

Transient Neurologic Dysfunction in Migraine

Rod Foroozan, MD^{a,*}, F. Michael Cutrer, MD^b

KEYWORDS

- Migraine • Aura • Persistent aura • Retinal migraine
- Pathophysiology • Genetics

One of the most striking characteristics of migraine is the occurrence of transient neurologic dysfunction during the course of acute attacks. The symptoms, collectively termed “aura,” are the source of significant concern when first experienced by migraineurs. The prominence of these symptoms in medical historical writings that pertain to migraine has obscured the fact that they occur in only about a quarter of migraine sufferers and that they do not occur in every attack experienced by those who have the aura. Although within the general population migraine is likely to be one of the most common if not the most common setting for the combination of neurologic symptoms and headache, it is by no means the only setting in which the combination occurs. Care should be taken that neurologic symptoms identified as “migrainous” are truly consistent with the aura in terms of duration, development, and quality. Misidentification of neurologic symptoms as migrainous may delay correct diagnosis and treatment.

In this article we will discuss the aura as it occurs in the context of a migraine attack and review each of the major types: visual, sensory, and language aura. Because visual aura is the most common and the most well studied, it will be discussed in some detail and a thorough differential diagnosis presented.

GENERAL CLINICAL FEATURES OF MIGRAINE WITH AURA

Until the most recent International Headache Society (IHS) criteria were published in 2004 (International Classification of Headache Disorders 2 [ICHD2], 2004), the aura was classified into four types: (1) visual aura, by far the most common; (2) sensory aura and (3) language aura, which occur less commonly; and (4) motor aura, the least common. At present, the International Headache Society recognizes motor aura as

^a Department of Ophthalmology, Baylor College of Medicine, Cullen Eye Institute, 6565 Fannin NC-205, Houston, TX 77030, USA

^b Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55902, USA

* Corresponding author.

E-mail address: foroozan@bcm.tmc.edu (R. Foroozan).

a key manifestation of a specific type of migraine, hemiplegic migraine (HM). The reclassification is based on increasing genetic data in the familial hemiplegic form of hemiplegic migraine. While a detailed discussion of familial hemiplegic migraine (FHM) is beyond the scope of this review, it should be pointed out that patients with FHM usually report typical auras also.

Migraine with typical aura is a recurrent condition characterized by reversible neurologic symptoms, which typically develop over 5 to 20 minutes and resolve within 60 minutes. Migraine headache usually follows the aura, although, less commonly, pain may not be present. Visual symptoms are the most common manifestations in migraine aura. Typical aura with migraine has been characterized by the following criteria put forward by the IHS,¹ and the sensitivity and specificity of these criteria appear to be high:²

- A. At least two attacks fulfill criteria B to E
- B. Fully reversible visual or sensory or speech symptoms but no motor weakness
- C. At least two of the three following:
 1. Homonymous visual symptoms includes positive features (flickering lights, spots, lines) or negative features (loss of vision) or unilateral sensory symptoms
 2. At least one symptom develops gradually within 5 minutes or different symptoms occur in succession
 3. Each symptom lasts between 5 and 60 minutes
- D. Headache that meets criteria for B–D for migraine without aura, begins during the aura, or follows the aura within 60 minutes
- E. Not attributed to another disorder

There are certain characteristics of visual and sensory auras that may be used to distinguish them from ischemia-related symptoms. Both sensory and visual auras have a slow migratory or spreading quality in which symptoms slowly spread across the affected body part or the visual field, followed by a gradual return to normal function in the areas first affected after 20 to 60 minutes. This spreading quality is not characteristic of an ischemic event in which neurologic deficits tend to appear somewhat suddenly and tend to be equally distributed within the relevant vascular territory.³ In stroke, the affected area can certainly expand as blood flow drops in additional vessels; however, ischemic change is a more step-wise and less a smoothly spreading process. Although a migratory pattern is also seen in partial seizure disorders, its progression is generally much more rapid. Neither ischemia nor seizure are associated with the return of function in the areas first affected, even as symptoms are simultaneously appearing in newly affected areas.

Another feature which is suggestive of migraine aura is a tendency for different neurologic symptoms to occur sequentially. Almost all patients experiencing more than one type of aura during a single attack first recount the appearance of one aura type (most often visual), which is then followed by another aura type. Some patients experience all three typical auras in sequence during a single attack. In almost twenty years of asking patients to describe their aura, none have reported the appearance of all aura types at the same time.³ In contrast to migraine aura, the simultaneous manifestation of multiple types of neurologic symptoms is, however, quite common in cerebral ischemia.

