Article ▸ Ocular Manifestations of Migraines and Their Clinical Implications in the Optometric Setting

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ABSTRACT

Ocular manifestations of migraines can present in many modalities other than the traditional visual aura. This review describes the current theories of migraine pathophysiology, emphasizing the relationship between the brain and the vascular system. Many variations of visual field defects, retinal anomalies, and other neuro-ophthalmic conditions may present with migraine. A significant association exists between migraines and normal tension glaucoma, which may influence our treatment and management of patients exhibiting these two conditions. Migraine sufferers often show symptoms of visual discomfort out of proportion to those experienced by the general population, even when they are not experiencing a migraine. Through administration of the pattern glare test, optometrists can better isolate individuals particularly affected by these visual triggers and manage them through the use of ophthalmic tints designed to reduce symptoms of discomfort. Conditions like transient ischemic attacks and epilepsy can often present in similar ways to visual aura, so recognizing subtle differences in presentation becomes particularly important when managing patients complaining of visual symptoms.

Keywords: migraine, normal tension glaucoma, pattern glare, visual aura, visual field defects

Introduction

Since 3000 BC and the days of Hippocrates, migraines have been known to be directly linked with vision.[1] Both migraine triggers and symptoms are often largely visual.[1] According to the International Headache Society classification, a migraine is defined as a headache attack lasting 4-72 hours and consisting of at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or avoidance of routine physical activity. It must also be accompanied by nausea and/or vomiting or photophobia and/or phonophobia.[2] A migraine aura may or may not be accompanied by a headache. The aura must consist of one or more of the following: fully reversible positive or negative visual symptoms, fully reversible positive or negative sensory symptoms, and/or fully reversible dysphasic speech disturbance.[3] It must also consist of at least two of these features: homonymous visual symptoms and/or unilateral sensory symptoms, at least one aura symptom developing gradually over >/= five minutes and/or different aura symptoms occurring in succession over >/= five minutes, and each symptom lasting between five and sixty minutes.[3] Migraine is a very common disorder, affecting about 29.5 million Americans.[4,5]

Visual auras are the most common type of aura and can present in many different ways, including scotomas, photophobia, metamorphopsia, blurry vision, and the classic fortification spectrum, or zigzag-patterned moving angular lines.[4] Although the number and lengths of lines may vary, the general pattern remains about the same, both within individuals and when comparing between different observers.[5] The speed of aura visual hallucinations tends to increase as they move into the patient's peripheral visual field.[5]

Current Theories in Migraine Pathophysiology

Within the last twenty years, a number of different theories of migraine pathophysiology have been proposed. Despite their diversity, many scientists agree that it is an interaction between both vascular and neurological processes in migraine patients that causes the attacks.[6] One major neurological theory that has many visual implications is the theory of visual cortex hyper-excitability. The concept behind this theory is that patients with migraines, especially migraines with aura, show a greater level of excitability in this area of the brain when exposed to the same stimulus as do the controls.[7] A technique called trans-cranial magnetic stimulation has been used to determine excitement thresholds in these patients. During this technique, a stimulator is placed on the occipital area of the scalp, and the level of stimulus intensity is increased in small increments until the least level at which the stimulus can be detected (or cause cortical excitement) is reached.[7]

The lower threshold for excitability found in migraine patients, when compared to controls, may explain their general aversion to lights, certain patterns, and other modes of visual stimulation.[8] In other words, visual stimuli that have a neutral effect on controls cause discomfort in patients with migraines because of this lower threshold for cortical excitability. This theory may also form the basis for the development of cortical spreading depression, which is the current proposed mechanism for auras. In cortical spreading depression, a lack of neuronal activity spreads across the cortex, beginning in the visual cortex.[7] The same heightened susceptibility to excitement from low-level stimuli is mirrored in the neurons' increased susceptibility to cascading inactivity and cell depolarization.[7] That is, cortical spreading depression can occur in anyone, but migraine patients' lower thresholds for stimulation, as

demonstrated in the hyper-excitability theory, make it more likely to occur in these individuals.

