe of the left cerebellum (in [b]; Montreal Neurological Institute -12-62-9; $k_E = 152$; $Z_E = 3.28$, $P = .001$) were metabolically more active in patients with "visual snow." The figure was thresholded at $P \leq .001$.

However, this predisposition to palinopsia in migraineurs might perpetuate mechanisms of palinopsia in VS resulting in a higher prevalence and continuous presence.[5] For the key migraine symptom photophobia,[6] recent studies have suggested a pain-mediated increase in light sensitivity.[19] In VS, such mechanism is unlikely due to the low prevalence of chronic headache in patients with *continuous* VS and photophobia.[5] In contrast, photophobia as a symptom of the VS syndrome might be perpetuated by comorbid migraine in a non-pain-mediated manner. This is less clear for tinnitus, which is not a classical migrainous symptom[20] although migraine attack-associated episodes of tinnitus have been reported.[21] Tinnitus could be interpreted as noise within the acoustic system. The similarity to "TV-snow," ie, "TV-noise," has previously led to the interpretation that tinnitus might be the clinical correlate of the affection of the acoustic system by VS-like mechanisms.[5] In our study, tinnitus was also more prevalent in VS patients with comorbid migraine and thus behaved like the additional visual symptoms supporting that the VS syndrome might indeed include the non-visual symptom tinnitus.

In [^{18}F]-FDG PET, the right lingual gyrus and the anterior lobe of the left cerebellum were metabolically more active in patients with VS when compared with healthy controls. This first objective correlate of VS strongly suggests the VS syndrome is a neurological condition. This has important consequences for communication with patients, who have been frequently diagnosed as having a psychogenic disorder or as being malingerers. The relevance of the (trend) hypermetabolism of the left cerebellum is unclear. The cerebellum's key function for vision is extraocular motility.[22] Only little is known about its role in visual perception, but cerebellar disease has been associated with difficulties in depth perception[23] or with a phenomenon called upside-down vision.[24,25] When analyzed visually, this area seems to extend laterally and rostrally to the left lingual gyrus (Figure) possibly reflecting the relatively low spatial resolution of PET. Such bilateral hypermetabolism in the lingual gyrus might be a signature of hyperactivity of the visual system in VS. Interestingly, the same area showed hyperperfusion in [^{15}O]-water PET during high luminous stimulation in migraineurs[26] and during low light stimulation in spontaneous

migraine attacks indicating relevance for the migrainous phenomenon photophobia.[27] To put our finding into a broader neurobiological context, it has to be stated that the lingual gyrus is also involved in visual memory[28] and different higher order functions of vision, such as the perception of color,[29] the identification of facial expressions of emotions,[30] or grapheme-color synesthesia.[31] This broad involvement of the lingual gyrus in visual post-processing including photophobia during migraine attacks indicates that VS might also be a disorder of visual post-processing.

One limitation of the imaging part of the study is the higher prevalence of migraineurs in the VS group in comparison with the control group. This could potentially bias the results by showing an effect from migraine rather than from VS – or by "masking" VS correlates in PET by the presence of migraine in the VS group. To address this issue, future studies with pure VS patients without history of migraine or with migraineurs without VS as controls would be necessary. However, we believe that the hypermetabolism in our patients is VS related and not a migraine effect since not all subjects with VS had a history of migraine and, importantly, several recent studies were not able to show hypermetabolism in *interictal* migraineurs in comparison with controls despite including only migraineurs.[8,9,32] In addition, it is unlikely the metabolism data were biased by the higher number of patients with history of migraine aura in the VS group since only one third of VS patients had comorbid aura. Further, the analysis was adjusted for migraine aura and none of our subjects had experienced an episode of typical migraine aura during the distribution period of the tracer or during the scanning.

CONCLUSION

In a substantial cohort of patients with the "visual snow" (VS) syndrome, migraine is associated with an increased prevalence of the additional symptoms of palinopsia, photopsia, photophobia, nyctalopia, and tinnitus suggesting a more severe phenotype, although not with entoptic phenomena. VS patients with migraine might thus be more interested in participating in studies on VS than patients without migraine, creating a bias of migraine prevalence in such studies and an overestimation of the relevance of migraine for VS pathophysiology. In contrast to migraine, comorbidity of typical migraine aura did not alter the phenotype of the VS syndrome. The high prevalence of typical migraine aura in VS patients therefore is not associated with a worsening of the additional visual symptoms and thus not with an overestimation of aura prevalence in VS. This might indicate a pathophysiological overlap of VS and typical migraine aura despite the distinct clinical presentation. [^{18}F]-FDG PET revealed an objective correlate for VS symptoms. The unique pattern of hypermetabolism in the lingual gyrus in patients with VS has not been shown for *interictal* migraineurs alone. VS is thus a syndrome distinct from migraine, although the hyperperfusion of this area *during* migrainous photophobia indicates a potential pathophysiological overlap of both conditions and possibly reflects the perpetuation of the additional visual symptoms in VS patients by comorbid migraine. Understanding this overlap in more detail will be crucial to develop treatment strategies for this disabling neurological disorder in the future.

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INVITED LECTURE

The role of the visual system in migraine: an update

R. Allan Purdy

Abstract The visual system plays a prominent role in migraine headache, especially migraine with aura. Anatomical and functional studies in migraine are showing an increasing role linking the visual system to migraine and its multiple and complex clinical expressions. Recent research on photophobia highlights the progress of our understanding of these relationships. This review overviews a practicing neurologist's view of some of the roles of the visual system in migraine and how a clinical understanding of this relationship is enhanced by recent research and discovery in this in this important area.

Keywords Migraine · Aura · Visual system · Photophobia

Introduction

The visual system plays a large role in the diagnosis of many neurological disorders; however, in migraine, in particular, it has special significance. Migraine is mainly migraine without aura [1], followed by migraine with aura, in which the visual system plays a prominent, interesting and increasingly intriguing role. In migraine without aura vision it is not totally excluded, given that one of the major criteria for the diagnosis of migraine is 'photophobia' [1]. It is unclear whether photophobia is photo-sensitivity, as in pain worse with light, as opposed to photo-allodynia, where light is bothersome in and off itself. A recent study [2] of the pathways for photophobia suggests photo-allodynia and not photo-sensitivity maybe more important. This paper will give an overview of few of the clinical aspects of the role of the visual system in migraine, along with some relevant research.

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Clinical discussion

Beginning with the visual cortex and moving in towards the eye, in the opposite direction to usual clinical localization, that being peripheral to central, might be a good way to overview this topic. Starting with the cortex is important because of the majority of the visual aura manifestations of migraine arise from the occipital cortex [1].

Pathophysiologically, these visual phenomena appear to arise from a cortical spreading depression (CSD) [3] beginning in the occipital cortex, predominantly in one hemisphere, spreading anterior over cortex to produce various simple and complex visual symptoms, from scintillating scotoma and hemifield loss, and other less defined visual phenomena. The visual symptoms are numerous and have been documented in excellent reviews [4, 5].

Scintillating scotomas and fortification spectra as aura are among the commonest visual symptoms accompanying "migraine with aura" [1, 5, 6]. Other phenomena such as micropsia, macropsia, altered colour perception, monocular vision loss, diplopia, and autonomic symptoms and signs such; as ptosis, lacrimation, pupillary abnormalities have been all been described in migraine [1, 4, 5].

After headache, visual manifestations are the most common symptoms of migraine with aura, occurring commonly, in one study 99% of patients experienced visual aura at least some of the time [7]. Classically scintillating scotoma moves slowly across the visual field, and from an aerial view resemble the walls of a fortress, and is thus referred to as a

"fortification spectra" [1, 5]. Positive auras include phosphenes (flashing lights), heat waves, kaleidoscope effects and fragmented "cracked glass" vision, while negative auras range from tunnel vision and scotomas to homonymous hemianopia and transient cortical blindness [4, 5].

In a study of 100 patients [6], 39% had visual auras with their first headache and subsequently 19% had aura with every attack. The aura lasted 1–30 min in most patients and started peripherally in 56%. The most common phenomena described were small bright dots (42%), flashes of light (39%), "blind spots" (32%), and "foggy vision" (27%). Fortification spectra were reported by only 20%. They concluded that migraine visual aura is a pleomorphic and complex symptom and that many patients not qualifying for the diagnostic criteria of migraine with aura, as proposed by the International Headache Society [8] unequivocally present with visual phenomena that strongly suggest this diagnosis.

In another large study [9], aura was studied in different migraine types. In total, 952 migraine patients were studied to determine aura frequency, duration, time to headache, characteristics and percentage of headaches that had aura. The findings were 38% of patients with IHS 1.1–1.5 migraine reported aura, 38.1% of females and 33.0% of males. Aura occurred on average in 19.7% of headaches, the average aura duration was 27.3 min, and aura was followed by headache on average in 10.4 min. Visual disturbances occurred in 92.1% and aura without visual aura was rare. Aura frequency was highest in a more 'full-blown' migraine attack. Visual aura was the overwhelming aura symptom.

In an electronic questionnaire study of migraine aura and related phenomena, Vincent et al. [10] explored the effect of migraine on cortical physiology before the attacks. Recognizing that visual symptoms were common during aura, they looked at other cortical areas near the visual cortex and found these areas produced symptoms and impairment in migraine. Their study showed significantly more patients reported symptoms in the migraine with aura group than the migraine without aura group. Thus, 72.2% with migraine with aura, and 48.6% of migraine without aura patients showed dysfunctions suggestive of prosopagnosia, dyschromatopsia, ideational apraxia, alien hand syndrome, proper name anomia or aphasia, which varied in severity and duration and build up in a successive manner. They concluded that migraineurs revealed less evident symptoms, which are not usually considered during routine history taking. They suggested that spreading depression most likely underlies these aura symptoms and found that interictal involvement indicates that migraine with and without aura are not completely silent outside attacks, and that both types of migraine may share common mechanisms.

Even visual hallucinations in migraine hold great interest for neurologists as outlined in a detailed and fascinating article by Schott [11] where he contends that the visual aura of migraine is a subjective phenomenon, and what the migraineur experiences is necessarily inaccessible to others. He explores how graphic illustrations can be valuable in differential diagnosis, from a variety of non-migrainous causes. Illustration, during an attack is seen as a powerful tool allowing the subjective experience to be made more objective and may lead to further insight into some of the cerebral disturbances which relate to migraine aura.

Two new entities appear in [1] including "Typical aura without headache" (IHS 1.2.3), and "Persistent aura without infarction" (IHS 1.5.3) which are of interest to neurologists, who see patients with a typical visual aura but no headache, previously called 'acephalgic migraine'. The IHS discussion notes indicate that while some patients have aura without headache exclusively, it is more common that as patients age, their headache may lose its migrainous characteristics or cease altogether, leaving only the aura as a 'late life migraine accompaniment' [12, 13]. Persistent aura without infarction refers to a syndrome in which the aura symptoms persist for more than 1 week without radiographic evidence of infarction [1].

Retinal migraine

In the retina, the entity of retinal migraine becomes manifest. Retinal migraines are uncommon and defined by attacks of monocular scotoma or blindness lasting <1 h, associated with headaches [1]. Vasospasm of the retinal circulation maybe the mechanism of the amaurosis in retinal migraine, and has been observed clinically [14]. The ICHD-2 criteria [1] for retinal migraine require reversible positive or negative monocular symptoms followed by or accompanying a typical migraine headache.

A recent review [15] summarizes the clinical features and prognosis of 46 patients (six new cases and 40 from the literature) with retinal migraine [1]. They found retinal migraine most common in women in the second to third decade of life and contrary [1] criteria most have a history of migraine with aura. In the typical attack, monocular visual features consist of partial or complete visual loss lasting <1 h and on the same side as the headache. Nearly half of the reported cases with recurrent transient monocular visual loss subsequently experienced permanent monocular visual loss. Their findings suggested that irreversible visual loss is part of the retinal migraine spectrum, perhaps representing an ocular form of migrainous infarction.

Ophthalmoplegic migraine (OM)

This entity has been known for some time and is currently classified under the ICHD-2 [1] as a cranial neuropathy, whereas in the past it was considered to be a type of migraine under ICHD-1 [9]. Enhancing lesions of the third nerve shown on MR scanning suggested a potential cause and may not be a primary headache disorder [16, 17]. In a recent editorial [18] it was suggested that OM maybe a syndrome with primary and secondary causes, with the former being primary in the absence of a lesion and secondary if a lesion is found on an enhanced scan; it was suggested that if the lesion resolved between attacks then it is likely to represent a recurrent demyelinating or inflammatory cranial mononeuropathy, while in some cases, the lesion turned out to be a tumor. The author suggested that the ICHD Classification may have to be revised as did the authors of a clinical paper in the same journal reporting more cases of OM [19].

Genetics

A most interesting recent study [20] of a large pedigree with typical migraine aura examined whether TRESK (TWIK-related spinal cord potassium channel) is involved in migraine. A mutation in this gene, encoding the two-pore domain potassium channel, was found and could help lead to a better understanding of a common hereditary type of migraine as well as its pathogenesis and therapy.

Photophobia

Another area of intense interest is photophobia, as the criteria for migraine suggests sensitivity to light worsens the headache, more of a trigger than anything else, and what might be considered 'photosensitivity' [1]. In a recent significant publication [2] suggested a neural mechanism for exacerbation of headache by light. They found that exacerbation of migraine headache by light is prevalent among blind individuals who maintain non-image-forming photoregulation in the face of massive rod/cone degeneration. They identified dura-sensitive neurons in the posterior thalamus of the rate whose activity was distinctly modulated by light and whose axons projected extensively across somatosensory, visual and associative cortices. The cell bodies and dendrites of such neurons were apposed by axons originating from retinal ganglion cells (RGCs), predominantly from intrinsically photosensitive RGCs, the principle conduit of non-image-forming photoregulation. They proposed that photoregulation of migraine headache is exerted by a non-image-forming retinal pathway that modulates the activity of dura-sensitive thalamocortical neurons.

A most interesting study regarding the asymmetry of visual function in migraine with aura, correlating with lateralization of headache and aura was recently published [21]. They explored this asymmetry in 47 migraineurs with aura (MA), who were not taking prophylactic medications, and 62 controls with the same age range (16–59). They concluded that the lateralized changes present in patients suggested that the visual dysfunction occurs at a cortical level, and the correlation with the side of the aura suggests that dysfunction is most likely to occur in an area of pre-existing anomaly of neural function.

Visual aura mechanisms

CSD has also been demonstrated in patients without visual aura [22]. On the other hand, recent eloquent reviews of CSD and its role in migraine pathophysiology have been published [23, 24]. It was noted that spreading depression is a slowly propagated wave of depolarization of neurons and glial cells, followed by a subsequent sustained suppression of spontaneous neuronal activity, along with complex and variable changes in vascular size and flow as well as changes in energy metabolism [24]. A study of 26 migraineurs with postgeniculate or visual cortex lesion demonstrated that such pathology was significantly associated with complete cessation of migraine visual auras; and the postgeniculate pathways were probably a critical factor in the appearance of migraine with aura and thus by extension propagation of CSD [25].

The clinical progression of Lashley's visual aura correlates exactly to the rate of CSD described by Leao of (3 mm/min) [Lashley and Leao] [3, 26]. Studies with functional MRI brain oxygen level dependent (BOLD) signal confirm this velocity calculation [27]. Thus, the connection between CSD and this type of visual aura, scintillating scotoma, seems to be well established; however, the explanation for other visual phenomena in migraine remains less clear.

Using transmagnetic stimulation is providing interesting results in that a study by Young and colleagues [28] provoked phosphene perception in migraineurs and controls using transcranial magnetic stimulation, and showed that phosphenes could be induced in migraineurs at much lower stimulation intensities compared with controls. Migraineurs with aura required even lower stimulation intensities than migraineurs without aura, further suggesting hyperexcitability of components of the visual system in the brains of migraineurs.

Finally, a recent article [29] overviewed the history of migraine with aura and CSD and reviewed the seminal reports and studies in this area and noted that the human studies on CSD showed initial hyperemia followed by prolonged hypoperfusion. In summation, the critical studies moved the science from ischemia to CSD and onto to the brain itself, which 'paved the way for subsequent discoveries of brainstem mechanisms' [30] in migraine pathogenesis.

Secondary irritatative lesions causing visual aura

Visual aura is a common presenting symptom of migraine to both neurologists and ophthalmologists. In the vast majority of cases, the diagnosis can be made without the need for further investigations. In one recent study [31], they reviewed nine patients and a further 31 cases from the literature who experienced visual aura fulfilling the diagnostic criteria for migraines, but caused by focal occipital pathology. They concluded that any disease process that is able to create a state of neuronal hyperexcitability can increase an individual's susceptibility to the development of cortical spreading depression, the electrophysiological correlate of the visual aura.

Conclusion

Overall, there is a plethora of symptoms and signs in the visual system that occurring during migraine and it requires special clinical acumen, knowledge and skill to sort these out in any individual patient. Time spent however in studying the visual system in migraine and related disorders will reward the clinician and their patients with better understanding and management of their migraine headaches.

In summary, migraine aura has many manifestations, it is most often visual, and it is associated with a variety of visual phenomena. Susceptibility to migraine is likely caused by a hyper-excitability of the brain, lowering the threshold for the induction of cortical spreading depression. Structural, functional and metabolic abnormalities of the visual system play a major role in this hyper-excitability, and studies of the visual system are central to migraine research.

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Conflict of interest The author declares that there is no actual or potential conflict of interest in relation to this article.