In addition, migraine aura often has a biphasic quality inherent in its neurologic symptoms—with positive phenomena (eg, shimmering lights, zigzagging visual disturbances, or tingling paresthesias) appearing first, only to be followed within

a few minutes by negative symptoms (eg, scotoma, loss of visual image or numbness, or loss of sensation). Ischemic events do not tend to exhibit a bimodal progression of symptoms and while there may be a biphasic progression in the course of a seizure, progression is likely to occur at a much faster rate. In the language aura, making the same biphasic analogy is more difficult. While patients experiencing the language aura report both paraphasic errors and word retrieval errors (abnormal function), migraineurs seldom become mute (loss of function) during language aura. Assessing basic language function is complex given the importance of context. Obtaining accurate descriptions of language dysfunction during aura is also problematic because of the difficulties in laying down precise memories while language is disturbed.

The unilateral motor symptoms previously considered motor aura before their reassignment to the HM category actually differ in a couple of basic characteristics from the more common forms of aura. There is no apparent spread of symptoms over the course of an hour. In FHM, motor symptoms do not have positive and negative phases. No twitching or migratory spasm before weakness is noted by patients with hemiplegic migraine. However, the most prominent difference is the much greater average duration of motor weakness with HM. Patients with HM often have unilateral weakness for hours to days—which is much longer than the 60 minutes or less reported in the other aura types. As our knowledge of the pathophysiological mechanisms of each aura type improves, so will our understanding of whether or not the motor aura arises from a process analogous to those underlying the more common aura types.

EPIDEMIOLOGY OF MIGRAINE AURA

In a large population-based study, nosographic analysis of migraine aura from the mid 1990's, 163 patients were identified with migraine aura in a random, Danish sampling of 4,000 people.⁴ In this sample, visual aura was by far the most common symptom, occurring in 99% of subjects; this was followed by sensory and, then, by language auras. In 64% of patients, only visual aura occurred; whereas the other aura types typically happened in combination with another aura type (usually visual).⁵ Among 491 patients with migraine with aura, drawn from 1148 migraine patients entered into the Mayo Clinic Headache Registry, 489 (99%) reported having at least two episodes of visual aura, 225 (45%) language aura, 198 (40%) sensory aura, and 53 (11%) motor aura. Also noted in this population was a higher occurrence of nonvisual aura symptoms in the absence of visual disturbance (Cutrer, unpublished data, 2006).

TRANSIENT NEUROLOGIC DISTURBANCE IN MIGRAINE

Visual System Disturbance

Afferent visual dysfunction associated with migraine

Migraine is one of the most commonly seen disorders which cause transient visual loss. Afferent visual dysfunction is the most common sensory symptom in migraine with aura. Although efferent dysfunction has been reported with migraine (ophthalmoplegic migraine),⁶ we will focus solely on the afferent manifestation of visual loss and visual hallucinations.

Migraine visual aura

One classic form of visual aura is the fortification spectra (teichopsia), a jagged figure which builds or spreads outward (more commonly than inward) and leaves variable areas of visual loss behind (**Fig. 1**).^{3,7,8} The fortification lines are typically arranged at right angles to one another and begin from a paracentral area or “germ” (**Fig. 2**).⁷