Rather than the cortex showing increased excitability in migraine patients, some propose that a decreased inhibition is the underlying problem. Following trans-cranial magnetic stimulation, patients undergo a cortical silent period (CSP) showing little to no cortical activity.[9] In a study performed by Maier et al., this period lasted a significantly shorter time in individuals experiencing migraines with aura.[9] This reduction was unrelated to levels of outside stressors and is likely due to a reduced GABA-ergic cortical inhibition.[9] In normal patients, the thalamo-cortical interaction within the brain consists of brief periods of excitation followed by longer periods of GABA-induced inhibition.[10] In people with migraine with aura who show reduced inhibition, this thalamo-cortical loop is thought to be dysfunctional.[9]

The concept of habituation, or the ability to ignore a stimulus once it is presented multiple times, may also come into play. This phenomenon was first reported in 1995 in relation to VEP stimuli,[11] but it has been shown to apply in the auditory and tactile arenas as well. Going somewhat against the theories of cortical hyper-excitability or reduced inhibition, this theory states that migraine patients have an impaired habituation to stimuli because of a reduced level of baseline cortical activity before the stimulus is introduced.[12] This lower initial activation level means it takes migraine patients longer to reach the same threshold level as controls. This threshold is the one at which habituation occurs.[12]

Patients with migraines with and without aura have been shown to have lower baseline serotonin levels than controls.[13] Serotonin is thought to play a role in the vascular system, namely vasoconstriction. Lower serotonin levels in the body may make it easier to set off the cortical spreading depression cascade. Just before and/or during a migraine attack, serotonin suddenly becomes much more available, which may trigger the pain.[13]

Migraines have long been known to be associated with cerebral vasculature.[6] Hypo-perfusion of cerebral blood vessels may cause migraines with aura to occur. The reason for the hypo-perfusion may be injury to the vessels in these patients, an increased blood viscosity, or even a dysfunctional vascular endothelium. This hypo-perfusion again makes it more likely for cortical spreading depression to occur.[6] The idea that migraine patients are hypersensitive to stimuli could mean that this hypersensitivity triggers a neurovascular response. Trigeminal sensory nerves supplying intracranial arteries are activated to cause vasodilation, resulting in pain.[14]

Visual Field Defects Associated with Migraine

Migraines with and without aura can cause a wide range of visual field defects similar to those seen in serious neurological and vascular conditions. This makes baseline visual field testing essential in the optometric examination of a migraine sufferer. Homonymous hemianopic defects of transient and permanent duration have been shown to be caused by migraines. One case was reported in 2011 of a twenty-seven-year-old white female with a history of migraine with aura two to four times per week.[15] She exhibited an incomplete right homonymous hemianopia upon first day of presentation. One week later, her defect had almost completely resolved, with only mild residual right hemifield loss in the left eye.[15] Other visual field defects are permanent, usually fluctuating in the beginning of the attack and then remaining unchanged after a few months. Defects may become permanent if the patient has a lack of physiological tolerance for prolonged hypo-perfusion.[16]

Inferior altitudinal defects have also been documented in patients with migraine with and without aura. One case was reported in 2010 of a twenty-five-year-old female with migraine with aura who exhibited an inferior altitudinal defect that resolved in six months.[17] Defects like these may remain for extended periods of time due to the reduction in cerebral blood flow to the occipital lobe caused by cortical spreading depression.[17] This is likely the same cause responsible for persistent migraine aura without infarction, a type of migraine lasting a week or more.[17]

Complete transient monocular blindness is a rarely reported phenomenon and is seen more commonly in patients with migraine without aura.[18] Shorter in duration than the typical aura, it is more commonly reported in females and is usually experienced only once in a lifetime. Retinal spreading depression is the ocular analog of cortical spreading depression, in which a lack of neuronal activity spreads throughout the retinal tissue.[18] Underlying clotting disorders may make transient monocular blindness more likely, thereby lowering the threshold for retinal spreading depression to occur.

Color vision deficits revealing S-cone deficiencies have been documented in association with migraines. Short wavelength automated perimetry (SWAP) visual field defects with great variability have been seen in these patients, likely due to these S-cone abnormalities causing difficulty viewing blue and yellow targets.[19] A wide range of visual field defects typically associated with glaucoma have also been reported in association with migraines in patients with otherwise normal ocular health. Because of the great variation in defects seen, including migraine patients in the normative database for visual field testing could present a problem.