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The role of visual system in migraine

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Abstract The visual system is involved in different ways in migraine. Visual auras are the most common form of migraine aura. It may consist of positive or negative visual symptoms and cortical spreading depression is felt to be the phenomenon that underlies it. Even in migraine without aura, vision it is not totally excluded given that one of the major criteria for the diagnosis of migraine is photophobia. In persistent visual aura, patients refer symptoms defined as visual snow and television static. In retinal migraine unilateral decreased vision or complete visual loss occurs. Ophthalmoplegic migraine is characterized by palsy of one among the three ocular motor nerves. Migraine visual aura, particularly when occurring without headache, is a diagnosis of exclusion. Imaging studies and laboratory tests should exclude neurologic disease, included seizures and central nervous system tumor, ocular pathologies, carotid or cardiac disease, thrombosis and connective tissue disease.

Keywords Migraine aura · Photophobia · Visual snow · Retinal migraine · Ophthalmoplegic migraine

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Introduction

In 60% of migraineurs, warning signs occur and they can begin insidiously hours to days before the onset of headache. Among the migraine auras, visual auras are the most common (99%) followed by somatosensory (40%), motor (18%) and speech difficulties (20%), symptoms that may be present in the same or different moments of the attack [1].

The visual system can be involved in different ways and different forms of migraine.

The visual system in migraine

Migraine with visual aura affects about 8% of the population and it is about three times less common than migraine without aura. Migraine with or without aura may coexist in 13% of migraineurs and about 19% of patients had aura symptoms with every headache attack [1, 2]. Headache generally follows the aura in 93% of patients.

The visual aura may be unilateral (70%) or bilateral (30%) and may consist of positive or negative visual phenomena. It commonly begins in the centrolateral area of the visual field with alteration of visual perception due to visual loss or presence of bright spots and may evolve into a small scotoma [3]. This symptom may progress over a period of 5 min to 1 h to involve a hemifield or a quadrant of visual field with the expanding margin that may have the appearance of zigzagging lines or geometric shapes known as fortification spectra or teichopsia. Positive visual phenomena may assume a C-shape or a crescent with shimmering edges (scintillations) with or without color. Simple flashes (phosphenes), white or colored dots, bean-like forms, bright bars of light may also be seen. The presence

of scintillations distinguishes auras from transient ischemic attacks. Other visual auras such as foggy vision, looking through water and complex visual hallucinations and negative phenomena such as hemianopsia or quadrantanopsia, scotomas, tunnel vision and complete blindness can also occur. Normal central vision returns as the disturbance migrates peripherally, usually in less than 30 min, with a total duration of less than 60 min.

"Alice in wonderland" syndrome typically affect young children who refer micropsia and telopsia (objects appear smaller and further away than they are), condition often associated with acute bilateral occipital pole lesion, seldom at the onset of migraine attack [4].

The primary striatal visual cortex may be the site of origin of the negative visual phenomena, although the visual unimodal association areas and other extrastriate areas can also be involved. With the exception of phosphenes, the migraine positive visual phenomena seem related to involvement not only of the primary visual area but also of the associative heteromodal zones adjacent to the parieto-occipital fissures and to the superior temporal sulci and the pre-occipital notch. The participation of white matter tracts linking the visual areas to the frontal lobes may generate atypical symptoms [5]. The evidence that visual evoked potentials (VEPs) seem to not differ in migraineurs and healthy subjects, may indicate that there is not an anatomical permanent damage along the visual pathway. However, VEPs may not be the most reliable neurophysiological hallmark in migraine [3, 4, 6].

Involvement of the retina and optic nerve structures, as a consequence of a vasospastic etiology in migraine with aura, has been investigated with Spectral Domain Optical Coherence Tomography although data from different studies are not homogeneous. Reduction of peripapillary retinal nerve fiber layer (pRNFL) thickness in the temporal or in the upper optic nerve quadrants that have been reported by some authors was not confirmed by others [7–11]. On comparing migraineurs with aura and chronic headache patients we also did not identify differences in pRNFL and ganglion cell layer [12].

Cortical spreading depression (CSD) is felt to be the phenomenon that underlies migraine aura. It is a wave of hyper-excitation followed by suppression spreads at a speed of around 3–6 mm/min across areas of contiguous parenchyma without respecting specific neurovascular boundaries of functional cortex. CSD causes release of excitatory and pro-inflammatory mediators which are capable of activating meningeal and perivascular nociceptive neurons causing trigeminovascular activation and dural mast cell degranulation, culminating in a sterile neurogenic inflammation which may prolong headache pain [1, 5]. In patients with spontaneous and evoked migraine auras, hemodynamic alterations, not always respecting specific vascular territory, were reported by multimodal MRI techniques including perfusion-weighted imaging and blood oxygen level dependent (BOLD) imaging [1].

A recent fMRI study reported an abnormal resting-state visual network functional connectivity in the absence of structural or microstructural abnormalities not related to clinical parameters of migraine severity [13]. In the same study, the resting-state fMRI data are in line with recent EEG findings suggesting a close relationship between the aura phenomenon and neural connectivity in migraine during photic stimulation, supporting that lingual gyrus is crucial in photophobia and in trigeminal pain multisensory integration also in patients with migraine without aura.

Persistent migraine visual aura can also occur and it is supposed that it may be due to recurrent waves of CSD. Positive visual phenomena are the typical manifestation in persistent migraine visual aura most commonly consisting of formed or unformed visual hallucinations sometimes covering the entire visual field of both eyes. Metamorphopsia and palinopsia are rarely reported. The diagnosis of persistent migraine visual aura should be made if seizures, toxic-metabolic conditions, retinal inflammatory conditions and psychiatric disease have been excluded. For the International Headache Society, persistent migraine aura may fulfill criteria for migraine with aura and one or more aura symptoms persisting for more than 2 weeks. The condition is associated with absence of neuroimaging finds suggesting infarction or EEG abnormalities and with normal ophthalmological examination. Two descriptive patterns have been common in these patients: visual snow, sometimes referred to as primary persistent visual disturbance, and television static. Schankin and colleagues performed a PET study on patients with visual snow and found metabolic hyper activation at the lingual gyrus without any abnormality on diffusion or perfusion-weighted MRI [14]. In some patients persistent visual aura may resolve spontaneously in a period of weeks to months, in some others it decreased with antiepileptic agents including lamotrigine and valproate while in there are patients who poorly respond to treatment with migraine prophylactics or antiepileptic medication [15].

Not all typical migraine aura episodes are followed by or associated with migraine headache. Among migraineurs with aura, 38% of patients may show also typical migraine aura without headache while exclusive aura without headache can occurs in 4% of subjects [16]. The pathophysiologic explanation might suggest existence of some silent-pain areas that can be involved in the migraine attack before the adjacent cortical pain regions so that patients refer only visual symptoms and not headache. The fact that not all patients with aura developed headache suggest that both are still separate phenomena. Therefore, some drugs

(e.g. lamotrigine) are effective in preventing migraine with aura without great advantage in migraine without aura attacks.

Even in migraine without aura, vision is not totally excluded given that one of the major criteria for the diagnosis of migraine is photophobia and it can occur as a premonitory symptom being present in around 50% of patients [17]. The causes of this hypersensitivity to light is unknown: a PET study suggested that activations in the extrastriate visual cortex are directly linked to increased sensitivity to light in the premonitory phase [18]. It is unclear whether photophobia is photosensitivity, as in pain worse with light, as opposed to photo-allodynia, where light is bothersome in and off itself. Light may exacerbate headache through involvement of photosensitive retinal ganglion cells, those cells that do not have image-forming functions but are involved in the regulation of the circadian rhythm and the adaptation of pupillary size to light, then the visual pathway from the optic chiasm to the pulvinar and progressively towards the somatosensitive cortex and the visual and visual-associated cortex [19]. Complete cessation of migraine visual aura was showed in a study of 26 migraineurs with post-geniculate or visual cortex lesion [5].

In the retinal migraine, patient reports unilateral decreasing vision or complete visual loss, flashes, and a shade over a portion of the visual field. In most patients visual symptoms last less than 30 min. It may be difficult to differentiate monocular transient visual loss (TVL) or retinal migraine from a migraine aura because patients have difficulties in distinguishing monocular visual loss from visual loss occurring within the same hemifield of both eyes. The mechanism in common between migraine and TVL is the transient loss of perfusion related to vasospasm that may cause an impairment of the circulation to the choroid and/or optic nerve, but there is not a conclusive evidence cause-effect, even if in migraine-associated anterior ischemic optic neuropathy the onset of visual loss is often temporally related to the episode of migraine headache.

Treatment of migraine can have side effects on visual system structure. Ergotamine derivatives are known to cause vasoconstriction and may cause unwanted ischemic side effects such as stroke and myocardial infarction or ischemic optic neuropathy .

A possible link between migraine and normal tension glaucoma was evoked and the pathophysiology of both could be substained from a disregulation of the vascular system, as it is the Raynaud's phenomenon which sometimes coexists [20].

Ophthalmoplegic migraine is a rare subtype of migraine in which only one among the three ocular motor nerves is involved, often the third cranial nerve characteristically with sparing of pupil activity. The oculomotor palsy begins at the peak of a migraine attack and persists for days to weeks after the headache phase. The resolution is complete even if, rarely, a residual paresis may persist after repeated attacks. In the acute stage, MRI may show thickening and enhancement of the oculomotor nerve at its exit from the midbrain and the signal becomes less intense during the quiescent phase. Early treatment with steroids can accelerate the resolution of headache and ophthalmoplegia from weeks to few days. The pathogenesis of ophthalmoplegic migraine is still unknown and the hypothesis includes compression, ischemia, demyelination and vascular anomaly. It has been also proposed an involvement of the trigeminovascular system since neuropeptides released during the migraine attack cross the relatively open blood–brain barrier at the oculomotor nerve exit inducing a sterile inflammation and causing ophthalmoplegia [3].

Among migraineurs, 10–24%, mainly adolescent girls, are affected from basilar migraine, the so-called symptoms arise from the territory supplied by the basilar artery, the brainstem, cerebellum and the occipital cortex. Bilateral visual disturbance, diplopia, vertigo, dizziness, dysarthria, ataxia, paresthesias, fainting and loss of consciousness precede headache. The typical aura goes on for around 60 min. Individuals reporting migraine with brainstem aura have been found to carry mutations in the CACNA1A or ATP1A2 genes in some cases, but no causative mutation has been found across all subjects [21].

Another migraine manifestation can be isolated pupil dilation, occurring usually in young women sometimes alternating the side in different episodes. In some patients anisocoria increases in bright light and is associated with accommodation impairment suggesting a parasympathetic paresis; while in others can be due to sympathetic overactivity. The pupil may remain dilated for hours or weeks. There is no ptosis or ocular motility disorder differentiating this condition from oculomotor nerve palsy.

Differential diagnosis

The migraine aura, particularly when not associated with headache, is a diagnosis of exclusion. Imaging studies and laboratory tests should exclude neurologic disease, included seizures and central nervous system tumor, ocular pathologies, carotid or cardiac disease, thrombosis and connective tissue disease.

Persistent visual loss may occur as a result from stroke involving the posterior visual pathways. The precise relationship between migraine and stroke remains unclear, even if migraine with aura, oral contraceptives and smoke may increase the risk of stroke in female patients with migraine [22].

Conclusions

Visual and ophthalmologic signs and symptoms are commonly reported by patients with migraine. The relationship between the migraine aura and headache is not clear: the majority of patients with migraine never experience visual aura, many patients who have migraine with aura may also have attacks of headache without aura and sometimes aura without headache is reported. Ophthalmologists have a fundamental role in the differential diagnosis and establishing the amount of visual system involvement in migraine. Susceptibility to migraine seems to be caused by a hyper-excitability of the brain, lowering the threshold for the induction of CSD, a wave of spreading cortical hyperexcitation followed by depression, a process that most likely thought to be the underlying cause of aura. Different phenotypes of migraine may be possible and combined since during the attack some no-pain areas with visual activities may be involved in the CSD before or without the commitment of adjacent cortical pain regions so that some patients may complain only visual symptoms but not headache. Structural, functional and metabolic abnormalities within the visual system are on the basis of this hyperexcitability and imaging investigations are required to better diagnose and treat migraine.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to the publication of this article.

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Feature Article

The Visual System in Migraine: From the Bench Side to the Office

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Background.—Throughout history, migraine-associated visual symptoms have puzzled patients, doctors, and neuroscientists. The visual aspects of migraine extend far beyond the aura phenomena, and have several clinical implications.

Methods.—A narrative review was conducted, beginning with migraine mechanisms, then followed by pertinent aspects of the anatomy of visual pathways, clinical features, implications of the visual system on therapy, migraine on visually impaired populations, treatment of visual auras and ocular (retinal) migraine, effect of prophylactic migraine treatments on visual aura, visual symptoms induced by anti-migraine or anti-headache drugs, and differential diagnosis.

Results.—A comprehensive narrative review from both basic and clinical standpoints on the visual aspects of migraine was attained; however, the results were biased to provide any useful information for the clinician.

Conclusion.—This paper achieved its goals of addressing and condensing information on the pathophysiology of the visual aspects of migraine and its clinical aspects, especially with regards to therapy, making it useful not only for those unfamiliar to the theme but to experienced physicians as well.

Key words: visual system, migraine, migraine with aura, migraine aura, migraine treatment

Abbreviations: CADASIL cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CSD cortical spreading depression, FHM familiar hemiplegic migraine, MA migraine with aura, MoA migraine without aura, MUMS migraine with unilateral motor symptoms, TiACG topiramate-induced acute angle-closure glaucoma, V cortical visual areas

(*Headache* 2015;55;S1:84-98)

Translating to the clinical setting epidemiological and experimental findings is a challenging task. However, an understanding of the clinical aspects of a study might help us determine better treatment solutions. The clinical aspects of migraine have puzzled neuroscientists for decades. Bridging the clinical aspects of migraine to the results of the experiments designed to solve them is essential to stimulate a critical assessment of the clinical phenomena. It also helps demystify experimental findings.

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BASIC PRINCIPLES

Migraine Mechanisms.—Migraine is thought to be the result of the existence of several different conditions. Genetic factors have been strongly associated since the publication of the results of studies focused

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on twins showing the higher concordance rates for migraine among monozygous twins. More recent studies of familiar hemiplegic migraine (FHM) mutations reinforced the role of genetic abnormalities, more specifically, the CACNA1A and ATP1A2, among others, encoding an α1 subunit of the voltage-gated P/Q calcium channel and a NaK-ATPase, respectively. However, those findings were not found in common migraine, and genetic abnormalities are not alone able to explain the occurrence of migraine. This is evident whenever we face the inter- and intra-individual variations of the disease, which suggest that other factors, such as age, hormonal levels, psychosocial environment, metabolic changes and dietary triggers, play a significant role in the mechanisms of migraine occurrence.

Nevertheless, it is possible to observe the lack of an integrated physiopathology for migraine. The pathophysiology of migraine attacks may be summarized as follows:[1,2]

1. The premonitory phase, characterized by activation of various subcortical (posterolateral hypothalamus, midbrain tegmental area and substantia nigra, periaqueductal grey, dorsal pons) and cortical zones (occipital, temporal, and prefrontal) leading to nonfocal neurological symptoms such as mood swings, tiredness, neck stiffness, yawning, thirst, urination, nausea, and photophobia.
2. The aura mechanism may be exclusive to the occurrence of migraine with aura (MA) but the mechanisms underlying the pain phase are probably similar between MA and migraine without aura (MoA).
3. The cortical spreading depression (CSD) phenomenon is the best candidate responsible for the onset of aura. Moreover, it has the potential to trigger trigeminovascular activation through (1) extracellular ion shifts marked by the increase in extracellular potassium and glutamate and the decrease in extracellular calcium, all of which function as depolarizing forces; (2) the blood–brain barrier opening, which allows access of molecules implicated in nociception to the dura mater, a structure sensitive to pain; and (3) the involvement of the adjacent pial arteries and their trigeminal innervation.
4. Pial and extracerebral arteries may act as the source of pain. This is reinforced by the dilation of these vessels, which occurs in both MA and MoA. The authors of this paper propose to characterize migraine as a neurovascular condition including abnormalities in neural centers, such as the hypothalamus and brainstem areas, responsible for controlling the autonomic and cerebrovascular functions.
5. Migraine is subject to central modulation as occurring in the central processing of other types of pain.

A more complex scenario emerges when we consider autonomic stress and emotional factors – arising in areas not directly associated with nociception – in the process of migraine predisposition. The involvement of the limbic system and hypothalamus with the trigeminovascular pathway has been recently suggested to be a bidirectional trafficking mechanism by Burstein and Jakubowski. This model involves the higher centers, the trigeminovascular neurons, the superior salivatory nucleus, and the sphenopalatine ganglion, with mutual activation of the limbic system/hypothalamus and the trigeminovascular system.[3]

Anatomy of the Visual Pathways and Migraine.— Migraine mechanisms may generate symptoms related to dysfunction of several parts of the visual system.

Retina.—The first step of light stimuli is the retina.[4] The retina is subject to the occurrence of spreading depression[5] and, consequently, to the migraine aura. A recent paper reported on optical coherence tomography measured a significant thinning of the retinal nerve fiber layer, ganglion cell layer, and in migraineurs with aura as compared with migraineurs without aura and healthy controls.[6] Retinal migraine (aura) involves the occurrence of monocular positive phenomena or negative phenomena such as a progressive loss of vision that progresses from the periphery to the center, and back from the center to the periphery, a feature that might help to distinguish it from the spotty confluence of retinal vasospasm.[7,8]

Optic Nerves and Optic Chiasm.—The optic nerves and the optic chiasm are commonly not linked

to migraine pathophysiology, and their role in the migraine process appear to be only in regards to the transmission of the abnormalities originated in the retina and surrounding structures of the visual system.