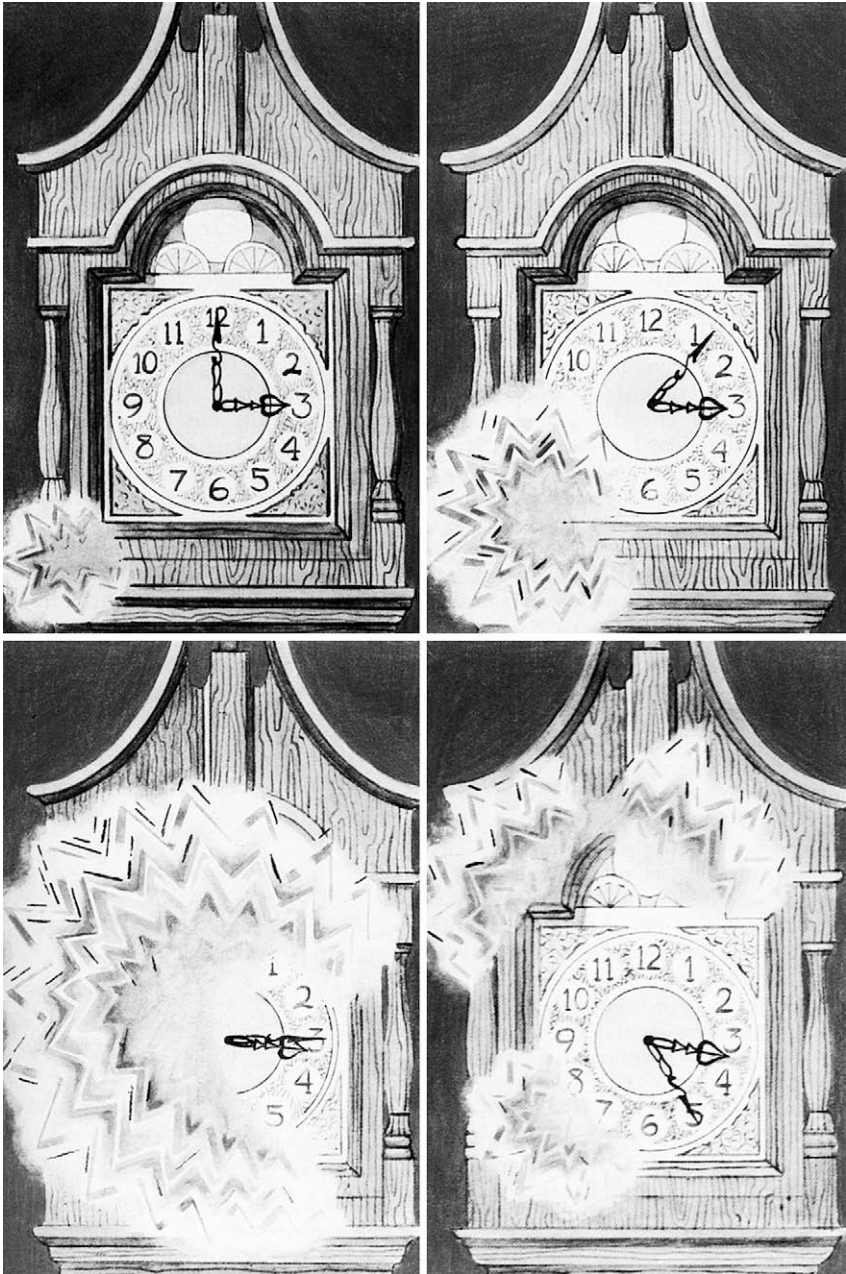


Fig. 1. Classical migrainous scintillating scotoma march and expansion of fortification figures. Initial small paracentral scotoma (*top left*). Enlarging scotoma 7 minutes later (*top right*). Scotoma obscuring much of central vision 15 minutes later (*bottom left*). Break-up of scotoma at 20 minutes (*bottom right*). From Hupp SL, Kline LB, Corbett JJ. Visual disturbances of migraine. *Surv Ophthalmol* 1989;33(4):221–36; with permission.

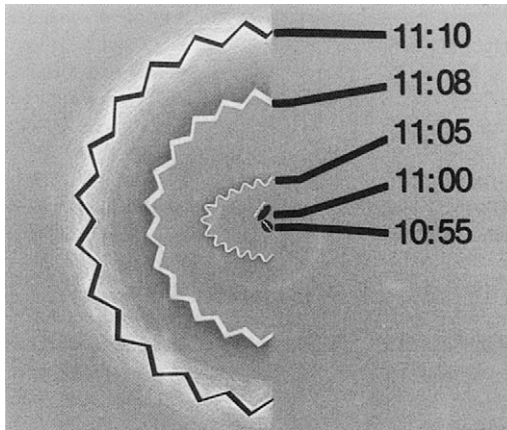


Fig. 2. Expansion of the visual aura of migraine from a "germ" in the paracentral visual field occurring over 15 minutes. *Reproduced from* Hupp SL, Kline LB, Corbett JJ. Visual disturbances of migraine. *Surv Ophthalmol* 1989;33(4):221–36; with permission.