Retinal Conditions Caused by Migraine

A retinal migraine presents with fully reversible monocular positive and/or negative visual phenomena that may or may not be accompanied by a migraine headache.[20] A headache fulfilling the criteria for migraine without aura must begin within sixty minutes of the presenting visual symptoms.[20] Retinal migraines may be accompanied by numerous physical signs, including macular pallor, optic disc pallor (early finding), optic disc hyperemia (late finding), constriction of retinal arterioles, and even retinal nerve fiber layer defects (late finding).[21]

Retinal Infarct

Retinal infarcts can be caused by migraine.[22] However, ischemic, embolic, and infectious causes must always be ruled out when a patient presents with a retinal cotton wool spot, as well as (less commonly) toxic, immune-mediated, and neoplastic etiologies.[23] In young and otherwise healthy patients, CBC with differential and ANA are essential to rule out subtle underlying causes, including autoimmune disorders.[23]

Artery Occlusion

A small number of cases of artery occlusions secondary to migraine have been documented, most commonly among young females. Many show recurring episodes and some occur during the migraine attack. The likely cause for this phenomenon is ocular vasospasm which cuts off blood flow to a particular region of the retina.[24] One case was documented in 2011 of an otherwise healthy forty-eight-year-old male with history of migraine with aura. He had experienced episodes of transient visual disturbances lasting forty-five to sixty minutes every three to four months within the last year. These visual disturbances were not associated with headache and thus could be considered a migraine aura without headache. He experienced a left superior hemi-retinal artery occlusion resulting in an inferior altitudinal visual field defect. Complete resolution was seen in just two months.[24]

Vasospastic syndrome is a non-specific disorder associated with migraines that presents with symptoms of hypersensitivity to stimuli, such as cold or emotional stress.[24] It includes vasospasms throughout the body but is most easily visualized in the retina. Ocular manifestations can include corneal edema, ischemia, and retinal artery and vein occlusions. Patients exhibiting this disorder, especially along with migraines, will often be started on calcium channel blockers as prophylaxis against future vision loss.[24]

Neuro-ophthalmic Conditions Associated with Migraine

Ischemic Optic Neuropathy

Both anterior (more commonly) and posterior ischemic optic neuropathies have been rarely reported to be caused by migraine with and without aura. This is more likely to occur in patients with other vascular risk factors, such as hypertension or oral contraceptive use.[25]

Ophthalmoplegic Migraine

Included in the International Headache Society classification for migraines up until 1998, ophthalmoplegic migraines may not actually be migraines at all. Originally, it was thought that the wall of the carotid artery could become edematous during a severe migraine attack, pressing on the third cranial nerve as it traverses through the cavernous sinus, thereby causing the frightening neurological symptoms associated with the condition.[26] Now, some consider it to be a type of demyelinating illness that may be caused by a previous viral infection.[26] MRI with contrast of a patient with ophthalmoplegic migraine shows enhancement of the third cranial nerve, an appearance also seen in other demyelinating diseases. On the other hand, ischemic causes of ophthalmoplegia such as diabetes do not show this enhancement.[26]

In an ophthalmoplegic migraine, the inflamed third cranial nerve probably irritates the trigeminal nerve, which triggers a headache. Repeated activation of the trigeminal nerve-vascular system causes neuropeptides to be released, inducing nerve edema.[26] In general, these patients will be previous migraine sufferers and will experience an increase in frequency and severity of migraines immediately leading up to the attack.[27] The headache is usually on the same side as the ophthalmoplegia and presents with symptoms of diplopia. Dilated pupil, mild ptosis, and extraocular muscle deficiencies of varying severity may be seen. Although the third cranial nerve is by far the most commonly affected, paresis of the other ocular cranial nerves (four and six) may also occur. Recovery is usually seen within days to weeks.[27]

The condition almost always first presents in childhood; however, adult-onset variants have been documented.[26] In childhood, the condition much more commonly presents with recurrent, painful, pupil-involved third nerve palsies with enhancement on MRI.[26] The adult-onset variant usually presents with single-episode, pupil-sparing sixth nerve palsy.[26] If the third nerve is involved, it will also be pupil-sparing, and enhancement on MRI is rare. The common factor in childhood and adult-onset is migraine with severe pain.[26]