Superior Colliculi, Pretectal Nuclei, and Suprachiasmatic Nucleus.—There is revealing information concerning a relationship of the aforementioned structures with migraine, in spite of the role of the superior *colliculi* in parasympathetic aspects of migraine,[9] in photophobia, and in the chronification of migraine.[10] Regarding the suprachiasmatic nucleus, Zurak has theorized that it may possibly be involved in the visual (and other) prodromal symptoms of migraine, such as photophobia.[11]

Optic Radiations.—The optic radiations are also not listed as relevant in migraine development, although visual quadrantanopsia auras may resemble optic radiations compromise.

Visual Cortex.—The visual cortex is perhaps the segment of the visual system that harbors most of the migraine visual system with the exception of photophobia. Cortical visual disturbances can be divided into negative (hemianopsia, quadrantanopsia, scotoma) and positive (phosphene, teichopsia, metamorphopsia, macropsia, micropsia, teleopsia, diplopia, dyschromatopsia, paleo-agnosia, hallucinatory disturbances) disorders.[12] Negative visual phenomena appear to involve mostly the primary striatal visual cortex, the visual unimodal association areas (V2, V3, V4) and other extrastriate areas (V3/VP, V3A, V4v).[13,14] Conversely, perhaps with the exception of phosphenes, the migraine positive visual phenomena seem to involve more frequently other areas, not only the primary visual area, and the associative heteromodal zones adjacent to the parieto-occipital fissures and those adjacent to the superior temporal sulci and the pre-occipital notch.[15] The participation of white matter tracts linking the visual areas to the frontal lobes, which generate atypical aura symptoms, has also been described.[16] Furthermore, the occurrence of migraine auras overriding dreams is an example of the complexity of the aura phenomena regarding its projection on to the imagery generated either by the visual cortex itself or by the hippocampal and parahippocampal lobes memory banks.[17]

THE VISUAL SYSTEM AND MIGRAINE: CLINICAL ASPECTS

Visual system abnormalities are frequently associated with migraine.[18,19] The visual aura is one of the most evident phenomena implicating the visual function in migraine. Photophobia is an important clinical feature and a criterion for the diagnosis of migraine.[20] Furthermore, some migraine subtypes, such as retinal, are characterized by the visual abnormalities. The mechanisms underlying the association between visual system and migraine have been scrutinized by recent studies.

Simple and Complex Visual Migraine Triggers.— There is extensive literature quoting intense light stimuli in the triggering of migraine attacks. Sunlight is mentioned by migraineurs as one of the main triggers of their attacks, and less frequently, the exposure to other sources of bright light is mentioned as well. However, complex visual stimuli may occasionally be found to be a trigger of MA attacks, such as in the case described by Cao et al.[21] In migraine attacks triggered by complex visual stimuli, the pattern of complex visual stimulus does not seem to be often stereotyped among different individuals, except one. For example, while the patient described by Cao et al had MA attacks triggered by watching a basketball while playing, we saw a patient whose migraine attacks were triggered by any kind of polka dotted tissues.

Photophobia and the Mechanisms of Visual Allodynia.—Photophobia arises in different conditions involving the anterior segment of the eye and some intracranial abnormalities, such as migraine. It is possible a difference exists between the mechanisms of the symptom arising in these 2 different scenarios. Although migraine-type photophobia is a frequent complaint among migraineurs, insufficient attention has been paid to this matter.[18]

The occipital cortex has a primary role in visual function and is the largest afferent pathway. An extremely dynamic structure shows a continuous neuroplasticity. This neuroplasticity is modulated by environmental and internal stimuli during the entire individual's lifespan, ie, the occipital cortex is influenced and as a result affects several other extra-occipital encephalic structures conditional to their functions.[22] During headache episodes and especially

during migraine, the occipital cortex has a pivotal role in which it contributes actively, affecting, and/or being influenced by several other ongoing neural abnormal activities.

In the course of a migraine aura episode, and even during MoA attacks, a hypoperfusion of the occipital lobe takes place, coined as "spreading *oligemia*" by Olesen et al.[23] This state of hypoperfusion seems to be related to the neural process of migraine rather than a cephalic pain display, since the occipital cortex *oligemia* persists even after the resolution of a migraine headache.[24] Repeated migraine episodes may lead to an abnormal resting (interictal) state of the occipital cortex,[25] and as a result illustrate the migraine-induced neuroplasticity.

The bulk of the basic research and clinical/paraclinical studies – which include psychophysical investigation, electrophysiologic methods, and functional neuroimaging – performed to clarify the visual system involvement in migraine consistently point to visual cortex hyperexcitability in migraineurs.[18,26] These findings are in agreement with the inferred role of the increased extracellular glutamate in FHM mechanisms of pain and with evidence of magnesium and mitochondrial abnormalities in patients with migraine.[26]

The mechanisms underlying the cortical hyperexcitability could be a matter of debate. As proposed by Chronicle et al, it is possible that a hypofunction of GABAergic interneurons in the occipital cortex exists, which may perhaps be responsible for the hyperexcitability, which is suggested to be essential for the initiation of CSD.[18,27]

A community-based study has challenged the relevance of the occipital cortex in migraine since the prevalence of migraine in blind individuals[28] is similar to the one experienced by the general population.[29] However, migraine attacks were found to be more severe in blind migraineurs than in visually normal individuals, a fact that proposes a relationship of the occipital lobe with the modulation of the headache.[30]

Multimodal integration at the cellular level is a feature found in some cortical zones. Bimodal neuronal zones are present in the premotor ventral zone, in the putamen, in the postcentral, and parietal *giri*, in Brodmann 7b area in the ventral intraparietal cortex.[31] These neurons may react simultaneously to both visual and tactile stimuli. The visual stimuli reach the visual cortex from where they project to the somatosensory cortex and vice versa. This physiologic mechanism allows the integration of visual and somatosensory information mainly for the face, arms, and upper trunk zones, leading to visual-spatial mapping.[32] These findings suggest that the sense of vision is a participant of the sensorial modules. The somatosensory-visual module is a quite well-known example of this physiologic arrangement. In this modular unit, the optic nerve and the trigeminal nerve display active participation.

Illustrating this interaction, we have shown that individuals who became blind before the age of 12 years have a lower pain threshold than visually normal controls.[33] This study suggested a modular arrangement between nociception and vision. Anatomically, the visual cortex of blind individuals is normal[34] as the cerebral blood flow, glucose metabolism, and oxygen consumption, proposing that in this scenario the occipital cortex is involved in different functions other than vision.[35-37] These neuroplasticity arrangements seem to occur up to the age of 14 years, an age coincident to puberty and with the reduction of supernumerary synapses in the occipital cortex.[38-40] In spite of having stronger migraine attacks than visually normal migraineurs,[30] blind migraineurs have higher pain thresholds,[33] validating the active participation of the occipital cortex in pain thresholds. We have demonstrated this participation in the past by showing migraineurs who displayed an interictal intense-light triggered reduction in the cranial and cervical pain thresholds in migraineurs when compared with normal controls.[41]

Noseda and Burstein define photophobia according to the reported symptoms and use this classification system to propose similar mechanisms of afferent integration present in subcortical areas:[42]

1. Exacerbation of headache caused by light: the nonimage-forming functions of the visual system, responsible for activities such as the regulation of the circadian rhythm and the adaptation of pupillary size to light, involve the intrinsically

photosensitive retinal ganglion cells. This pathway may explain the mechanism through which photic signals activate the trigeminovascular system, making use of a convergence of both systems in the posterior thalamus and projection to the somatosensory cortex.

2. Abnormal sensitivity to light: The same structure and convergence of the visual and trigeminovascular systems with projection to the visual cortex may explain the mechanism underlying the visual system activation by nociceptive signals.
3. Ocular pain induced by light (photo-oculodynia): Light may indirectly activate intraocular trigeminal nociceptors, a model for this phenomenon proposed by Okamoto et al.[43] The photic signals, in this model, activate sequentially the olivary pretectal nucleus, the superior salivatory nucleus, and the sphenopalatine ganglion which releases parasympathetic peptides that induce vasodilation, neurogenic inflammation, and trigeminal nociceptor activation.

In conclusion, the abnormal pain thresholds are found after the triggering of visual discomfort caused by light. It may well reflect a component of photophobia that could be coined as "visual allodynia."

Hallucinatory Visual Phenomena and the Nature of Migraine Aura.—In Greek, aura means "breeze," a significance that addresses the steadily progressive nature of the aura symptoms.[16] Leão was the first neuroscientist to speculate whether his findings of the "spreading cortical depression" could also be associated with migraine aura. Decades later, Lauritzen resurrected Leão's hypotheses, and the role of Leão's CSD was attested pivotal in the generation of MA symptoms, with a less intense but still relevant participation in MoA.[44] CSD seems to be recurrent in the visual and somatosensory cortical zones, but it is well known that *sulci* or cortical zones do not limit CSD, but that larger anatomical landmarks such as the Sylvian fissure are able to do so. However, CSD may reach other distant cortical zones, as described by Vincent and Hadjikhani.[16] Leão demonstrated in the rabbit's cortex that the CSD *phenomenon* was composed of a shorter excitatory phase followed by a longer inhibitory phase. Some authors with different statistical models employed to explain different aura patterns[45,46] have tried deciphering how these cortical phenomena translate to aura symptoms.

Clinical Aspects of Visual Aura and of Ocular (Retinal) Migraine.—The nature of the Greek word for aura ("breeze") must be remembered while clinically interviewing a patient presenting symptoms of MA: any "migraineur" reporting abrupt-onset visual or non-visual migraine auras must have their diagnosis challenged, since migraine auras usually display a steady progressive presentation.[7,20] The striking variety of visual symptoms of aura was well described by several authors, and the interested reader ought to take a look after the recent papers of Queiroz et al[47,48] and Aleci and Liboni.[49] The most puzzling cases are those of familial and sporadic hemiplegic migraine,[20] prolonged migraine aura without infarction,[20] migraine with unilateral motor symptoms (MUMS),[50] and migraine-related persistent visual phenomena.[51] Despite the great similarity, some of these syndromes combine or have isolated either positive (somatosensory, visual, auditory, vestibular) or negative (visual, somatosensory, and/or motor) phenomena. However, the physiological meaning of those symptoms may be different – while Goadsby hypothesized MUMS to be secondary to hemineglect,[52] the condition coined as persistent visual *phenomena* (a condition similar to migraine visual aura, which might last months to years) are more likely to be related to continuous excitatory *phenomena*.[51]

Retinal migraine is diagnosed by carefully studying the patient's history, but it may possibly be identified by more attentive patients. Symptoms consist of various positive or negative visual *phenomena*, which may progress to tunnel-like vision, sometimes reaching transient monocular blindness.[8,20] The exclusion of other etiologies is strongly recommended by experts in the subject matter.

DOES THE RELATIONSHIP OF THE VISUAL SYSTEM WITH MIGRAINE GIVE US THE POSSIBILITY OF SPECIFIC THERAPEUTIC INTERVENTIONS?

As with any other disease, the mechanisms may provide us with clues for the suitable therapeutic

method to be employed. In some surveys, exposure to bright light or to sunlight was one of the most frequently reported migraine triggers. Not only did many migraineurs report visual stimuli to trigger their migraine headaches, but among these, many also report visual stimuli to determine visual stress or discomfort.

While most texts concerning the treatment of migraine highlight avoidance of triggering stimuli, Martin challenged this approach, reasoning that coping with those stimuli would be more interesting.[53] Nevertheless, there are few available studies on the avoidance/modification of these stimuli on the prevention of migraine, such as: (1) patient or parents-answered surveys; (2) experimental studies; (3) case reports; (4) surveys on visually impaired populations. In this section, the non-pharmacological and pharmacological therapeutic approaches involving the visual system are reviewed and discussed.

Patient or Parents-Answered Surveys on Visual Migraine Triggers.—In a 2003 abstract, Francis[54] reported that a large proportion (60%) of 1800 pediatric and adolescent patients in a 4-year period of follow-up (drawn from an original population of 4900 patients diagnosed with migraine) identified visual stimuli as migraine triggers. Not surprisingly, 85% of mothers and 12% of fathers not only had a history of migraine but also seemed to share the same triggers. Patients were instructed to avoid triggering stimuli by wearing a hat with a wide brim, sunglasses, and make use of umbrellas in order to avoid sun exposure. The prevention of visual triggers decreased migraine frequency by more than 50% in 52% of the study patients. Unfortunately, the complete study has never been published in detail in an indexed journal.

Experimental Studies in Humans.—In 2002, Wilkins et al compared the use of "optimal" tinted spectacles with "control" (non-optimal) tinted glasses for the prevention of migraine.[55] Their trial included 21 migraineurs of whom 17 completed the study. The study population was not homogeneous since some patients seemed to become chronic, slightly before or during the trial, some patients abused analgesics and, for a single patient, prophylactic therapy had just been prescribed. The response to tinted glasses was tested by asking patients to choose between 10 different colored overlays to identify the one that best improved the accuracy of reading. Four patients dropped out at this phase. After a full optometric evaluation, the examiner, based on the patients' responses to the different colors tested, established the "optimal" chromaticity of the glasses. The patients were not told which was the "optimal" chromaticity. The majority of "optimal" tinted lenses were of various shades of blue. After a 1-month baseline period, "optimal" and "control" spectacles were used for 6 weeks interspersed by a 2-week washout. The frequency of headache was greater when the "control" tint was worn (1-tailed *t*-test; $t[16] = 1.417$, $P = .08$). This study had been preceded by an open-label pilot study, in which 20 patients were followed up for a range of 8 months to 4.5 years after they received the glasses (mean of 2 years, 1 month). Among the patients, 15 (75%) reported a decrease in the frequency of headaches after they began wearing the tinted glasses.

More recently, Huang et al proved that precision ophthalmic tints decreased cortical activation to visual activation of the occipital cortex in migraineurs, compared with gray spectacles or control colored lenses.[56] The study involved 11 migraineurs and 11 age- and sex-matched non-headache controls. Precision ophthalmic lenses not only decreased visual discomfort to an extent of 70% ($P = .005$), but also reduced cortical activation to stressful visual stimuli as measured by fMRI in several extra-striate cortical visual areas (V) such as V2, V3 ($P < .01$ and $P < .005$, respectively), V3A, and V4 ($P < .01$) (paired *t*-test). This study like others[57] suggests that colored tints can have therapeutic effects in cases with visually triggered migraine.

Case Reports.—A single case reported by our group described a patient whose computer's lower screen frequency (60 Hz) would trigger headaches, while this would not occur when a computer of the same model at a higher screen flicker frequency (75 Hz) was used.[58] We theorized that the 75 Hz screen frequency was far above the usual fusion frequency threshold and consequently prevented the patient from triggering a migraine episode. This kind of prevention might be important in devices such as the night vision goggles, worn by aircraft pilots. There is a single case report of

a pilot, claiming that spatial disorientation episodes were associated with a migraine episode, triggered by the scintillations in the screen of his night vision goggles.[59]

Surveys on Visually Impaired Populations.—A local survey in a visually impaired population provided us with an unexpected result: visually impaired individuals in Brazil had a migraine 6-month prevalence very close to that of the visually normal population.[28] Further research proved the migraine intensity to be greater in the visually impaired migraineurs than in non-visually impaired migraineurs, a discovery that suggested that visual stimuli were not essential for migraine expression or severity.[30] However, visually impaired migraineurs with a slight perception of light reported intense photophobia during their migraine headaches, and therefore reinforced the relevance of light avoidance even in this scenario.

THE TREATMENT OF VISUAL AURAS

Migraine auras, thought to be typically "innocent," may be disproportionally frightening to patients. There have been several reports on the effect of different migraine treatments administered during a migraine aura episode. Some demonstrated a substantial worsening of migraine aura with the use of subcutaneous sumatriptan.[60-62] Controlled studies have shown no effect of subcutaneous sumatriptan (6 mg)[63] or oral eletriptan[64] on migraine aura. A study reported a positive effect of oral sumatriptan (100 mg) on the migraine symptoms when administered during the aura phase.[65] Intravenous magnesium sulphate was reported to be effective[66] and superior to both dipyrone and placebo in the treatment of migraine auras.[67] A combination of *Ginkgo biloba* (60 mg), coenzyme Q10 (11 mg), and vitamin B2 (8.7 mg) given immediately after the beginning of an aura was reported to reduce the duration of migraine auras.[68] However, the study lacked a double-blind placebo-controlled design and patients could take their usual analgesic medication that was not detailed regarding type, dose, and timing.