There are often scintillations (which may be the most common visual symptom in migraine visual aura) that assume a semicircle or C shape, surrounding an area of visual loss (scotoma). The scintillations may be white, gray, or have colors similar to a kaleidoscope. Visual field defects often begin around fixation and spread outward. Scintillating scotomas are typically within one hemifield. Most commonly, these visual symptoms last 20 to 30 minutes in their entirety.

Other characteristic visual phenomena associated with migraine include sparkles, visual distortion (metamorphopsia), the appearance of objects being too large (macropsia) or too small (micropsia), visual perseveration (palinopsia), and the appearance of multiple images (cerebral polyopia). General visual blurring, like looking through a film or water, even without clear visual field loss, may be present. Objects may be seen as shimmering (such as "heat waves" on pavement) or rotating. Distortions of body image have been described in the "Alice in Wonderland" syndrome, thought to be more common in younger patients with migraine aura.⁹ Central color vision loss (dyschromatopsia) and loss of facial recognition (prosopagnosia) may occur.¹⁰ Environmental tilt may be present. Patients may complain of excessive brightness or light sensitivity (photophobia).

For diagnostic purposes, it may be helpful to show illustrations of migraine aura to patients with similar visual phenomena. A number of authors have detailed their own experience with migraine visual aura, often with accompanying illustrations.³ A number of examples of visual hallucinations related to migraine are depicted by Schott.¹¹ Although each of these symptoms may be characteristic of migraine, other ocular and neurologic disorders may cause visual symptoms and should be distinguished from migraine visual aura (**Box 1**).

Migraine aura may occur in the absence of headache (previously termed acephalgic migraine or migrainous accompaniments). This has been labeled by the IHS as typical aura without headache. The aura fulfills all of the criteria for migraine with aura. Visual dysfunction is the most common feature of migraine aura without headache, occurring 75% of the time.⁷

Persistent migraine visual aura

Persistent migraine visual aura most commonly consists of positive visual phenomena. These most commonly are formed (shapes or figures) or unformed (lights

Box 1**Causes of transient visual disturbance of afferent visual system****Monocular**

- Refractive error—myopia
- Vitreoretinal traction
- Inflammation—vitritis/retinitis/optic neuritis
- Amaurosis fugax—retinal microembolism
- Papilledema
- Optic disc drusen
- Congenital dysplasia of the optic disc
- Coagulopathies
- Vasculitis
- Hypotension—arrhythmia/orthostatic
- Anemia
- Ocular migraine

Binocular

- Migraine
- Seizure
- Occipital mass lesion—tumor or arteriovenous malformation
- Occipital ischemia—embolic, vasculitis, hypoperfusion

Reprinted from Hupp SL, Kline LB, Corbett JJ. Visual disturbances of migraine. Surv Ophthalmol 1989;33(4):221–36; with permission.

or sparkles) visual hallucinations.¹² The hallucinations are rarely more complex (metamorphopsia, palinopsia). Other ocular and neurologic conditions may cause these types of visual symptoms so that the diagnosis of persistent migraine visual aura is generally one of exclusion. There are no clear guidelines as to what tests should be performed to exclude other conditions (for example seizures, toxic-metabolic conditions, retinal inflammatory conditions, and psychiatric disease) which may cause persistent visual symptoms.

The IHS lists persistent migraine aura as a diagnosis with the following criteria:¹

Previous attacks fulfilling criteria for migraine with aura.

The present attack is typical of previous attacks, but one or more aura symptoms persist for more than 2 weeks.

Not attributed to another disorder.

There are no neuroimaging findings suggesting infarction. Most patients have hallucinations which are unformed and cover the entire visual field of both eyes. Although in some patients there is a clear history of migraine before the onset of symptoms,¹³ in others the link to migraine is more tenuous. Prior reports have noted that most patients with persistent migraine visual aura have no abnormalities on routine neuroimaging, electroencephalography, and ophthalmic examination. One report has noted hyperhomocysteinaemia in two patients with persistent visual auras which spontaneously resolved, but a cause-and-effect relationship remains unclear.¹⁴

Two descriptive patterns have been particularly common in patients with persistent visual aura. One is “visual snow” (sometimes referred to as primary persistent visual disturbance); the other is “television static.” There have been Web sites created with forums for discussion for patients with these symptoms (eg, www.visualsnow.com). Some patients notice symptoms only under certain lighting conditions or in certain circumstances. Not all patients with these symptoms have a clear history of migraine and, in some, the diagnosis of persistent migraine visual aura has been inferred because no other causes were evident. These visual symptoms may represent a distinct clinical disorder. Some authors have suggested that they be regarded as distinct from those with persistent migraine visual aura.¹⁵