Pupillary Defects

Relative afferent pupillary defect (RAPD) can be seen in association with migraine as a result of the aforementioned retinal or neuro-ophthalmic conditions that can result from migraines. Benign episodic unilateral mydriasis and Adie's tonic pupil have also been seen as a direct result of migraines.[28] Benign episodic unilateral mydriasis usually occurs immediately prior to or during the attack. It is likely underdiagnosed in these patients due to its transient (usually lasting thirty minutes or less) and often asymptomatic nature. Some hypothesize that this finding is a less severe form of ophthalmoplegic migraine, affecting the third cranial nerve. Others believe it is an atypical form of aura, caused by hyperactivity of the sympathetic nervous system.[28] Adie's tonic pupil is overall more commonly found in migraine sufferers and has been documented to occur during the migraine attack.[29] Most episodes persist after the migraine. In these cases, the pupillary condition is likely to result from a vasospasm creating ischemia to post-ganglionic parasympathetic fibers.[29]

Migraines and Normal Tension Glaucoma

A definite association exists between migraines and normal tension glaucoma (NTG).[30] Migraines with and without aura are more common in patients with NTG than in the general population, likely due to a common vascular etiology. NTG is also more common in patients with migraines. The

Collaborative Normal Tension Glaucoma Study found a 2.58-fold increase in the incidence of NTG in patients with migraines than those without. The presence of migraines may also increase the likelihood for the progression of this form of glaucoma. In these patients, a vasospasm likely creates ischemia to the optic nerve, resulting in glaucomatous defects.[30]

It has been recently suggested that treatment of NTG with a topical prostaglandin can have dual benefit to the patient by also acting to reduce migraine symptoms.[31] In 2006, a fifty-seven-year-old female with history of frequent migraines about three times weekly, low blood pressure, and peripheral vasospasm (all risk factors for NTG) was started on treatment with latanoprost. After initiating treatment, she reported experiencing no migraines at all for an entire year, with no changes in lifestyle factors involved. When the latanoprost was later discontinued due to adverse drug reactions, her headaches returned with the same frequency and severity with which she had presented a year prior.[31]

Latanoprost is a prostaglandin F2A analog.[32] Because prostaglandin F2A increases uveoscleral outflow through relaxation of the ciliary muscle, it also causes a relief of brow pain often associated with migraine.[31] It improves ocular bloodflow and perfusion pressure while causing vasoconstriction, an antidote to the vasodilation thought to be involved in migraine pathogenesis. Sumatriptans, oral medications for migraine prophylaxis, also work by vasoconstriction.[31]

Topical beta blockers may also act to reduce migraine symptoms.[33] Oral beta blockers are well-known migraine treatments, but topical administration may have more of an effect than we think. In 2011, an otherwise healthy fifty-two-year-old male with a history of migraine presented complaining of a prolonged recent visual disturbance.[33] Automated visual field examination revealed a bilateral superior arcuate defect. Showing cup-to-disc ratios of 0.6 and 0.7, his optic nerves were examined via optical coherence tomography (OCT) and revealed no significant retinal nerve fiber layer thinning associated with the defect.[33] His intraocular pressure measurement was consistently low (between 12 and 14 mm of Hg). Three months later, his visual field defect had progressed, and despite no change in OCT, he was started on latanoprost due to the risk of NTG.[33] At his next three-month visit, he continued to complain of migraine with aura and showed a progression of the left field defect.[30] Timolol-LA 0.5% was then added to his treatment regimen.[33] At the next follow-up visit another three months later, the patient reported resolution of the migraines, and automated visual field testing showed complete resolution of the superior defect in both eyes.[33]

It is likely that this patient's visual field defects were due to his migraine attacks and that the initiation of timolol-LA 0.5% treatment acted to resolve the patient's visual field defect and migraine pain symptoms.[33] Topical timolol maleate 0.5% has been shown to reach concentrations of 0.5 ng/mL in the blood plasma within four hours of instillation. Because of this systemic involvement, it has been reported to reduce the frequency and severity of migraine symptoms.[33] Oral beta blockers, including oral timolol, have long been used for migraine prophylaxis. Beta blockers work by preventing the dilation of blood vessels, which occurs during migraines, causing pain.[34] They also regulate the firing rate of gray matter neurons.[35] Some beta blockers may in addition block certain serotonin receptors (5-HT2C & 5-HT2B).[35] As previously discussed, serotonin likely plays a role in migraine attacks; baseline serotonin levels in migraine sufferers are low but increase to much higher levels just leading up to the attack, when the blocking of receptors is beneficial in decreasing severity of symptoms.