However, the acute treatment of visual auras is reasonable only for patients with prolonged auras when the duration of the symptoms may justify therapy. In this scenario, recently sumatriptan was reported to prolong for several months a hemiplegic migraine attack in a single patient out of 76 treated patients.[69] Conversely, a case series reported on different oral triptans, on the symptoms of patients with basilar migraine, including controlling migraine aura, presented visual symptoms in 3 out of 13 patients.[70] We have reported on a single case in which prolonged migraine aura was improved by 100 mg of oral sumatriptan.[71] The use of triptans, irrespective of their efficacy, is challenged by the possibility of vascular complications, such as optic nerve ischemia,[72] a risk dismissed by Velentgas et al.[73] In a "proof of concept" open-label study of 11 individuals from 7 families conducted by Kaube et al, 25 hemiplegic migraine attacks were treated with 25 mg of intranasal ketamine each.[74] The 5 patients who responded to therapy and decided to keep on taking intranasal ketamine had their visual auras improved regarding duration and severity as well as the associated motor and/or somatosensory symptoms. A double-blinded, randomized parallel group-controlled study was conducted investigating the effect of 25 mg intranasal ketamine on migraine with prolonged aura in 30 migraineurs using 2 mg intranasal midazolam as an active control.[75] Each subject recorded data from 3 migraine episodes. From 30 patients, 18 completed the trial, 9 in each group. In both groups, the duration of the aura was decreased by 3 hours, but a significant reduction in aura intensity was observed only in the ketamine group. Two patients in each group presented visual aura.[75]

Small case series and case reports on patients whereby hemiplegic migraine attacks or attacks of migraine with long-lasting auras were controlled with intravenous verapamil have been published.[76-78] Most of those cases presented visual aura. We have reported a small retrospective case series of patients with hemiplegic migraine (n = 3, only 1 familial) and migraine with unilateral motor symptoms (n = 1).[79] Two attacks were treated in 3 patients and one in another patient. One of the treated patients had no response to intravenous ketamine. The doses of intravenous verapamil ranged from 5 to 7.5 mg. The neurological deficits were reversed using verapamil in all patients, but not one of our cases presented visual

symptoms.[79] Other medications have been reported to control prolonged visual auras, *status aura migrainosus*, either in hemiplegic migraine or in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) patients. These include orally administered acetazolamide (250 mg b.i.d. or t.i.d.),[80-83] oral divalproex (250 mg b.i.d. to 500 mg b.i.d.),[84] and intravenously administered valproic acid[85] or furosemide.[86,87] We have followed a single case of CADASIL with divalproate orally administered, the visual *status aura migrainosus* was controlled, with recurrence only once after 10 years in a single, short, and easily controlled episode. Migraine-related persistent visual *phenomena*[51] were reported to respond to lamotrigine, a membrane-stabilizing drug, although evidence is scanty.[88] The case of an elderly patient with a *status aura migrainosus* associated with contralateral carotid stenosis, whose aura cleared after endarterectomy was reported,[89] but it was unproven whether the patient did or did not take additional antiplatelet therapy.

THE TREATMENT OF OCULAR (RETINAL) MIGRAINE

Ocular or retinal migraine is a rare condition, in which a frequent monocular migraine aura impairs the monocular vision. Its diagnosis ought to be done only after the exclusion of other medical conditions. Given the potential risk of worsening any underlying vasospasm, medications with vasoconstrictive properties such as triptans and ergotamines should not be used. Although some patients respond to β-blockers, it is usually not recommended as a first-line agent because of their theoretical potential for arteriolar vasoconstriction.[90,91] In one patient with a long-standing history of migraine who experienced simultaneous bilateral retinal arteriolar spasm, treatment with sublingual nifedipine (10 mg), sublingual nitroglycerin (0.8 mg), and oral acetazolamide (500 mg) was effective.[92]

Episodes of ocular migraine may be prevented by the regular use of oral nifedipine, and perhaps by verapamil and few other drugs, but Evans and Grosberg favor the use of aspirin and/or neuromodulators such as valproate, topiramate, amitriptyline, and nortriptyline, reasoning that no treatment has been consistently tested.[8] In general, patients should be instructed to control hypertension and avoid smoking and migraine triggers such as stress, hormonal contraceptive pills and strenuous exercise.

EFFECT OF PROPHYLACTIC TREATMENTS OF MIGRAINE ON VISUAL AURA

Most trials on migraine prophylaxis have included patients with MoA and patients with MA or with both forms of migraine; only a few details of the preventative effect of treatment on migraine aura were described.

Few studies have focused on the prevention of migraine aura. The most well known are those on the effect of lamotrigine on migraine aura. In 2 double-blind trials, lamotrigine was effective in the prophylaxis of MA but not of MoA.[93-97] A review of a trial with topiramate has shown that it not only prevented both migraine with and without aura but also prevented the occurrence of migraine auras.[98] In a 6-month open-label trial of levetiracetam for the prophylaxis of MA, Brighina et al have shown levetiracetam to be effective on preventing both the aura and the headache.[99] More recently, in a proof-of-concept paper that reported both an experimental arm and a clinical arm, amiloride was tried in a group of 7 patients with medically intractable migraine with persistent aura who were followed up for 6 to 24 months.[100] All patients had persistent visual auras intermingled with other types of aura. Quoting the authors: "amiloride substantially reduced both frequency of aura and headache severity in four of seven patients receiving 10 to 20 mg/day." Side effects consisted of polyuria (n = 2) and mild reversible hyperkalemia (n = 1). The length of time needed for amiloride to become effective was not described.[100] A retrospective study on the effect of extended-cycle transvaginal ring contraception on migraine aura (transvaginal rings contained 0.120 mg etonogestrel/15 µg ethinyl estradiol) was recently published. Migraine auras were significantly reduced by this therapeutic approach, which also controlled menstrual-related migraine.[101] Since the cerebrovascular ischemic *phenomena* in patients bearing MA are related to aura frequency and to estrogen levels,

perhaps the effectiveness of this approach outweighs the risk brought by hormonal therapy. Flunarizine[102] and verapamil[76-78] were individually reported as effective in the prevention of hemiplegic migraine. The same is true for valproate and lamotrigine, which administered together or separately were reported to be effective for this population.[83] Papers consisted usually of case reports and small, open-label case series or retrospective studies, and results cannot be generalized. In our experience, oral verapamil in usual therapeutic doses fails to prevent prolonged auras, visual or not. A novel avenue of knowledge was brought by the recognition of the association of MA and patent *foramen ovale*. It was found that anti-aggregant drugs such as clopidogrel[103] and ticlopidine[104] were effective to prevent the associated migraine, including migraine aura. An earlier study had also shown picotamide (an European antiplatelet drug) prevented MA.[105] The effectiveness of anti-aggregant drugs to prevent migraine aura not associated with patent *foramen ovale* was never adequately tested.

VISUAL SYMPTOMS INDUCED BY ANTI-MIGRAINE OR ANTI-HEADACHE DRUGS

Ibuprofen can cause blurred vision, refractive changes, diplopia, color vision changes, and dry eye. Rarely, permanent vision and visual field loss may occur. Indomethacin may cause whorl-like opacities. Patients may complain of photophobia, and retinal pigment epithelium or retinal changes might occur. *Pseudotumor cerebri* can occur with any non-steroidal anti-inflammatory drugs.[106] Cyproheptadine and pizotifen may cause reduced tears, diplopia, dilated pupils, and increased intraocular pressure; β-blockers may lead to dry eyes, reduced accommodation, and decreased intraocular pressure; amitriptyline may result in diplopia, dilated pupils, and increased intraocular pressure.[107] Tricyclics' anticholinergic effects are known to cause blurred vision, usually because of cycloplegia and mydriasis. The affected eyes are not able to focus on near objects (presbyopia). Chlorpromazine may cause an abnormal pigmentation of the eyelids, interpalpebral conjunctiva, cornea, and lenses. It may also cause corneal keratopathy and rarely severe corneal edema. Chlorpromazine rarely induces pigmentary and granular retinopathies.[108] Abtahi et al comprehensively reviewed the effects of topiramate in the eye.[109] According to their review, the most common ophthalmic complication of topiramate is acute onset of ciliochoroidal effusion syndrome, which ranges from transient topiramate-induced myopic shift to severe bilateral topiramate-induced acute angle-closure glaucoma (TiACG), but massive choroidal effusion and detachment were also described. While myopic shift lead to visual blurring and myopia, TiACG causes visual blurring, luminous halo around objects, headache, and eye pain, symptoms that may be confused with those of migraine. Both condition remit at topiramate withdrawal but TiACG may not respond to medications usually used to treat this syndrome and may lead to cataract, uveitis, and permanent visual loss. Less frequent neurological symptoms described in patients taking topiramate include peripheral visual field defects, trichomegaly, blepharospasm, *myokymia*, *oculogyric* crisis, and periorbital edema, retinal degenerative conditions, retinal lesions and ocular inflammatory reactions.[109] Lithium was reported to cause eye irritation, downbeat nystagmus and rarely abnormal protrusion of the eyeball, and optic disc swelling (papilloedema).[108]

DIFFERENTIAL DIAGNOSIS

Despite the fact that primary headaches are still the main etiology underlying photophobia and visual aura, a word must be said regarding their differential diagnosis. Readers may find the paper by Shams and Plant summarizing and stratifying the medical approach to visual auras according to their clinical features and associated conditions of interest. The authors reason that patients who present visual auras without headache, visual auras lasting less than 5 minutes, or age above 40, without a history of migraine, ought to have their migraine diagnosis questioned. They also advocate that patients presenting stereotypical visual auras, change in the features of long-standing auras, or increase in the frequency of visual auras, persistent or unexplained visual field defect or *scotoma* following a typical visual aura and/or associated seizures, should be submitted to

neuroimaging.[110] The issue of the differential diagnosis between visual aura and visual focal seizures has been discussed elsewhere.[111-113] Panayiotopoulos has detailed several differences between the epileptic and the migrainous visual phenomena.[111,112] According to Panayiotopoulos, visual seizures normally last for seconds, in some cases 1-3 minutes; episodes with longer duration have been reported very rarely by patients.[112] Epileptic elementary visual seizures are often reported, occurring in multiple clusters, hallucinatory phenomena consisting of colored and small circular flashing or multiplying patterns in a temporal hemifield.[111,112] The differential diagnosis may perhaps prove to be hard in patients with Gastaut's idiopathic occipital lobe epilepsy, who present with elementary visual seizures followed by severe post-ictal headaches.[112-114] Occipital lobe vascular malformations may present with either occipital lobe visual seizures; those symptoms are related to occipital lobe apoplexy[115] or as migraine with visual aura.[116] Occipital lobe tumors may also display the same symptoms,[117] but in such cases, atypical features or associated neurological symptoms or signs are likely to lead to the correct diagnosis. Eventually, cerebrovascular conditions may present with aura-like symptoms. Kunkel noted that in contrast to migraine visual auras, visual symptoms related to transient ischemic attacks consist of static, dark dimming of vision lasting 3-10 minutes.[118] Vascular dissections of either the carotid arteries or the vertebral arteries may present with symptoms mimicking MA.[119,120] Retinal disease, recurrent emboli, coagulopathy, or vasculitis should be suspected whenever atypical visual symptoms are present and recurrent, with duration longer than 60 minutes.[118]

CONCLUSION

Subverting the words of Hamlet "I could be bounded in a nutshell, and count myself a king of infinite space,"[121] we should remark that this quite small but not so discrete topic "visual aspects of migraine" is quite rich on its clinical implications. Mastering this theme will help any neurologist to give more comprehensive and better care for his/her migraine patients.

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Visual motion processing in migraine: Enhanced motion after-effects are related to display contrast, visual symptoms, visual triggers and attack frequency

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Abstract

Background: Visual after-effects are illusions that occur after prolonged viewing of visual displays. The motion after-effect (MAE), for example, is an illusory impression of motion after viewing moving displays: subsequently, stationary displays appear to drift in the opposite direction. After-effects have been used extensively in basic vision research and in clinical settings, and are enhanced in migraine.

Objective: The objective of this article is to assess associations between (1) MAE duration and visual symptoms experienced during/between migraine/headache attacks, and (2) visual stimuli reported as migraine/headache triggers.

Methods: The MAE was elicited after viewing motion for 45 seconds. MAE duration was tested for three test contrast displays (high, medium, low). Participants also completed a headache questionnaire that included migraine/headache triggers.

Results: For each test contrast, the MAE was prolonged in migraine. MAE duration was associated with photophobia; visual triggers (flicker, striped patterns); and migraine or headache frequency.

Conclusions: Group differences on various visual tasks have been attributed to abnormal cortical processing in migraine, such as hyperexcitability, heightened responsiveness and/or a lack of intra-cortical inhibition. The results are not consistent with hyperexcitability simply from a general lack of inhibition. Alternative multi-stage models are discussed and suggestions for further research are recommended, including visual tests in clinical assessments/clinical trials.

Keywords

Migraine, adaptation, motion perception, motion after-effect, contrast, visual perception, cortical processing, visual triggers, flicker, stripes, photophobia

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Introduction

Migraine is a common neurological condition that is characterised by recurrent and severe headaches. Most people will have experienced headaches where they can identify the cause, such as headaches resulting from stress, tiredness, dehydration or, in women, hormonal factors. For many, these headaches are easily resolved with rest, sleep, or over-the-counter medication. The same factors, however, can trigger migraine as well as other types of headache, as can certain environmental stimuli, such as visual patterns, flickering lights, noises and smells (1–5). In the case of migraine, the headache and associated symptoms are more serious and, in many cases, migraine can have a debilitating effect on a person's everyday life, impacting on work, education, social and family activities, particularly when people susceptible to environmental or visual triggers encounter them unexpectedly. In this report, the term *migraine* refers to headaches and associated symptoms that meet the diagnostic criteria for migraine (see Method section), and the term *headache*

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refers to other, benign, headaches experienced by the non-migraine/control comparison group.

Stripes and flicker are ubiquitous in the environment. People can be exposed to flicker from sunlight through trees or gratings, from badly maintained lighting, by working in environments that are lit with older fluorescent lamps operated at 50 or 60 Hz, by using liquid crystal display (LCD) screens with a flickering back-light or cathode ray tube (CRT) screens that have refresh rates less than 100 Hz. Flicker appears in images on television (TV) and in the cinema and, more recently, in the images displayed on projection screens at subway/train stations and in pubs and bars. Stripes appear on clothing, escalator treads, gratings, window blinds and some art designed for public spaces. Glare can result from windows, from halogen or light-emitting diode (LED) spotlights, from LED car head and tail lights, and from other overhead lighting that is visible in the peripheral field of view. Inadvertent, and thereby unexpected, exposure to these migraine and headache triggers can severely disrupt a person's quality of life as, if it triggers migraine or headache, it affects their ability to work, study, or have family or social interactions.

Symptoms associated with migraine, such as photophobia and phonophobia, nausea and vomiting, and intense, pulsating pain exacerbated by even routine physical activity, explain the frequent anecdotal reports that the best solution is to rest in a quiet, dark room and try to sleep. In migraine with aura, other transient neurological symptoms (commonly visual, sometimes somatosensory, sometimes involving speech) can further impact on people's ability to interact with the world and the people around them. Aura symptoms usually precede the headache by up to 60 minutes and the sensory ones typically move or spread during that time.

Aura symptoms vary in severity. The visual symptoms usually involve a partial loss of vision, often in one quadrant or hemifield, which is preceded by positive symptoms superimposed on whatever the person is looking at. The positive symptoms include the classic fortification spectra, which is a jagged or zigzag collection of lines that starts centrally and grows, shimmering, over time. Others report simpler stars and phosphenes, or they have the impression of looking at the world through running water. People also report double vision, or tunnel vision, a loss of vision, or more elaborate distortions such as in the relative sizes of parts of images (or of the person's own body image). Somatosensory aura symptoms typically involve pins and needles, tingling or numbness on one side of the face or body, but can extend to hemiplegia. The reported language difficulties are reminiscent of either of the aphasias described by Broca (difficulty finding appropriate words), or Wernicke (fluent output but little content). Evidently, people who experience these symptoms will have a loss of productivity at home, work or in education and a reduction in their quality of life beyond that which results from a severe headache.

The pathophysiology underlying the variety of symptoms involved in migraine is still not entirely understood despite numerous psychophysical, electrophysiological and imaging studies. Visual function has been frequently tested in migraine, in between attacks, due to (i) the ability of visual stimuli to induce a migraine attack, (ii) the intense sensitivity to light (photophobia) that patients typically experience during an attack and (iii) the fact that aura symptoms are commonly visual (4–8). Some people with migraine also report sensitivity to light in between attacks, and use sunglasses to try to alleviate it. Although these issues have motivated research into visual processing in migraine, there has been relatively little research into how they may all be related. Most of the literature has focussed on visual triggers (see Shepherd (5) for a review). The present study sought to assess associations between visual triggers, visual symptoms and performance on a visual task using the perception of motion.

Many visual tasks have been employed previously to compare performance in migraine and control groups, involving, for example, the perception of attributes such as colour, orientation with real and illusory lines, flicker, visual discomfort, as well as performance differences using visual search and visual masking tasks (reviewed in Shepherd (8)). There have also been a number of studies that have examined several aspects of the perception of motion. For example, performance on visual motion-processing paradigms such as pattern adaptation, threshold discrimination and threshold detection using local, global and relative motion tasks has been reported to differ between migraine and control groups. Generally, when there are group differences, the migraine group's performance is impaired (9–12). Although different authors often propose different models of anomaly, there is a general consensus that abnormal cortical processing is an underlying factor in the pathophysiology of migraine and underlies these group differences in motion perception.

The experimental paradigm used here, pattern adaptation, has recently revealed large differences in performance between migraine and control groups (13,14). Pattern adaptation may involve adaptation at multiple stages within the visual system, from the retina to early and later cortical areas, but it certainly involves the cortex and reflects specific interactions between groups of neurons (13–16). Current understanding of these interactions makes pattern adaptation an ideal tool to assess proposed models of cortical function in

migraine. In pattern adaptation, participants simply look at a display for some time, or 'adapt' to the display, and then selective effects of the adaptation on the perception of subsequent displays are examined. Any selective effects, or illusions, are described as after-effects of the adaptation, and have been used to infer the existence of neurons or pathways selective for particular attributes of the adapting display long before their existence was confirmed with single neuron recordings.