The cause of persistent migraine visual aura remains unclear, but may be related to abnormal cortical neuronal inhibition. Single photon emission computed tomography and perfusion MRI have been reported to be abnormal during the persistent aura, which lasted 7 months, within one hemifield of a patient.¹⁶ Perfusion MRI performed after the symptoms resolved was normal. Cortical spreading edema, with restricted diffusion which spontaneously resolved, has been noted in a patient with persistent migraine visual aura.¹⁷ However, in patients with persistent visual aura (visual snow) no abnormality was noted on diffusion- or perfusion-weighted MRI.¹⁵

In some patients persistent aura may resolve spontaneously after a period of weeks to months; however, in others they may persist. Treatment of persistent visual aura has been attempted on a patient-by-patient basis, without clear success for one particular agent. Some success has been reported with antiepileptic agents including lamotrigine and valproate.^{18,19}

Persistent visual loss

Although most commonly transient, visual loss associated with migraine may be persistent. The visual loss may include loss of visual acuity or visual field. Fixed visual loss associated with migraine has been reported from involvement of multiple areas of the afferent visual pathway. Although migraine has been associated with pathology in each of these sites in the visual pathway, conclusive evidence is largely still lacking to support a definitive cause-and-effect relationship.

Retinopathy (choroidopathy) Persistent visual loss related to migraine has been described from retinal artery and vein occlusions, and retinal hemorrhages (see section on retinal migraine). Central serous choroidopathy and choroidopathy presumably from ischemia have been attributed to migraine.²⁰

Anterior ischemic optic neuropathy Anterior ischemic optic neuropathy (AION) is thought to involve infarction of the optic nerve head. It is the most common acute optic neuropathy which affects patients over the age of 50 years. Painless visual loss occurs over a period of days and is associated with signs of an optic neuropathy including a relative afferent pupillary defect (when unilateral or asymmetric), dyschromatopsia, and nerve fiber bundle or central visual field defects. Optic disc edema is present acutely, presumably because the anterior portion of the optic nerve is affected, and there is subsequent resolution of the disc swelling and the development of optic disc pallor over weeks to months.

Patients in whom migraine has been reported to be a cause of AION have generally been younger (under the age of 50 years).²¹⁻²⁵ Most patients reported with migraine-associated AION developed unilateral optic neuropathy, and were women. The severity of visual loss is variable with visual acuities from 20/15 (with mild nerve fiber bundle visual field defects) to light perception. In some patients reported to have migraine-associated AION, including the youngest reported, an 11 year old with sickle cell trait,

the diagnosis is not clear because there was no documentation of optic disc edema.²⁶ The onset of visual loss has been temporally related to an episode of migraine headache, and in all reported patients there was a history of chronic migraine.

Posterior ischemic optic neuropathy Posterior ischemic optic neuropathy (PION) is an uncommon type of ischemic optic neuropathy, which results from infarction of the intraorbital, intracanalicular, or intracranial optic nerve. The diagnosis of PION is made after other causes of retrobulbar optic neuropathy have been excluded. The clinical findings are similar to AION except that, acutely following the ischemic event in PION, fundusoscopic examination of the optic discs is normal, in contradistinction to the presence of optic disc edema in AION.

Three patients (in two reports) with migraine-associated PION have been reported.^{27,28} All three were women in their 20s who developed unilateral optic neuropathy with little or no loss of visual acuity and nerve fiber bundle type visual field defects. Two of the three patients had no other identifiable vascular risk factors apart from migraine.

Optic neuropathy related to ergotamine derivatives and treatment of migraine Ergot derivatives are known to cause vasoconstriction and may cause unwanted ischemic side effects such as stroke and myocardial infarction. Two reports of ischemic optic neuropathy^{29,30} and a third with bilateral “papillitis” and optic disc edema with a macular star³¹ have been reported. Ergotamine-induced vasospasm was suggested as the cause.