Visual Discomfort, Ophthalmic Tints, and the Pattern Glare Test

Pattern glare is a term used to describe the perceptual distortions (for example, artificial motion of lines) experienced by individuals while viewing a pattern of a certain spatial frequency.[36] Pattern glare is often bothersome for migraine sufferers, as well as for people suffering from disorders such as epilepsy or dyslexia. This hypersensitivity to pattern glare may be due to cortical hyper-excitability. Resultant symptoms are often referred to as visual stress. The spatial frequency causing maximum visual discomfort for these patients is at or around 2.5 cycles per degree, close to the spatial frequency at which contrast sensitivity is at its highest.[36]

Ophthalmic tints, mainly blues and greens, have been shown to reduce these patients' levels of visual discomfort by decreasing the level of cortical hyper-excitability.[37] In an fMRI study of migraine patients affected by visual stress, it was shown that the V2 region of the visual cortex is the main source of hyper-activation when viewing patterns. This region receives excitatory input from V1 during the viewing. When precision ophthalmic tints chosen by patients prior to the fMRI to relieve the maximum amount of visual discomfort are introduced, normalization of activation levels and spatial frequency tuning is seen in V2. Also, looking through blue- and green-tinted lenses helps to normalize the blue-yellow deficient visual systems seen in many migraine patients. Therefore, these tinted lenses have the potential to prevent migraine attack in individuals sensitive to visual triggers; they may make it more difficult for cortical spreading depression to occur. Control-colored or gray lenses do not have the same effect.[37]

Screening patients for visual stress is important in that it allows eye care professionals to pinpoint patients who would benefit from precision ophthalmic tints while engaging in visually demanding activities such as reading or computer work. The pattern glare test is a time-efficient way of performing this screening. During this test, the patient is shown three bar gratings of varying spatial frequency (low, medium, and high).[38] The patient then views the fixation dot in the center of the pattern (held at 40 cm) for five seconds. After this period, the patient will be given a form consisting of a series of yes or no questions designed to help rate the

level of visual discomfort experienced while viewing that particular pattern. The more yes responses, the higher the level of visual discomfort.[38]

Patients are asked whether they experienced the following visual distortions: colors, blurring of lines, bending of lines, shimmer/flicker, fading, shadowy shapes, and other effects (to be specified by the patient).[38] They are also asked to report whether they experienced the distortions on the right side of their visual field, the left side, or both. Patients with migraine with visual aura will more commonly experience perceptual distortions on the side of the visual field in which the aura normally occurs. The second (medium spatial frequency) pattern is designed to be at the level of spatial frequency causing maximum discomfort; thus, the visually sensitive migraine patient will have the most yes responses on this portion of the test. Care must be taken when administering this test to known epileptics, as pattern two has been shown to induce seizures in some of these patients.[38]

Recognizing Potentially Severe Migraine Mimics

Transient Ischemic Attack

Migraine and transient ischemic attacks (TIAs) can present with remarkably similar symptoms, including transient visual and speech disturbances. Although there can be exceptions to the rules, the key differentiating factor is duration: TIAs usually have an acute onset and last less than five minutes, whereas migraines present more gradually and last longer.[39] While migraines can show positive or negative visual symptoms, TIAs show mostly negative. The patient's history is also important to take into account; if he or she has experienced prior episodes in the past, migraine is more likely.[35] Migraine aura without headache mimics TIA the greatest, making the differentiation very difficult without proper diagnostic tests. Risk factors are also important to keep in mind when working with patients with these two conditions; migraine with visual aura makes a patient twice as likely to experience a stroke later on in life.[40]