It is now known that, early in the visual system, the visual scene is effectively deconstructed, with specialised pathways and areas for the coding of different attributes such as motion, orientation, spatial frequency, depth, colour, and more. This separation begins as early as the retina and continues throughout the early and later visual cortical areas. One clear indication that some of the effects of adaptation are cortical is their ability to transfer inter-ocularly: that is, if the adapting display is viewed with one eye only, but the test display is presented to the other eye, the after-effect/illusion is still seen, although it may be at a weaker intensity (15,16). Binocular cells, which are activated by displays presented to either eye, are first found in abundance in the primary (striate/V1) visual cortex (17,18). After-effects have been used as a non-invasive way to assess the basic organisation of the visual system and, subsequently, to assess models of cortical function in clinical conditions such as epilepsy (19,20), schizophrenia (21,22), Parkinson's disease (21) as well as migraine (13,14,23).

The motion after-effect (MAE) is the illusory impression of motion that is experienced after steadily gazing at a moving pattern. If an observer looks at a waterfall for a few minutes and then transfers their gaze to the foliage beside the fall, the foliage appears to drift upwards, the opposite direction to the original motion (15,24). The effect can be seen after prolonged exposure to coherent motion in any particular direction, or other moving displays such as those that expand, shrink, or rotate. Once the motion stops, any subsequently presented display seems to drift in the opposite direction.

The MAE reflects adaptation in direction selective neurons tuned to the direction of motion presented during the adapting display (8,25–28). Cortical neurons produce a steady low level of spontaneous activity when not engaged by any stimulus. If a visual display contains elements with a certain motion direction and speed that activates particular neurons then, initially, they will respond vigorously. Over time, however, their response declines and, when the pattern is removed, the neurons appear unresponsive for a period of time as they take time to 'recover'. During that time, the spontaneous activity of all other neurons sensitive to different motion directions exceeds that of the suppressed neurons. This produces a biased distribution of spontaneous activity that, overall, is similar to activity produced by slow motion in the opposite direction and results in the perceived after-effect (29,30). How long the adapted neurons remain suppressed, and hence how long the illusion persists, depends on several factors, one of which is the contrast of the adapting and test displays. Keck et al. (31) reported that the magnitude of the MAE increased with increasing adaptation contrast or with decreasing test contrast, i.e. it was maximal for high adapting contrasts paired with low-test contrasts. It was concluded that the imbalance in activity between adapted and unadapted cells was greater for low-test contrasts than for high, which resulted in the prolonged MAE. Shepherd (13,14) found that the MAE was more pronounced in migraine, that is, it lasted longer than in the control group when using medium- or high-contrast adapting and test displays (Michelson contrasts of 30% (reference Shepherd (14)) or 78% (reference Shepherd (13))).

Various authors have reported increased pattern sensitivity in migraine, also referred to as pattern glare or visual discomfort (3,14,32–37). These terms refer to the perceptual distortions (colours, shadowy shapes, shimmer and/or motion) and discomfort that can be experienced when viewing high-contrast, mid-spatial frequency, striped patterns. Some of the perceptual distortions have been attributed to fixation instability and accommodative changes, whereas others have been attributed to an abnormal spread of cortical activation to neighbouring neurons due to the massive excitation generated by the striped pattern (see Shepherd (8) for further details). Shepherd (13,14) reported positive correlations between MAE duration and pattern sensitivity: the MAEs experienced by those who saw illusions in high-contrast striped patterns were longer than those who did not. These high-contrast patterns are reported to be capable of inducing migraine if viewed for prolonged periods of time. Shepherd (13,14) also reported positive correlations between the MAE and visual migraine triggers: the MAE experienced by those who reported visual stimuli could trigger their attacks were longer than those who did not.

Here, the relationships between the MAE and display contrast, various visual migraine triggers and visual symptoms were explored. Trials consisted of three test contrasts (high, medium and low). The adaptation contrast was kept constant (medium). Based on previous research (31), larger effects were predicted for low- compared to high-contrast test displays in both groups. Several group differences were expected: (i) the migraine groups (with and without aura) were predicted to have longer MAEs than the control group across all test contrast conditions; (ii) the MAEs were predicted to be longer for those in the migraine groups

who reported visual triggers and visual symptoms; (iii) there would be no significant differences between the migraine sub-groups with and without aura (13,14). The earlier work used a composite measure of susceptibility to visual triggers, whereas here individual visual triggers and symptoms were examined separately.

Method

Participants

Twenty-two migraine and 11 control participants were recruited from advertisements and an existing migraine database at Birkbeck College, London. Participants received a small honorarium for their time and expenses. There were 11 migraine participants with visual aura (VA, nine female, two male, mean age ± one standard deviation (SD): 29 ± 5 years, range 22–36 years, mode 24 years, median 30 years); 11 migraine participants without aura (MO, 10 female, 1 male, age: 27 ± 6 years, range 21–41 years, mode 21 years, median 28 years) and 11 control participants (nine female, two male; age: 30 ± 6 years, range 23–42 years, mode 21 years, median 28 years). Sample size is consistent with previous research.

All participants completed either a migraine or a headache questionnaire, detailing the characteristics of their migraine/headache symptoms, their frequency and duration, and possible migraine/headache triggers. The trigger list included visual stimuli: flickering light; striped patterns; alternating light and shade (such as dappled sunshine, transitions from sunshine to shade or vice versa); and other visual stimuli that they volunteered. Examples of these other visual stimuli were lattices, glare, high contrasts (e.g. sun reflected off chrome or water), computer use, TV and cinema, particularly three-dimensional (3D) cinema. Participants were asked if each item commonly, occasionally or never triggered migraine or headache. The data were coded as yes (commonly or occasionally), or no, for each item.

All in the migraine group fulfilled the International Headache Society (IHS) criteria for migraine (38). None in the control group experienced regular or severe headaches that fulfilled IHS criteria. Of the control participants who reported having headaches, they were tension type, sinus related, or due to dehydration. All testing was performed when participants appeared symptom free and no participant had experienced a migraine/headache 48 hours on either side of the test session. None of the participants were on prophylactic medication for any condition, nor had they taken any acute medication within 48 hours of the test session. None reported having any other neurological condition, nor any condition that can affect eyesight. All participants had a monocular and binocular visual acuity of at least 20/25, with or without optometric correction.

The study received ethical approval from Birkbeck's Department of Psychological Sciences Ethical Committee. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki (1991).

Apparatus/Materials

MAE. The displays were created using experimental scripts developed in C in conjunction with C routines from the Video Toolbox (39). The stimuli were presented on a 21-inch flat-screen CRT monitor (LaCie) connected to an Apple Macintosh G4 computer. The CRT monitor had a spatial and temporal resolution of 1280×960 pixels, and 100 Hz, respectively. Trials consisted of an adapting and test display that together elicited the MAE.

Adapting display. A 14-degree square window displayed random light and mid-grey pixels (average luminance = 30 cdm^{-2}, Michelson contrast = 30%) moving coherently upwards at a speed of 3 degrees/second. The adapting display was presented for 45 seconds. Participants were seated 60 cm from the monitor in an otherwise dark room. The experiment consisted of 12 trials, divided into three blocks, one for each test display contrast (the adaptation contrast was always the same). Block order was randomised. Thus, the experiment had a mixed (3×3) quasi-experimental design, with contrast as the within-subjects factor and group as the between. The experiment was preceded by six practice trials (two for each test contrast level). During presentation of the adapting displays, participants were asked to look at a fixation point at the centre of the screen whilst paying attention to the whole display. Apart from a change in CRT size, the adapting displays (contrast, duration, size, speed) were identical to one of the conditions used previously by Shepherd (14). Test display contrast, however, differed to that earlier study: the medium test display contrast was the same in both studies, but, in this study, a higher and lower contrast test display was added (see below).

Test displays. Immediately after adaptation, participants were presented with a test display. Test displays contained random, stationary, light to dark-grey pixels, which resembled that of a snapshot taken of a detuned TV. Three different contrast test displays were used – high (Michelson contrast 78%), medium (30%) and low (0.1%). All test displays had the same mean luminance as the adapting display (30 cdm^{-2}). The presentation of a test display immediately after the adapting display elicited the illusion of slow, downward motion.

When the stationary test display appeared, participants were asked to try not to blink and to indicate when the illusory motion stopped by pressing a key on the computer keyboard. The experimental session lasted between 75 and 90 minutes. Participants initiated each trial with a key press and so could sit quietly between trials, in the darkened room, if they wished to pause or take a break. In between trials, the CRT displayed a uniform grey screen (luminance 30 cdm^{-2}) together with a small, centrally located, information window asking participants to push the enter key to continue with the next trial. The information window also informed participants whether the next trial would be the same (which occurred four times in succession within each block of trials); or whether the contrast of the test displays was to change at the start of a new block of four trials. As with all the previous studies (11,13,14,23), an experimenter was present throughout the experimental session to ensure the participants understood the task and were looking at the adapting and test displays.

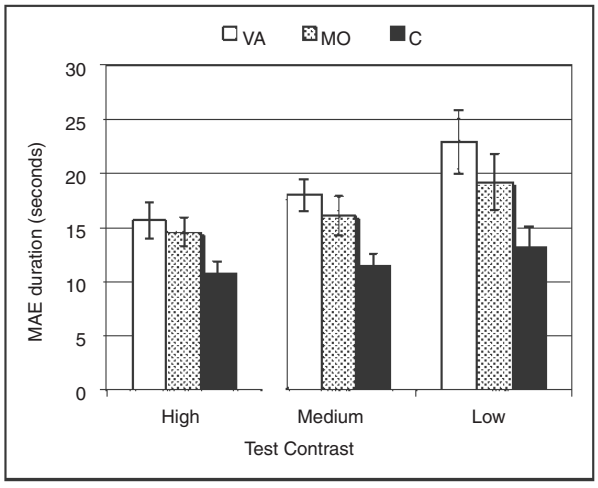

Figure 1. MAE data: Means (±SE) of the MAE duration for the migraine and control groups for high-, medium- and low-contrast test displays. MAE: motion after-effect; VA: migraine with visual aura; MO: migraine without aura; C: control group; SE: standard error.

Results

The data were assessed using PASW statistics version 20 (SPSS Inc, Chicago, IL, USA). The data from each group were normally distributed (Kolmogorov-Smirnov tests, $p > 0.05$), so group differences were assessed with analysis of variance (ANOVA), *t*-tests, Pearson's correlation coefficient (r) and the point-biserial correlation coefficient (r_{pb}). When sphericity was violated in the ANOVA (which occurred for effects of contrast, see below), the degrees of freedom were adjusted using the Greenhouse-Geisser epsilon.

Average MAE durations for each group in each condition are shown in Figure 1. Several trends are clear. Overall, as expected, the MAE lasted longer in both migraine groups than in the control group for all three contrast test displays, and the MAE was greatest in those with VA. Secondly, high-contrast test displays produced the shortest MAEs and low contrast, the longest, for all three groups. This was also as expected. A three (group) × three (test display contrast) mixed ANOVA produced a significant main effect of group [$F(2,30) = 6.5$, $p = 0.005$] confirming the overall MAE duration (collapsed across test display contrast) was greater in the migraine groups. Three planned comparisons revealed that the overall MAE durations for the VA and MO groups differed significantly from the control group (VA vs C: $p = 0.003$; MO vs C: $p = 0.028$; one-tailed tests, Bonferroni corrected), whereas they did not differ significantly from each other ($p = 0.93$, two-tailed test, Bonferroni corrected). The main effect of contrast was significant, confirming that low contrast test displays elicited longer MAEs than high [$F(1.7,\ 50.1) = 10.4$, $p < 0.001$). Pairwise comparisons revealed that, collapsed across groups, the MAE for the low- and high-contrast test displays differed significantly ($p = 0.002$), as did the MAE for the medium- and high-contrast test displays ($p = 0.02$) whereas the MAE for the low- and medium-contrast test displays did not differ significantly ($p = 0.21$, all comparisons Bonferroni corrected). The group × contrast interaction was not significant [$F(3.3,\ 50.1) < 1$, $p = 0.45$].

Scores from the questionnaire items that dealt with light, visual symptoms and potential migraine/headache triggers are presented in Table 1. The migraine participants were asked about their migraines, the control participants were asked about their headaches. As expected, more people in the migraine groups reported visual symptoms, during and between attacks, such as photophobia and light sensitivity, compared to the control group. Similarly, more people with migraine endorsed the various visual triggers compared to the control group. At least one visual trigger was endorsed by 20 of the participants (six VA, nine MO, five C), two were endorsed by 14 (five VA, five MO, four C), three were endorsed by seven (three VA, four MO, 0 C) and just one endorsed all four options (one VA). The most frequently endorsed visual trigger was flicker (16/33), followed by striped patterns and 'other visual stimuli' such as TVs, computer screens or cinema (9/33 each, see Table 1 for a breakdown by group). The most frequently endorsed pair of visual triggers was flicker and stripes (four VA, four MO, one C). Also included in Table 1 are averages for migraine and/or headache frequency and the time elapsed since the last migraine or

Table 1. Columns labelled VA, MO, C: Migraine and headache characteristics related to light, visual triggers and migraine frequency.

				r TEST DISPLAY CONTRAST			r_{pb} TEST DISPLAY CONTRAST		
	VA	MO	C	High	Medium	Low	High	Medium	Low
Number with photophobia during migraine/headache ($N = 33$)	10	10	2				0.32[a]	0.43[a]	0.45**
Number with light sensitivity between migraine/headache ($N = 33$)	2	5	3				0.04	0.05	0.27
Average number of days since last migraine/headache ($N = 33$)	14 (4)	10 (2)	55 (23)	−0.29	−0.29	−0.36			
Average number of migraines/ headaches in last 3 months ($N = 33$)	6 (2)	7 (2)	1 (—)	0.23	0.56[a]	0.46[a]			
Average number of migraines/ headaches in last 12 months ($N = 33$)	34 (12)	27 (6)	6 (2)	0.21	0.46[a]	0.51[a]			
Average number of years with migraine ($N = 22$)	13 (2)	13 (2)	—	−0.27	0.1	−0.22			
Number reporting visual triggers of migraine/headache ($N = 33$)									
Flicker	5	7	4				0.07	0.21	0.34[a]
Stripes	4	4	1				0.27	0.56[a]	0.51[a]
Light and shade	1	4	2				−0.06	0.07	0.02
Other visual	4	3	3				−0.15	−0.19	−0.13
(e.g. Television, computer, cinema)									
Number reporting visual triggers of migraine ($N = 22$)									
Flicker	5	7	—				0.06	0.25	0.36[a]
Stripes	4	4	—				0.13	0.52[a]	0.42[a]
Light and shade	1	4	—				−0.004	0.20	0.10
Other visual	4	3	—				−0.19	−0.22	−0.14
(e.g. Television, computer, cinema)									

Standard errors are in parentheses. Columns labelled r (Pearson's correlation coefficient) and r_{pb} (point-biserial correlation coefficient, for yes/no questionnaire answers) show the associations between each of the questionnaire items and the duration of the MAE with each contrast of the test displays (high, medium, low). Pearson's and point biserial correlation coefficients. [a]Significance at $p < 0.05$; **$p < 0.005$; bold upright: one-tailed tests, based on previous research; bold italic: two-tailed tests. N = number of participants; VA: visual aura; MO: migraine without aura; C: control; MAE: motion after-effect.

headache. The migraine groups reported more frequent headaches and had experienced headache more recently than the control group.

Shepherd (13,14) reported that the length of the MAE in migraine was greatest in those who reported having visual migraine triggers. This association was confirmed here for striped patterns and MAE duration with the medium- and low-contrast test displays (medium: $r_{pb(22)} = 0.52$, $p = 0.01$; low: $r_{pb(22)} = 0.42$, $p = 0.03$, one-tailed tests), and for flicker and MAE duration with the low-contrast test displays ($r_{pb(22)} = 0.36$, $p = 0.04$, one-tailed, see Table 1). These associations persisted when the migraine and control groups were combined (Table 1), which will be returned to in the Discussion (striped patterns as a trigger correlated with MAE duration with the medium- and low-contrast test displays; flicker as a trigger correlated with MAE duration with low-contrast test displays: $r_{pb(33)} = 0.56$, $p = 0.001$; $r_{pb(33)} = 0.52$, $p = 0.001$; $r_{pb(33)} = 0.34$, $p = 0.03$; respectively).

Photophobia during either a migraine or headache correlated significantly with the MAE duration for each test display contrast (high: $r_{pb(33)} = 0.32$, $p = 0.03$; medium: $r_{pb(33)} = 0.43$, $p = 0.01$; low: $r_{pb(33)} = 0.45$, $p = 0.01$; one-tailed tests). The MAE duration for the medium- and low-contrast test displays also correlated significantly with the frequency of migraine and headache (three-month frequency, medium contrast: $r_{(33)} = 0.56$, $p = 0.001$; low contrast: $r_{(33)} = 0.46$, $p = 0.01$; 12-month frequency, medium contrast: $r_{(33)} = 0.46$, $p = 0.01$; low contrast $r_{(33)} = 0.51$, $p = 0.004$; two-tailed tests; cf. Shepherd (13,14)). See Table 1 for full details of the correlations between MAE duration for each test display contrast and each questionnaire item. For the migraine group alone, there was a significant association between the MAE duration for the medium-contrast test displays and the number of days since the last migraine attack ($r_{(22)} = -0.41$, $p = 0.03$, one-tailed) and migraine frequency assessed over the last three months ($r_{(22)} = 0.46$, $p = 0.02$, one-tailed). There was a trend for an association between the MAE duration for the medium-contrast test displays and migraine frequency assessed over the last 12 months, and there was a significant association between the MAE duration for the low-contrast test displays and migraine frequency ($r_{(22)} = 0.34$, $p = 0.06$, $r_{(22)} = 0.44$, $p = 0.03$, one-tailed tests).