Migraine and optic disc drusen Optic disc drusen (hyaline bodies) are crystalline structures located within the anterior portion of the optic nerve. They occur in about 1 in 500 people and are bilateral in 75% of patients.³² The precise pathophysiology of optic disc drusen remains unclear, but continued calcium deposition due to abnormal axonal metabolism is thought to be the underlying cause. Optic disc drusen may be buried (not visible ophthalmoscopically) before they become visible during ophthalmoscopy. In both cases the optic disc may become elevated or swollen and resemble optic disc edema from elevated intracranial pressure. Patients are typically asymptomatic or have mild nerve fiber bundle visual field defects;³³ however, vascular complications, including retinal artery occlusions, retinal parapapillary hemorrhages,³⁴ and AION, have been reported in patients with optic disc drusen.

An association of migraine and optic disc drusen has been reported.³⁵ A 25 year old with migraine had sequential central retinal artery occlusions over an 8 year period and was found to have optic disc drusen.³⁶ The authors suggested that optic disc drusen and migraine may have combined to cause the visual loss. They also suggested that the apparent association of migraine and optic disc drusen may reflect the referral of patients with headache and elevated optic discs. Given how common each of these disorders is, the association between migraine and optic disc drusen may be coincidental.

Migraine and stroke Persistent visual loss may occur as a result from stroke involving the posterior visual pathways.^{37,38} The precise relationship between migraine and stroke remains unclear. Some studies have suggested that oral contraceptives may increase the risk of stroke in patients with migraine. Migraine aura has been reported to be risk factor for stroke in young women.³⁷ The IHS specifies that migrainous infarction occurs when the stroke can be directly attributable to migraine.¹

Stroke from migraine would be expected to cause a homonymous hemianopia,³⁹ an exception being the unilateral temporal visual field loss associated with the temporal crescent syndrome.

Retinal migraine

Migraine has long been listed as one cause of monocular transient visual loss (TVL). The assumption has been that transient loss of perfusion of the ocular circulation may occur in a similar fashion that is thought to occur in relation to vasospasm from migraine. The terminology for this potential process has been confusing and has included “ocular migraine” and “retinal migraine.” The term retinal migraine has been attributed to Carroll’s⁴⁰ description in 1970. In addition, the assumption has been that only the retinal circulation may be involved. However, TVL may also occur from impairment of the circulation to the choroid or optic nerve.

Visual symptoms include graying of vision or complete visual loss, sparkles or flashes, and a shade over a portion of the visual field in one eye. In most patients visual symptoms last less than 30 minutes.⁷ Some of the ambiguity in the diagnosis of TVL from migraine comes from the difficulty patients have distinguishing monocular visual loss from visual loss within the same hemifield in both eyes.⁴¹ In addition, monocular temporal visual symptoms from disorders of the visual cortex (temporal crescent syndrome) may cause confusion with disorders involving the anterior visual pathways. As alternative theories of the pathogenesis of migraine have evolved, so has the notion that retinal migraine is a common cause of TVL.

The IHS has provided criteria for the diagnosis of retinal migraine.¹ They include:

Description:

Repeated attacks of monocular visual disturbance, including scintillations, scotomata, or blindness, associated with migraine headache

Diagnostic criteria:

- A. At least two attacks fulfilling criteria B and C
- B. Fully reversible monocular positive or negative visual phenomena (scintillations, scotomata, or blindness) confirmed by examination during an attack or (after proper instruction) by the patient’s drawing of a monocular field defect during an attack
- C. Headache, fulfilling criteria B–D for Migraine without aura begins during the visual symptoms or follows them within 60 minutes
- D. Normal ophthalmologic examination between attacks
- E. Not attributed to another disorder

The criteria suggest that retinal migraine is a cause for recurrent, stereotypical episodes of monocular TVL which occurs during a migraine headache.⁴² The criteria also imply that before the diagnosis of retinal migraine is made patients should undergo a thorough evaluation to exclude other causes of monocular TVL.