Epilepsy

A patient presenting with nausea/vomiting accompanied by photopsia and/or other visual disturbances can just as likely be experiencing an epileptic attack as a migraine attack.[41] Seizures may or may not be accompanied by visible motor symptoms and/or headache. As with TIAs, recognizing duration is essential: seizures have a more acute onset and shorter duration than migraines. The neurological symptoms are more quickly spreading in epilepsy and are often localized to one side, whereas in migraines the headache and aura can switch sides. Visual hallucinations also look different in migraines and epilepsy. While a migraine aura is often made up of black and white patterns, seizures often present with multi-colored forms.[41] Often, epileptics will show structural abnormalities on MRI and pathognomonic patterns on EEG that will make the diagnosis more clear.[42]

Space-occupying Lesions

Because space-occupying lesions can present with such a wide variance of symptoms, often very similar to migraine, knowing the warning signs to look out for in patient presentation can provide the information needed for proper imaging referral. Important predictors indicating space-occupying lesions include but are not limited to: headache waking the patient from sleep, recent-onset headache, visual disturbance that is stagnant (not expanding like a typical aura), no family history of migraine, abnormal neurologic exam, and associated confusion.[43]

Giant Cell Arteritis

Although giant cell arteritis (GCA) is usually accompanied by other ocular signs (anterior ischemic optic neuropathy or artery occlusions) and systemic risk factors (including hypertension and heart disease), atypical presentations can mimic migraine. While in GCA vision loss starts out unilaterally and often moves to the other eye,[44] vision loss/visual disturbances in migraine can begin unilaterally or bilaterally. Whereas migraines are more commonly seen in younger patients, GCA is almost always seen in patients over fifty.[44] Also, like many other emergency conditions, GCA presents more acutely than a migraine.[44] In addition, it is often accompanied by other classic signs and symptoms, such as jaw claudication, weight loss, decreased appetite, tenderness near the temporal artery, and increased ESR and C-reactive protein.

Retrobulbar Optic Neuritis

Because of its characteristically normal fundus appearance, retrobulbar optic neuritis is significant in the differential diagnosis considered by eye care providers when a patient presents with visual and/or neurological symptoms. Both migraine and retrobulbar optic neuritis can present with a wide range of visual field defects, are seen more commonly in the younger population, and can be associated with non-specific neurological symptoms such as weakness or numbness.[45] Generally speaking, retrobulbar optic neuritis can present exactly like a migraine but with more severe signs and symptoms. Color vision loss, pain on eye movement, and relative afferent pupillary defect are seen in the majority of optic neuritis cases. Each of these can accompany migraines but are less common, less severe, and usually last a shorter period of time. Chronic features of retrobulbar optic neuritis can last up to a year or more, so duration is again a main distinguishing factor.[45]

Arteriovenous Malformation

Migraine-mimicking symptoms in patients with arteriovenous malformation (AVM) are seen particularly when the AVM is located occipitally.[46] Just as in migraine sufferers, a wide range of visual field defects can be seen in AVM patients, some of which can be homonymous depending on the location.[46] In most migraine patients, the headache alternates sides and

usually occurs on the same side of the head as the aura. In contrast, in AVM patients, the headache is almost always on the same side each time, occurring on the side opposite to the visual disturbance.[47] Carotid bruit is a systemic sign common to many AVM patients that can provide a differentiating factor. Frequency of symptoms is also important; migraines usually do not occur daily, whereas AVM symptoms often do.[47,48]

Conclusion

Ocular manifestations of migraines vary widely beyond the traditional visual aura. Visual field defects can present with variable diversity and frequency. A number of retinal conditions, including retinal infarcts and artery occlusions; neuro-ophthalmic complications, including a range of pupillary defects, optic neuropathies, and ophthalmoplegia; and normal tension glaucoma have been documented in association with migraine. It is also important to keep in mind that many severe systemic and ocular conditions can present with very similar signs and symptoms to migraine, so recognizing key subtle differences becomes important in deciding which patients are most at risk and the timeline in which to order further testing. Migraine is a very common disorder, and many migraine sufferers will present to their primary eye care provider reporting visual symptoms or inquiring whether their headaches may be visually related. Being aware of the vast variety of ocular presentations possible can help eye care providers more effectively manage and treat these patients.

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