Discussion

As expected, the MAE in the migraine groups lasted longer than in the control group for all test display contrasts, and the low-contrast test displays produced the longest MAEs for both groups. Furthermore, as predicted, the MAEs were longer for those with visual triggers (striped patterns and flicker) and visual symptoms (VA and photophobia). Nevertheless, as has been found before, the differences between the migraine subgroups with and without aura were not statistically significant. Shepherd (13,14) suggested that (i) there may be a continuum of cortical anomaly in migraine regardless of aura symptoms, rather than qualitative differences between migraine subgroups, and that (ii) studies that do report differences between the migraine sub-groups, with and without aura, may have recruited participants for whom migraine classification co-varies with other factors, such as pattern sensitivity or susceptibility to visually triggered migraine. The associations between MAE duration and visual triggers reported here are consistent with these suggestions. As mentioned, the earlier work used a composite measure of susceptibility to visual triggers, whereas here individual visual triggers and visual symptoms were examined separately (Table 1). Photophobia and sensitivity to stripes and flicker, as migraine triggers, were all associated with the duration of the MAE: those who indicated these questionnaire items were migraine triggers had longer after-effects than those who did not.

Several members of the control group reported similar headache triggers (flicker, striped patterns, patterns of light and shade – transitions from light to dark, or vice versa or dappled sunshine – and, when asked to volunteer other headache triggers, cited visual items that were similar to those reported by the migraine group, such as, TV and cinema, computers, or bright sunshine when the sun is low in winter). This is consistent with a previous study of 180 participants (132 with migraine) which found that 60% of the migraine group, and 15% of the control group, cited similar visual stimuli as reliable migraine/headache triggers (5). Although visual triggers were more commonly endorsed by the migraine group, clearly similar features of the visual environment can induce headache as well, which would merit further study as it may lead to guidelines to influence the design of the environments in which people live and work to minimise the inadvertent triggering of both migraine and headache (see also Debney (1), Harle et al. (4) and Elias et al. (58)). This is returned to at the end of the Discussion.

The current finding of prolonged MAEs for low-, compared to high-, contrast test patterns is in line with those of Keck et al. (31), who also found longer MAEs for lower-contrast test patterns. As mentioned in the Introduction, the MAE is caused by a biased distribution of activity in direction-selective cells throughout the visual pathways from the retina to cortex, but certainly involving the cortex. The perception of something as stationary occurs only if cells responding to all directions exhibit the same level of activity. Once a set of direction-selective cells is suppressed, by adaptation, the overall distribution of activity in all cells tuned to all motion directions is biased and will give rise to an MAE. Thus, the after-effect results from a reduced response from adapted neurons, which is detectable against the activity generated in the whole population of direction-selective cells by the subsequent test displays (27–30,40). As soon as the adapting motion stops, however, the adapted cells start to recover and the length of that recovery, together with any residual response to the test patterns, determines the duration of the MAE. Since direction-selective cortical cells are also responsive to contrast, there would be a larger residual response in the adapted cells to the high-contrast test patterns than to the low, resulting in smaller MAEs for the high-contrast test patterns.

While speculative, this account can explain longer MAEs in migraine: if the residual response of the adapted neurons to each test display in the migraine group was lower than that in the control group, the result should be a more pronounced MAE in migraine,

as reported here. Consistent with this suggestion, there are reports that contrast sensitivity is impaired in migraine (33,34) and is related to relative motion thresholds (11). If contrast sensitivity is impaired, people with migraine viewing patterns of any contrast may see those patterns as having a lower contrast. Neither contrast sensitivity nor relative motion thresholds, however, involve adaptation. Recent research has, consequently, examined contrast sensitivity and MAE duration in the same participants to determine any formal associations between these two aspects of perception (23).

Shepherd (8,14) discussed various models of cortical function in migraine and concluded that prolonged MAEs are not consistent with a general cortical hyperexcitability. An early model suggested that hyperexcitability, in migraine, could result from a lack of cortical inhibition (35,41,42). Various neurophysiological and pharmacological studies have shown that inhibition is not, however, involved in adaptation in the visual cortex (striate), at least in cats (43,44). A simple lack of cortical inhibition in migraine is unlikely to explain the group differences reported here. Shepherd (13) instead suggested prolonged MAEs in migraine were consistent with a lack, or extended suppression, of cortical *excitatory* connections, or *increased* cortical inhibition in migraine.

Another model of cortical hyperexcitability in migraine is that it leads to greater background noise in the visual system and a greater response to incoming signals (10). If both signal and noise were elevated in proportion in migraine, then there would be little reason to expect differences between the migraine and control groups. Any greater suppression from larger signals elicited by the adapting displays would be lost in the greater background noise elicited by the test displays.

A third model has proposed hyperexcitability in migraine that results in increased general noise in the visual system, without entailing a greater response to incoming signals (9). Greater noise, against which the MAE signal must be detected, should produce weaker MAEs, as the MAE signal would be more readily masked by the elevated background noise. Again, this model is not supported by the present data. Furthermore, tasks designed to measure internal noise in the visual system have found no differences between migraine and control groups (12).

Fourth, hyperexcitability could raise the activity of direction-selective cells to a uniformly higher rate without increasing variability. In this case, the neuronal response elicited by a person with migraine may be comparable with another without migraine viewing a higher-contrast pattern, analogous to the increase in firing rate with contrast that is observed in direction-selective cells in physiological studies (45). This proposal appears consistent with pronounced aftereffects in migraine: stronger activity during adaptation could subsequently produce greater suppression in adapted cells. The test displays would elicit a uniformly higher level of activity in unadapted cells, so the dip in the activity of adapted cells should be readily detected. Because the MAE is maximal for low-contrast test displays combined with equal or higher-contrast adapting displays (30,31,46), however, this is also an unlikely explanation. Moreover, as mentioned above, it is not consistent with reports of impaired contrast sensitivity in migraine. Impaired contrast sensitivity should result in people with migraine perceiving the adapting and test display contrasts as *lower*, not higher.

An alternative explanation for prolonged aftereffects is that they are related to the reported lack of habituation and even increased amplitudes of visual evoked potentials (potentiation) in migraine, which may result from low cortical preactivation or hypoexcitability (reviewed in Tibber and Shepherd (47)). Habituation and adaptation share certain similarities: habituation is a decline in response to repetitive stimuli, whereas adaptation is a decline in response to continuous stimuli. Both reduce redundancy, protect against response saturation and conserve energy. Despite these similarities, a lack of habituation is clearly not mirrored by a simple lack of adaptation. During the adaptation, however, a potentiation of response over time would mean that, by the end of the adaptation, neurons tuned to the adapting motion would have responded more strongly, resulting in a greater suppression. To assess this explanation, it would be useful to compare migraine and control groups' performances for a range of shorter adaptation times (see, for example, van Wezel and Britten (27,28)). Ongoing research with adaptation times of 15, 30, 45 and 60 seconds has shown that MAEs occurred for each adaptation time; however, clear group differences appeared only with 45 and 60 seconds of adaptation. This is not consistent with a potentiation of response over time in migraine, but further research with a reasonable sample size is needed.

It is possible that one single model for differences in neuronal function in migraine is likely to be an oversimplification, and that different paradigms and visual tests, which tap different stages in the visual pathways, may reveal multiple types of altered neuronal processing (8,47). Tibber and Shepherd (47), using a colour adaptation task, reported differences that were consistent with either increased GABAergic inhibition, or increased GABAergic inhibition *and* glutaminergic excitation, at different sites of a particular *retinal* circuit. They suggested that conflicting models of migraine involving hyper- vs hypo-excitability, or increased vs decreased inhibition, might reflect differences in the

circuitry that is sequestered by each particular experimental paradigm. That is, different tasks engage different processing streams, and different stages within each stream. Each may respond or adapt differently, and these responses or adaptive responses may differ between migraine and control groups in distinct ways at different stages within the visual pathways.

Recent studies on adaptation have described adaptation throughout the visual pathways, from the retina, through the lateral geniculate nucleus (LGN), to the visual cortex, that are qualitatively different at different stages, at least in the anaesthetised mouse and primate (59,62). Those authors point out that such effects are ubiquitous across species studied (from invertebrates to vertebrates), and across sensory modalities. It is likely, therefore, that they share certain similarities with human adaptation (see Larrson and Harrison (60) and Stocker and Simoncelli (61) for examples of inherited, and discrete, effects of adaptation demonstrable in humans). Adaptation at one level (e.g. the retina, the LGN) will propagate through subsequent processing stages yielding adaptation effects at higher stages that are inherited from earlier stages, yet the higher stages can also become adapted themselves potentially in a different way.

As an aside, many studies of the MAE use drifting sine-wave gratings as adapting and test stimuli and are, therefore, likely to show adaptation of different cell groups at different stages in the visual system as some may adapt to motion, some to the spatial frequency of the sine-wave grating, and some to their combination (e.g. Larrson and Harrison (60)), which complicates interpretation of effects of adaptation and site(s) of adaptation. Furthermore, adaptation to the spatial frequency component of gratings in V1 is likely to swamp adaptation effects to motion at either V1 or at later sites. This is one of the reasons why random dot displays were used in this study as adapting and test stimuli, rather than gratings. The second reason was to minimise the chance of triggering migraine by using striped patterns during adaptation. The study by Larrson and Harrison (60) is one of the few to compare motion adaptation with sine-wave gratings and with random dot displays and looked for the effects of adaptation at different stages of processing, but within the cortex only. They report separable effects that can be seen at V1 and V5, most clearly shown with the random dot rather than the grating stimuli.

Returning to models of adaptation in migraine, Thabet et al. (63) have recently presented a model of flicker adaptation at three stages within the visual system, in which differences between migraine and control groups could occur at each stage, which was developed from a model of adaptation to orientation (62). That model involves both precortical and cortical sites, and changes in the adaptability of both inhibitory and excitatory neurons at different levels. Adaptation of excitatory neurons at early/monocular sites results in a modest adaptation in those binocular cells to which they are connected. Adaptation of inhibitory cells at early/monocular sites produces increased excitability in those binocular cells or sites that they had been inhibiting. Inhibitory circuits are proposed to be broadly tuned, so adaptation leads to increased excitability in a broad range of binocular cells from disinhibition. Their data on flicker adaptation were well fit by this model, and they suggested their data indicated there is stronger adaptation in migraine, particularly at the two monocular sites. It is difficult to get direct psychophysical evidence for such a model, but further research could combine psychophysics with imaging, as suggested by Karanovic et al. (37). This model is consistent with the earlier suggestions that one single model for differences in neuronal function in migraine is likely to be an over-simplification, and that different paradigms and visual tests, which drive different neural circuits and stages in the visual pathways, may indicate multiple types of altered neuronal processing in migraine rather than one general one (8,47).

Nevertheless, the consistent pattern of group differences, particularly for tasks involving motion, suggests separate/additional clinical uses for visual tasks and questionnaires on visual symptoms regardless of the underlying model used to explain the group differences. Briefly, in clinical settings, it would be useful to include questions about visual triggers, as well as visual symptoms, when taking a patient's headache history (see Mulleners et al. (56)). This would be beneficial when advising patients about identifying and avoiding environmental triggers. It would also be useful to include assessments of visual triggers and visual function in clinical trials. There are a growing number of reports that perceptual and electrophysiological measures can track both migraine periodicity and treatment outcome (33,48–55,57). Much of this research uses electrophysiological measures, which have few practical applications. Visual tests are simpler to administer and could be included in future clinical trials to replicate and extend these electrophysiological findings. There is recent interest in tracking changes in behavioural or electrophysiological measures throughout the migraine cycle (e.g. 52–54,57). In this study, there was a significant association between migraine frequency and MAE duration: the more frequent the migraine, the longer the MAE. Similarly, Shepherd et al. (11) found significant associations between a relative motion task and migraine frequency, the number of years experienced, and two measures of visual discomfort. If a simple visual test could be instrumentalised, it could result in an application patients could use at home to track their

migraine cycle and, perhaps, take evasive action to thwart an impending migraine attack.

A motion task is likely to be the most promising type of visual task to pursue in an applied or clinical setting. While pattern sensitivity/visual discomfort, and flicker tasks also show fairly consistent group differences (8,11,32–34,36,37,41,47,63), they are unlikely to be useful for repeated testing to track the migraine cycle as they do not always correlate significantly with migraine frequency or the time elapsed since the last attack (11,36,37,63) and both can trigger migraine. Motion tasks using random dot displays, rather than drifting gratings, are likely to be more useful as they have also shown replicable group differences, and can show associations with (i) migraine frequency, (ii) the time elapsed since the last attack, (iii) reports of visual triggers and (iv) pattern sensitivity/visual discomfort (11,13,14) and they are not aversive to look at (9–14,23). Ongoing research is addressing this possibility, using repeated tests on a visual motion task together with questionnaires on visual triggers and visual symptoms. The present study has highlighted some similarities in headache triggers between migraine and control groups (see also Shepherd (5)), so a large cohort of people with and without migraine is being recruited, initially with an online experiment.

In conclusion, the present data have revealed prolonged neuronal suppression following 45 seconds of visual adaptation in migraine with and without VA, which results in a longer perception of the MAE. The association between photophobia during an attack and MAE duration simply reflects the group differences between people with and without migraine, since more in the migraine group reported photophobia with their headaches (Table 1, see also Sandor et al. (57)). The associations between the duration of the MAE and visual triggers, however, are consistent with earlier reports (13,14) and extend that work by identifying flicker and striped patterns as more relevant triggers than other visual stimuli. Further studies are recommended to examine the usefulness of visual tasks to predict response to migraine treatments, and as a non-invasive tool to track changes that occur throughout the migraine cycle. Motion tasks offer a promising place to start, given the consistency of reports showing differences between migraine and control groups (9–14,23). Further research is also recommended to better define environmental visual triggers and their relationships with visual symptoms and migraine and headache. For example, it is unclear why striped patterns, cited as a visual trigger, correlated to a greater extent with MAE duration than flicker, since flicker and motion perception appear more intimately linked than the perception of stripes and motion. Further refinements to the assessment of the nature of flickering and striped visual triggers, and their relationship with performance measures, is recommended. A more structured questionnaire on visual triggers would be useful. A better understanding of the types of visual or environmental triggers of migraine and headache may lead to guidelines for the design of the environment in which people live and work, to minimise exposure to headache triggers, similar to those guidelines that exist for photosensitive epilepsy (64). Such guidelines appear long overdue considering the much higher prevalence rates of migraine.

Article highlights

- This study extends earlier work on motion perception in migraine by assessing one aspect of motion perception, the motion after-effect (MAE), together with an assessment of visual symptoms (visual aura, photophobia and light sensitivity) and visual triggers (flicker, stripes, patterns of light and shade, or other visual stimuli such as computer screens, cinema and high-contrast reflections).
- Patients with migraine who also have visual symptoms and visual migraine triggers show, inter-ictally, the largest differences in MAE duration, compared to the control group.
- This study replicates earlier reports of enhanced visual after-effects in migraine, showing that this simple visual test is capable of revealing large group differences, and thus may be a test that is useful to include in clinical trials or to track changes during the migraine cycle.
- This study confirms the usefulness of recording additional measures when performing visual tests in migraine, if the aim of the research is to provide evidence for or against models of anomalous visual processing in migraine.

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vision

Review

Visual Perception in Migraine: A Narrative Review

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Abstract: Migraine, the most frequent neurological ailment, affects visual processing during and between attacks. Most visual disturbances associated with migraine can be explained by increased neural hyperexcitability, as suggested by clinical, physiological and neuroimaging evidence. Here, we review how simple (e.g., patterns, color) visual functions can be affected in patients with migraine, describe the different complex manifestations of the so-called Alice in Wonderland Syndrome, and discuss how visual stimuli can trigger migraine attacks. We also reinforce the importance of a thorough, proactive examination of visual function in people with migraine.

Keywords: migraine aura; vision; Alice in Wonderland Syndrome

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1. Introduction

Vision consumes a substantial portion of brain processing in humans. Migraine, the most frequent neurological ailment, affects vision more than any other cerebral function, both during and between attacks. Visual experiences in patients with migraine vary vastly in nature, extent and intensity, suggesting that migraine affects the central nervous system (CNS) anatomically and functionally in many different ways, thereby disrupting several components of visual processing. Migraine visual symptoms are simple (positive or negative), or complex, which involve larger and more elaborate vision disturbances, such as the perception of fortification spectra and other illusions [1]. Based on the physiology of vision, migraine visual manifestations may serve as clues to a better understanding of the mechanisms underlying this intriguing condition. Here we provide a narrative review of visual manifestation associated with migraine.

2. The Excitable Migraine Brain: With Aura or without Aura, That Is the Question

It appears that susceptibility to migraine is related to an imbalance between excitatory and inhibitory systems. The origins of this imbalance have not been totally elucidated. Several hypotheses, however, can be put forward: (1) Abnormal function of ion channels—genes that have been associated with certain types of migraine, including the familial hemiplegic migraine CACNA1A, ATP1A2, and SCN1A genes [2], alter this balance in favor of increased excitability; (2) Abnormalities in the thalamus, which plays a major role in cortical excitability control [3]—in a study where we examined thalamus microstructure using a multiparametric approach, we showed microstructural differences in the lateroposterior and the pulvinar nuclei of patients with migraine compared with healthy control participants. Because both these thalamic nuclei are highly connected with visual striate and extrastriate cortices, these differences could be associated with an altered modulation of excitability in the visual cortex, facilitating the occurrence of cortical spreading depression (CSD) and visual aura. Finally, (3) sex hormones play a complex role in cortical excitability. It has been shown in an animal model that increased susceptibility to CSD is reduced after

ovariectomy, casting light on the much higher prevalence of migraine in females compared to males [4].

Differences in visual processing outside of migraine attacks have been studied for many years, using different techniques such as the recording of electrical/magnetic activity (electro-encephalography, EEG with visual evoked potential (VEP) also known as event-related potential (ERP), and magneto-encephalography, MEG). The electrical signal, recorded at the scalp, is expressed as positive (P) or negative (N) inflections at a certain time. For example, N270 is a negative signal peaking at 270 milliseconds that is typically seen in the occipito-temporal region in response to the perception of faces. Different studies have, on the other hand, provoked activation or deactivation of the cortex using transcranial magnetic stimulation (TMS) and compared brain excitability between groups. They tend to suggest a hyperexcitable brain and habituation deficits. We list below a series of findings revealed by these different methods.

TMS, a non-invasive technique that uses magnetic fields to stimulate the brain, has been used to probe brain excitability. Aurora et al. [5] found that their patients who had migraine with aura (MWA) showed a lower threshold excitability over the occipital cortex compared to healthy control participants, a finding that was replicated by Mullener and colleagues [6]. Batelli et al. [7] applied their stimulations more anteriorly and laterally, and examined visual cortical excitability by stimulating over area MT/V5 (an area involved with motion processing) in their MWA and migraine without aura (MWoA) patients. They found that both migraine types had hyperexcitability over this region, compared to healthy control participants. More recently, Brigo et al. [7] performed a meta-analysis of the TMS literature in migraine that included ten trials. They reported that both MWA and MWoA had statistically lower phosphene thresholds compared to healthy control participants using a circular coil for the stimulation, further supporting the hypothesis of a hyperexcitable visual cortex in migraine.

Visual processing starts in the retina, where axons of the ganglion cells form the optic nerve and project to the thalamus (lateral geniculate nucleus (LGN) and pulvinar) and the superior colliculus. The LGN sends its projections to the primary visual cortex—or V1—where the information is arranged in columns of specific orientation, as described by Hubel and Wiesel at the end of the 1950s [8]. As information moves up in the visual system's hierarchy, area V2 is organized to respond to contours, textures and location, and thereafter it is distributed into different attributes such as color, face perception, etc. The different visual phenomena in migraine are closely related to the organization and function of the visual system.

Electrical recordings (VEP/ERPs) have revealed abnormalities in the processing of patterns, color, and face processing, in people with migraine between attacks.

2.1. Patterns

Afra and colleagues [9] compared VEP during long periods (15 min) of repetitive pattern-reversal stimulation in MWA and MWoA patients interictally, as well as in healthy control participants. While habituation (i.e., a reduction in neural response to continuous stimuli) could be observed in healthy control participants, the signal remained stable in both groups of patients, showing an interictal habituation deficit in cortical information processing.

More recently, Fong et al. [10] used striped patterns of specific spatial frequencies (0.5, 3, and 13 cycles-per-degree) in MWA and MWoA subjects and healthy control participants. They found that people with migraine had a significantly increased N2 amplitude for stimuli with 13 cpd gratings and proposed that this is in support of the cortical hyperexcitation hypothesis in migraine.

2.2. Color

Color signals in V1 are treated in color cell clusters named blobs, which project to V2 where they form thin stripes before sending projections to the brain's color selective area in the inferior occipito-temporal region, which also has a specific retinotopic organization and

a distinct foveal representation [11]. Haigh et al. [12] compared the behavioral and neural responses to chromatic patterns of increasing separation in migraine groups with and without aura and in healthy control participants. In addition, they asked the participants to rate their level of discomfort during data acquisition. They found that while greater chromaticity separation increased neural excitation in both migraine and healthy control groups, only the migraine group rated gratings as being disproportionately uncomfortable, and they exhibited greater effects of chromaticity separation in ERP amplitude across occipital and parietal electrodes, consistent with a hyperexcitability of the visual system.

2.3. Face Processing

Face processing is a complex system that involves a network of brain areas, comprising the occipital face area (OFA) and the fusiform face area (FFA) (for review, see [13]). One of the neural signature of face processing is the N170 [14]. Akdeniz and colleagues [15] used ERP and measured the neural correlates underlying face and face pareidolia processing in migraine groups with and without aura and in a healthy control group, by examining the N170, Vertex Positive Potential (VPP) and N250 mean amplitudes and latencies, which were generally greater in the migraine groups. In line with the evidences discussed above, they concluded that patients with migraine demonstrate visual cortical hyperexcitability.

3. What Patients with Migraine See and Do Not See

The most remarkable migraine visual experiences are related to the aura (from the Greek αύρα—breeze). Aura consists of fully reversible neurological dysfunctions, isolated or in successive combinations, that develop gradually, typically before the headache phase of a migraine attack [16]. Beyond visual symptoms (the visual aura—VA—characterized by varying visual perceptions, such as scintillating zig-zag patterns), aura can include sensory and/or language disturbances in isolation or combined, but vision is the most frequent CNS dysfunction, present in 98–99% of the aura episodes [1,17]. Interestingly, "mental efficiency" has been reported as impaired during VA progression [18], suggesting a temporarily dysfunctional cortical processing during aura. Although migraine predominates in women, male and female MWA patients present aura to the same ~33–38% proportion. In a retrospective study including 952 patients, migraine auras lasted on average ~27 min. [19]. This is in accordance with a prospective analysis of 216 diary-recorded auras, in which the average duration was 30 min. [1] Queiroz et al. found retrospectively that 65.5% of specifically visual auras lasted 5 to 30 min [20].

The archetype of VA is the fortification spectra, or teichopsia (from the Greek "town wall" and "vision", as coined by Airy in 1870) [20,21] which accounts for ca. 40% of the reports [20]. This phenomenon—so characteristic that it may be considered almost as pathognomonic of migraine—is characterized by a series of complex interlacing angulated black-and-white (less frequently colorful) flickering and scintillating lines and bars that start as a small greyish spot in the visual field, more often paracentrally, less frequently at the center [21,22], growing over time from near the center towards the periphery, leaving a scotoma behind.

In the majority of the cases the visual phenomenon appears at the visual field contralateral to the headache, which appears from 0 to 60 min after the VA [21]. According to Queiroz et al., the gap between the end of the VA and the headache onset is less than 30 min in 65% of the cases [20]. The VA can occur always at the same side of the visual field (33%), vary from side to side (26%), be always bilateral (36%), or sometimes unilateral and bilateral (5%) [1]. This abnormality, which initially impairs the vision at a certain region of the visual field, expands progressively for 20 min or so to the periphery, assuming a "c" or a horseshoe shape, edged by typically bright and dark zigzag lines with bars and corners [21,23]. The inner angle in this c-shaped serration pattern, close to its center, was estimated as ~45°, increasing progressively until ~70° at the periphery [24]. A bean-shaped area, characterized by low visual acuity inside this zig-zag phenomenon, follows the expanding visual scintillation.

Edward Hare, self-observing 12 of his fortification spectra attacks, reported that the change in diameter of the "spectral figures" increased with time logarithmically, while the rate of oscillation diminished [25]. Another carefully self-observed and detailed collection of 1000 VAs of the fortification spectra type drawn over 20 years by a 71-year-old male suffering from migraine provided important insights on the propagation of the aura phenomenon. According to this databank, attacks originated mostly within 10° eccentricity in the visual field, propagating first predominantly in the lower nasal fields and spreading to the upper temporal fields [26]. The VA progression from the center to the periphery is more frequent then the opposite [27].

Other simpler aura visual patterns, isolated or in combination, include flashes of bright light, phosphenes (small bright dots), white spots described as "falling stars", focal visual field defects, hemianopia, foggy or blurred vision, "visual snow" [28], or dimness of vision [1,22]. Most aura symptoms present more than one of these symptoms, with blurred vision (25%) and bright flashes of light (25%) being the most frequent patterns [1].

Color changes have been reported less frequently in migraine. Colorful auras were identified by 40% of the subjects studied by Queiroz et al., 18.0% of them presenting VAs in color exclusively [20]. Apart from shorter duration (1–2 min), round and multicolored image perceptions have traditionally supported the diagnosis of visual partial epileptic seizures, contrary to angular, zig-zagged, frequently black-and-white longer perceptions, supposedly more frequent in migraine VA [29]. Colorful aura perceptions included rather small than large dots, lines, or the fortification spectrum [30,31]. In a retrospective study of VA in 122 patients with migraine, the patterns were described as black-and-white, black-and-silver, always colorful, both colorful and black-and-white, and without color in 30.3%, 20.5%, 18.0%, 22.2%, and 9.0%, respectively [20].

Photophobia, a sign of hyperexcitability, is one of the distinctive symptoms of migraine, including during the interictal phase [32]. Color perception changes and hypersensitivity have been reported in migraine, which theoretically could simply result from photophobia itself, or from a direct migraine effect on color processing [33]. Color perimetry has shown abnormal perceptions of red and blue in patients with migraine. In one study, the dysfunction in red perception was greater in MWA patients, who also present higher levels of photophobia [34]. During migraine attacks, green light reduced headache intensity in ~20% of the subjects, contrary to white, blue, amber, and red lights, which exacerbated the pain. According to the authors, these findings, associated with thalamic, visual evoked potentials, and electroretinographic studies suggest that photophobia and specific color aversions originate in the retina and thalamus rather than in cortical visual processing areas [35].

Color processing dysfunctions may be involved in migraine-induced visual misperceptions [36] as suggested by patients referring to dimmed colors/achromatopsia [37] or, more frequently, color exaggeration in general [38]. One of our patients claimed the red color becomes so aggressive that "it seems to attack me". Others describe vision as "if someone presses the color saturation button in a TV remote all way up".

Complex Visual Manifestations and the Alice in Wonderland Syndrome

The psychiatrist John Todd wrote that, "While there is wide appreciation of the fact that epileptic subjects, and their blood relatives, are prone to experience bizarre disturbances of the body image, few realize that essentially similar disorders affect migraine subjects and their families. As a result, many of these patients are unjustifiably dubbed 'neurotic' and referred to a psychiatrist, while others torture themselves with secret misgivings concerning their sanity" (page 701 of [39]). To group these altered bizarre misperceptions in size, shape or proportions of patient's bodies and other objects he proposed the expression "the syndrome of Alice in Wonderland" (AIWS), according to Lewis Carrol's book Alice's Adventures in Wonderland [39]. AIWS may occur as a manifestation of different diseases, such as migraine, epilepsy, infections, cerebrovascular, and psychiatric disorders [40].

Nonvisual AIWS phenomena and the occurrence in diseases other than migraine are beyond the scope of the present work.

AIWS, which most probably originates from dysfunctions at the temporo-parieto-occipital carrefour [41], involves different complex perceptions including the sensation of changes to the passage of time [42]. As illustrated by Sacks (pp. 94–95), "the term *cinematographic vision* denotes the nature of visual experience when the illusion of motion has been lost. At such times, the patient sees only a rapidly-flickering series of 'stills', as in a film run too slowly. The rate of flickering is of the same order as the scintillation-rate of migrainous scotomata or paresthesia (6 to 12 per second), but may accelerate during the course of the aura to restore the appearance of normal motion, or (in a particularly severe, delirious aura) the appearance of a continuously-modulated visual hallucination". The same author described mosaic vision like "the fracture of the visual image into irregular, crystalline, polygonal facets, dovetailed together as in a mosaic" [43].

Anatomically close to the temporo-parieto-occipital carrefour is the inferior right parietal lobule. This cortical area in the nondominant hemisphere and its connections with temporal and ventrolateral frontal cortices have been implicated in unilateral spatial neglect [44,45]. Interestingly, unilateral spatial neglect was reported in two patients with sporadic hemiplegic migraine. First, a 13-year-old girl experienced flickering light and blurred vision to the left hemifield occurring before the onset of a contralateral occipital headache, which was accompanied by mild left hemiparesis, left hemihypesthesia, and dysarthria. She collided frequently with obstacles on her left side and had a positive left neglect drawing test. All symptoms disappeared in 24 h [46]. Second, a 20-year-old woman with migraine with typical visual aura since the age of 15: during one of her attacks, she presented short-lasting scintillations in the right visual field, followed by a right-sided headache (14 h duration), together with left-sided paresthesia and hemiparesis, both persisting for four hours. Drawing tests confirmed a left unilateral spatial neglect that disappeared with the resolution of the neurological symptoms [47]. We speculate that transient visual neglect and attention deficits may be part of migraine aura more often than hitherto supposed. These phenomena could be overlooked because of short duration, subtle and difficult to recognize or describe symptomatology, and lack of proactive search among physicians. In this context, it is remarkable that patients with migraine presented interictally lower BOLD-fMRI activation of the right temporal parietal junction on visual attention tasks [48], which is in line with interictal findings that patients perform worse than control subjects in visuospatial tasks with shift in attention to the right [49]. Other nonvisual cortical dysfunctions documented during migraine aura, such as apraxias, are not within the scope of this review.

As many as 42 different visual phenomena have been related to AIWS, in which the symptomatology is characterized by distortions of real sensory perceptions, contrary to hallucination, typically considered to be constructions independent from real stimuli [40]. Many of these complex visual symptoms have been recognized as part of possible migraine visual symptoms (Table 1). A likely mechanistic account links migraine sight dysfunctions to secondary and tertiary cortical vision processing areas and their connections.

In a prospective study, auras with visual perception disturbances were characterized exclusively by complex symptoms (37%), experienced also with either one positive or one negative symptom (54%), or both (9%) [1]. More recently, a prospective study targeting AIWS symptoms with an ad hoc questionnaire revealed that up to 19% of patients in a tertiary referral headache unit reported symptoms related to AIWS [50].

Among bizarre visual temporary dysfunctions associated with migraine is prosopagnosia, or the inability to distinguish human faces. Face identity recognition is a specialized neurological ability that plays a crucial surviving function in mammals. It involves a dedicated cortical circuitry that includes parts of the inferior occipital gyrus and the occipital and temporal fusiform gyrus [51]. A series of reports indicate that patients with migraine may present difficulties in recognizing other people's faces to various degrees [37,38,52,53]. We have observed two patients who presented "hemiprosopagnosia" as part of their mi-

graine attacks (unpublished). One of these patients described a transitory prosopagnosia as part of her migraine aura that was restricted to one side of people's faces. She noticed this in other people, in her own image in a mirror, as well as in faces on a computer screen. The affected half face looked to her swirled, scrambled. Migraine-related prosopagnosia may be not restricted to MWA and perhaps is present in mild forms interictally, too [38,54].

Table 1. Migraine-related visual complex and unusual visual phenomena.

Abnormality	Reference
Lilliputian or Brobdingnagian vision (micropsia or macropsia): Objects or people perceived as too small or too large	[55]
Metamorphopsia: Objects or people are distorted, "*monstrous faces in others*" (MV), half of the observed face shifting upwards or downwards, or changes in lines or angles of the features of objects or faces	[1,56]
Misperceptions of body parts: segments of the body seen gigantically, transparent, perception of the body being split in two, vision of the hair growing quickly "*to cover all the floor*" (MV)	[55,56]
Teleopsia: Seeing objects as much farther. It may refer to walls, "*giving the impression of a much larger ambient, or just one object in particular*" (MV)	[1]
Pelopsia: Seeing objects as much nearer	[1]
Allesthesia: Objects are viewed inverted or at the opposite homonymous field	[55]
Polyopia: perception of objects or faces in many copies	[56]
Mononuclear diplopia	[57]
Tunnel vision	[22,30]
Prosopagnosia	[37,38,52,53]
Increased or decreased misperception in the rate of movement: "*book pages passing too quickly*", "*lights in a tunnel succeeding in astonishing speed*" (MV)	[56]
Apparent movement of stationary objects	[56]
Waviness of linear contours	[56]
Objects with sharper contours, with exaggerated perspective or without a third dimension, looking diagrammatic	[43]
Corona phenomena: perception of colored or shining border around objects	[1,56]
Oscillopsia	[1]
Fragmented visual perception resembling "cracked glass" Kaleidoscope-like, mosaic vision	[43]
Impression of seeing through water heat waves, like "*looking at a distance close to the asphalt pavement in a very hot day*" (MV)	[1]
"Like a negative of film"	[22,30]
Complex hallucinations	[22,30]
Anopia—transient cortical blindness	[30]

MV: personal observations.

4. Confusing Terminology: Retinal Migraine, Ophthalmic Migraine, Ocular Migraine

Different terms have been used to address visual symptoms in migraine. Appropriate terminology is critical because inaccurate descriptions have clinical and pathophysiological implications. "Ophthalmic migraine", "ocular migraine", "anterior visual pathway migraine", and "monocular migraine" are confusing and not listed in the current version of the international classification of headache disorders (ICHD-3) [16]. The appropriate name to describe migraine cases associated with aura characterized by visual symptoms is *migraine with aura*, coded as 1.2, or in case of a more specific diagnosis, *migraine with typical aura*, coded as 1.2.1. Aura is mechanistically a cortical phenomenon, retrochiasmatic in

nature, affecting, therefore, both visual fields as homonymous phenomena. "Ophthalmic" or "ocular" are inappropriate terms in this context because they imply an origin related to the eye.

Retinal migraine (RM), which likewise is often mistakenly termed, is listed in the ICHD-3 under the code 1.2.4. To fulfill these diagnostic criteria, patients must present fully reversible, monocular, positive and/or negative visual phenomena during an attack confirmed by clinical visual field examination and/or the patient's drawing of a monocular field defect. In practice, however, almost every patient tends to explain a homonymous visual field deficit as monocular. Physicians must confirm the nature of the visual defect by a careful history taking, particularly when dealing with patients with migraine. Because the distinction between a hemi-field deficit from a monocular visual deficit is particularly difficult, the physician must instruct the patient to alternately cover one and the opposite eye to address the putative unilaterality of the symptom.

The confirmation of RM diagnosis, which is characterized by monocular visual loss, is both difficult and rare, involving circulatory mechanisms. It is possible that the majority of RM cases published so far are not related to migraine at all [58]. The diagnostic confusion increases, for example, by RM reports without headache. In a review of 60 articles describing 142 patients with visual symptoms attributed to retinal migraine, 39 cases had had persistent visual loss because of central retinal artery occlusion (11 cases), cilioretinal artery occlusion (4 cases), focal retinal ischemia (1 case), central retinal vein occlusion (2 cases), ischemic optic neuropathy (6 cases), optic atrophy (5 cases), or no explanation (1 case). Among the 103 patients with transient visual loss considered as RM, only 16 had compatible clinical pictures. Furthermore, among transient monocular visual losses attributed to RM (or equivalent terms for this condition), 12 patients had segmental retinal vasospasm of arteries or veins, among which only one had headache, during or immediately after the visual loss, that did not satisfy the diagnostic criteria for migraine [59].

Other authors describe monocular teichopsias or spreading negative visual losses as blurring, "grey-outs", and "black-outs", leading partial (altitudinal, quadrantic, central, or arcuate) or complete blindness [60]. Once a visual deficit is confirmed as monocular, the differential diagnosis must involve causes of prechiasmatic lesions affecting the optic nerve, retina, blood vessels, or any tissue possibly involved with visual losses. After excluding all alternative possible causes, the ICHD-3 RM diagnostic criteria must be checked for final confirmation.

5. A Riddle behind Retinal Migraine

Spreading depression (SD), the cortical neurophysiological counterpart of migraine aura, has been observed in retinas in vitro. Isolated chick retina is a reliable, avascular, commonly studied retina SD model, in which the SD phenomenon changes the retina color, allowing visual observation of the slow SD propagation (typically 2–3 mm/min) [61,62]. Retinal SD has been addressed in other species, since the original observation in amphibians [63], including fish [64], mammals [65]—rat [66] and possibly cat [67]. One of the most important features of SD is its slow progression. Should retinal SD underlie the RM phenomenon, the monocular visual clinical deficit would probably mirror the SD slow spread and be characterized by an expanding, slowly progressing monocular visual deficit, edged by a scintillation or some kind of positive visual phenomenon. This is incompatible with RM cases described as sudden monocular total darkness [68].

In the case published by El Youssef et al. [69], the RM monocular changes are described as "seeing a curtain moving in nasal to temporal direction, disappearing gradually, followed by a left periorbital pulsatile headache lasting 10 min", but details on the progression, its pace and duration are not provided. The ictal fundus showed multiple vasoconstrictions at the left central retina, which disappeared after attack resolution. No evidence of a "spreading" pattern was documented [69]. It is possible that retinal vasospasm provokes retinal SD which in turn leads to retinal migraine symptoms.

Documentation on spreading depression in human retinas and its possible relation with retinal migraine, either in conjunction with transitory retinal ischemic events or not, is lacking. RM remains as a very rare and controversial disorder, not to be confused with migraine with aura.

6. Visual Aura and Blindness

VA does not depend on visual input, as it can remain with one or both eyes closed [31]. Visual auras can also be seen with eyes opened in complete darkness. Self-observing one of his own occasional visual fortification spectra progressions in a complete dark environment manifested as a typical expanding black-and-white flickering zig-zag "C" shape (never suffered a migraine headache), one of the authors (MV) remarked that the black components appear vividly and as distinguished from the dark background as the white parts, suggesting that both black and white perceptions are positive phenomena of equal intensity.

Because the visual physiology is intimately involved with migraine expression, VA and photophobia have been addressed in visually impaired patients with migraine (VIPM). We investigated the presence of migraine and VA manifestations in blind adult patients [70]. In our series of 200 visually impaired patients, 63 (32.7%) fulfilled the International Classification of Diseases (ICD-10) code H54—bilateral blindness criteria corresponding to visual acuity impairment categories 3 (worse than 20/400 or 0.05; equal or better than 20/1200), 4 (worse than 5/300 or 0.02; equal or better than light perception), or 5 (no light perception). (WHO Study Group on the Prevention of Blindness, Geneva, 6–10 November l972, WHO Technical Report Series No. 518, 1973).

Among those, 23 (37%) presented migraine, 8 of whom with aura, among which 7 of the were VA type (one subject presented aura exclusively as auditory perceptions). All patients became blind after birth (from age 5 to 51. Migraine started before blindness in 6 patients, right after blindness in one, and much later in one—the subject with "auditory aura"). Three patients presented typical VA, contrary to four with atypical presentations. VA symptoms were atypical because of length (too short, i.e., less than 5 min according to ICHD-3 [16], color (blue, silver, or fire-like, contrasting to usual descriptions in migraine), and/or shape (round shapes) patterns. Among the six amaurotic patients with previous VA, four failed to present aura after the onset of blindness. In one, the VA remained clinically unchanged. In the last patient the aura perception modified as vision deteriorated, and eventually disappeared (before blindness: scintillations; after blindness: perception of "waves colored as fire" and "sparks crossing the air"). Interestingly, the patient who became blind by the age of five and started experiencing migraine during adolescence, reported an "auditory aura" perceived as an uncharacteristic noise and no visual phenomena. Auditory manifestations suggesting an aura-like phenomenon are rarely described in migraine [71]. Our "auditory aura" case, similarly to other observations in VIPMs [72], suggests that acoustic aura could be more frequent among blind subjects, possibly as a result of overactivation and/or reorganization of cortical areas related to hearing in blind subjects.

A constant normal visual input is probably necessary for the phenotypical construct of the migraine VA, as indicated by the fact that the majority of the aura phenomena disappeared and/or were atypical in our VIPM. Although the patients in our series did not report photophobia after blindness onset (present in all but one previous to vision loss), sensitivity to light has been documented in blind patients with migraine [73]. This discrepancy can be related to methodological issues or to the fact that photophobia in these patients may depend on the integrity of non-image forming visual pathways originating in melanopsin-rich retinal ganglion cells which converge on thalamic trigeminal sensory pathways that carry pain signals during migraine attacks [35]. Therefore, the integrity of the optic nerve is necessary for the presence of photophobia in blind people with migraine. Contrary to subjects with complete optic nerve damages, blind patients with intact optic nerves may present light-induced headache exacerbation [74].

Temporary binocular blindness can rarely be present in people with migraine, usually as a single, isolated, totally reversible episode, not related with other aura symptoms. The duration can vary from seconds to 2 h. The mechanisms underlying bilateral blindness during migraine attacks remain obscure [75].

7. Interictal Visual Symptoms

Migraine is usually conceived as a paroxysmal disease characterized by headache attacks separated by asymptomatic interictal phases. However, clinical, physiological, and neuroimaging data indicate that the interictal phase differs from healthy control subjets in many aspects, including vision. Sensory processing is significantly different in people with migraine, who are more sensitive to visual, acoustic, odoriferous, and somatosensorial stimuli [76].

Afterimages consist of physiological positive or negative visual perceptions that persist following visual stimulation, according to ON and OFF activity in visual receptive fields [77]. Afterimages in people with migraine are shorter interictally as compared to healthy control participants, increase progressively during the two days immediately prior to an attack and reach the maximum on the headache day [78]. This suggests changes in visual processing at different points during the migraine cycle. Transient and steady-state visual-evoked potentials suggest a particular imbalance between excitation and inhibition in the visual cortex that occurs interictally [79].

7.1. Photophobia

During migraine attacks, photophobia is usually defined as exacerbation of the headache secondary to ambient light exposure. Other components of photophobia outside migraine attacks include aversion to light, and attacks triggered by light. People with MWA and MWoA report more interictal aversion to light, have more photophobia symptoms (such as wearing sunglasses) and lower mean visual stress thresholds as measured by grating pattern induced unpleasantness (grating patterns that are bothersome, painful to look at, or irritating to the eyes) than control participants [80,81].

Migraine interictal photophobia may correlate with anxiety, depression and sleep disorders [82], possibly pointing to a higher severity within the migraine phenotype spectrum. Mechanistically, bright light enhances the activity of thalamic trigeminovascular neurons that transmit pain from the meninges. Dura-sensitive thalamic neurons that receive direct input from melanopsin-containing photosensitive retinal ganglion cells project to cortical areas involved with pain processing and visual perception. This convergence of retina originating photic pathway onto the trigeminovascular thalamo-cortical pathway may provide an anatomo-pathophysiological substrate for light-induced migraine headache exacerbation [74].

Motivated by the angle-rich visual fortification pattern in the classic migraine visual aura, we used a fMRI-specific paradigm and found that activations in the visual cortex interictally were clearly distinct in people with migraine, indicating that the migrainous occipital cortex is especially responsive to vision of angles. In this study, visual stimuli consisted of 8 rows of 12 parallel oblique (30 degrees inclination) white bright bars on a black background, alternating rhythmically every half second with similar bars orientated 30 degrees to the opposite direction. In the control condition, all bars were parallel to each other. In the main conditions, a column of bars, either on the left or right side, was orientated towards the opposite direction, forming 60-degree angles with the remaining bars [83]. The stimulation threshold to induce phosphenes when transcranial magnetic stimulation is applied over the occipital cortex is lower in patients with migraine than in control participants [84]. Taken together, these data suggest that the visual cortex is relatively hyperexcitable in migraine on a constant basis, and during an attack, light enhances migraine headache severity.

7.2. Visual Discomfort

Marcus and colleagues reported that 82% of the people with migraine have an aversion to striped patterns [85]. In fact, a series of visual stimuli such as flicker, glares or stripes can trigger migraine and/or elicit discomfort or aversion [86]. In addition, Shepherd and colleagues reported that patients with migraine experience a greater number of visual illusions for black and white patterns, which may be associated with an imbalance between the excitatory and the inhibitory systems [86]. Patients with migraine report more illusions than control participants, regardless of the size of the stimulus; they also experience more discomfort when viewing the patterns [87,88]

7.3. Motion Sickness

The symptoms of motion sickness are related to a conflict between the visual system and the vestibular system. The brainstem also plays an important role in this phenomenon [89]. The incidence of motion sickness is higher in children with migraine (up to 45%, compared with 5% to 7% in children with nonmigraine headache, seizure disorders, or learning disabilities) [90], and a history of motion sickness is predictive of childhood migraine [91]. Later on, people with migraine have greater motion sickness susceptibility [92,93] because more than half are prone to it [94]. Although the exact reasons for increased susceptibility to motion sickness in migraine are not known [89], it is interesting to note that serotonin synthesis reduction (by tryptophan depletion) increases motion sickness and sensitivity to light, possibly through an imbalance between the inhibitory and the excitatory systems [95].

A recently recognized syndrome, persistent postural-perceptual dizziness—PPPD, refers to individuals who present non-spinning vertigo and a sense of unsteadiness [96]. A relationship between PPPD and migraine has been suggested [97]. Interestingly, PPPD can be visually triggered [98], as can motion sickness. Most likely motion sickness and PPPD intermingle. Further observations will cast light on the actual distinction between these two phenomena. People with migraine are also more susceptible than the general population to symptoms evoked by visual stimulation of movement [99,100].

8. Visual Stimuli as Migraine Triggers

Environmental trigger studies in migraine are greatly limited by methodological constraints related to patients' subjective interpretations. Objective, clear-cut stimuli are easier to address and allow firmer conclusions to be drawn. These include visual stimuli, which are recognized as some of the most frequent attack triggers. In addition, migraine-triggering visual stimuli are similar to patterns that trigger seizures, such as flickering/intermittent light and repetitive geometric patterns, or repetitive figures such as stripes [101,102], which is in line with the increased interictal photophobia possibly related to cortical hyperexcitability.

We have examined patients who had attacks induced by stripes, flickering, particular bright colors (e.g., an orange couch, a red wall), and visual patterns (e.g., a curtain with big red roses motifs). A frequent report as a trigger in our patients is driving during the night at a constant speed, staring successive, intermittent sources of light [103]. One of our cases, a young female migraine with aura patient, had attacks with aura triggered specifically by reading. She needed to stop reading every so often to avoid constant migraine attacks. In this patient, patterns having the same light intensity, or a meaningless sequence of random letters would not trigger any aura or headache, suggesting that the reading was the actual trigger factor. The reading discomfort in migraine can also be related to the visual characteristics of the text [86].

Up to 60% of people with migraine vs. 15% of control participants (subjects with headache not fulfilling IHS diagnostic criteria for migraine) report that visual patterns may trigger attacks [104]. Shepherd et al. used a comprehensive approach to study visual processing interictally in 28 migraine (14 migraine with aura, 14 migraine without aura) and 14 headache-free control participants. They assessed visual discomfort (also termed

pattern sensitivity or pattern glare) by gauging experiences of discomfort, illusions or distortions while viewing repetitive patterns such as stripes. They also assessed sensitivity to achromatic and chromatic patterns. They included a visual discomfort questionnaire, a hue test, a contrast sensitivity test, a migraine trigger inventory, and a stereopsis test [86]. In their study, MWA patients had more headaches triggered by visual stimuli than control participants. The most frequent triggers were flicker, followed by computer use, stripes, patterns of light and shade, television, cinema, and bright fluorescent pink and green color contrasts. In the MWoA group, computer use or overuse was the most frequent trigger, followed by flicker, patterns of light and shade, stripes, cinema, television, and high contrasts (abrupt transitions from light to dark, driving at night with oncoming car headlights). Visual discomfort was greater among patients, which was reduced by using colored gratings rather than achromatic (black-and-white).

For both patients and clinicians, it is relevant to explore possible visual triggers apart from the more frequently reported sunlight. Migraine aura and without aura are equally affected by possible visual triggers. Geometric patterns, sharp contrasts, colorful or black-and-white may trigger migraine attacks in sensitive subjects.

9. Vision and the Neural Underpinnings of the Migraine Related Visual Phenomena

The visual cortex represents a large portion of the brain, as it extends from the occipital cortex to the temporal and parietal cortices. Small lesions in the visual system can readily translate into symptoms such as a loss of part of the visual field. This may be one of the reasons why so many auras have visual manifestations. According to Aristides Leão, who discovered cortical spreading depression (CSD) in 1944 [105], "it seems well established that an essential part of the mechanism of CSD is transmission of a disturbance of cell membrane function, from one cell to its neighbors by diffusion of substances in the extracellular fluid. Therefore, close proximity of the cells certainly facilitates CSD. The density of packing of the cells varies with the region of the cortex, and is by far highest in the visual area. Thus, one would expect this area to be the most liable to suffer from CSD, and in fact visual symptoms are the most frequent in the migraine aura" [106] (p. 20).

In the first paper that related visual cortex organization with visual percept in migraine [107], we noticed that the symptoms experienced by participants with migraine—akin to TV visual snow—corresponded to the type of stimuli that are processed in the area where the origin of the CSD was located, namely V3A [108]. It is very possible, although it has never been demonstrated, that classical fortification spectra may relate to CSD initiating in V1, whereas other types of visual percepts such as flashes of color may start in area V8 [11], or difficulties with face recognition may be associated with activity in the fusiform face area, FFA [109].

Other more cognitively elaborate percepts such as the AIWS micro/macro/metamorphopsias may on the other hand come from associations area such as the parietal/temporal cortices. Interestingly, abnormal perfusion or metabolism were identified in the parietal lobes of patients with visual distortion of size or shape of objects, and in the temporal lobe of a patient with color misrecognition [74].

10. Conclusions

Migraine is a common neurological condition associated with visual processing abnormalities and various visual misperceptions across all of its phases, including the interictal phase. Such phenomena encompass rich, sometimes bizarre symptoms much beyond the frequently recognized aura and photophobia complaints. For some patients, migraine affect mostly vision, in the sense that the impact of the visual symptoms is much greater than the headache itself. A better understanding of what triggers their migraine may help them reduce the number of migraine attacks by avoiding these triggers. Most visual disturbances associated with migraine can be justified by increased neural hyperexcitability, as suggested by clinical, physiological and neuroimaging evidence. This is still debate because there may be distinct changes at different stages of the visual system. Therefore,

it may be more appropriate to consider VA as dysfunctions in visual processing [110]. Clinicians are encouraged to proactively search, correctly identify, classify and interpret migraine-related visual problems, which may help expand the present knowledge on the disease and optimize migraine care.

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