An extension of this definition (this point is controversial; see the next two paragraphs and the section on persistent visual loss) has included patients with persistent monocular visual loss, including those with retinal infarction, and even those who have had visual symptoms and fulfilled the other criteria but lacked the headache.⁴³ Some reports have included photographic evidence of retinal ischemia, including changes within the retinal vasculature, suggestive of central or branch retinal artery occlusions, which have occurred in the setting of an otherwise typical migraine headache.^{44–46}

The incidence of retinal migraine and the existence of the condition itself remain hotly contested topics.^{41,47–50} In a review, IHS criteria were used to identify 46 patients (6 new patients and 40 from the literature) with retinal migraine.⁴³ In some cases patients were included with incomplete evaluations of monocular visual loss when the episodes occurred in the context of migraine headaches. The typical attack was characterized by visual loss lasting less than 1 hour and occurring

on the same side as the headache. The authors of this report noted that patients with retinal migraine were more commonly women with aura. Symptoms could be negative (visual loss) or positive (scintillations). The monocular visual loss from retinal migraine may accompany or may precede the headache, whereas in migraine with aura the visual symptoms typically precede the headache. Forty-three percent of patients ultimately experienced permanent monocular visual loss, possibly representing a form of migrainous infarction. They noted that this high rate of permanent visual loss may suggest the benefit of prophylactic therapy. Finally, the authors proposed changing the term “retinal migraine” to “migraine associated with monocular visual symptoms.”

These findings differ from those of another report, a literature review, which used a more strict IHS definition and categorized 142 patients with transient (103 patients) or fixed (39 patients) visual symptoms attributed to retinal migraine reported in 60 different manuscripts.⁵¹ Of these, only 16 with monocular TVL had findings suggestive of retinal migraine. Only 5 fulfilled the criteria for definite retinal migraine. Furthermore, none of the patients with persistent visual loss (for example from retinal arterial occlusion and ischemic optic neuropathy) could be categorized as having definite retinal migraine. Instead they suggested that the cause of monocular TVL in the patients presumed to have retinal migraine may be vasospasm or some other cause of anterior visual pathway pathology in the presence of headache or eye pain. Patients with vasospasm involving the ocular circulation have responded favorably to calcium-channel blockers.⁵²

It appears that using a strict definition of retinal migraine proposed by the IHS, the majority of patients reported with monocular TVL and reported as having retinal migraine do not strictly fulfill the IHS criteria, and suggest the need for a thorough evaluation to exclude other causes of TVL. Nevertheless, there are some descriptions of monocular visual loss which appear to fit the criteria inarguably.⁵³

The underlying cause of retinal migraine remains unclear. The same two broad theories as for cortical migraine have been suggested: vasospasm, which may account for some patients with persistence of visual loss from arterial occlusion, and neuronal spreading depression. Thus far, the evidence for spreading depression within the retina has not been as supported as that for the cerebral cortex.⁵¹

Visual field loss in migraine

Visual field abnormalities related to migraine and migraine aura are well known⁵⁴ and, most commonly, resolve completely. However, there is also a high rate of visual field defects in patients with migraine who are otherwise visually asymptomatic between attacks.⁵⁵ Using automated perimetry, 21 (35%) of 60 patients with migraine were found to have some abnormality on visual field testing.⁵⁶ Visual field loss was more common in those who were older or had a longer duration of disease. In another study, 3 (20%) of 15 patients were noted to have deficits on automated perimetry.⁵⁷ Kinetic perimetry, performed at least 7 days after an episode of migraine, has also revealed defects which have improved over time.⁵⁸ Test-retest variability during automated perimetry has been noted to be increased in patients with migraine.⁵⁹ Both length of migraine history and frequency of attacks appear to correlate with lower sensitivity on perimetry.⁶⁰ Generalized decreased sensitivity and focal deficits can be seen.

Visual field deficits have been noted using short-wavelength automated perimetry,⁶¹ and some authors have suggested a deficit in a specific retinal circuit.⁶² Several reports have linked migraine with glaucoma, including low-tension glaucoma.⁶³ Visual field defects in some studies have suggested precortical (anterior visual pathway) pathology. A study of 16 patients with migraine (15 with aura), used both static and

temporally modulated targets with an automated perimeter. Perimetry was conducted 7 days after the onset of a headache. Visual field losses were noted with temporal modulation perimetry in 11 of 16 migraine patients, even in the presence of normal static visual fields. The authors suggested that this pattern is similar to that seen in the early stages of glaucoma.⁵⁷

Sensory System Dysfunction in Migraine

The migraine sensory aura most often starts as unilateral tingling or “paresthesias” in a hand or distal arm, which slowly migrates proximally, only to jump from the arm to the ipsilateral face before reaching the shoulder. The crawling, tingling sensation moves from the cheek and side of the nose, across the perioral region and lips, then spreads inside the mouth, to involve the ipsilateral buccal mucosa and half of the tongue.³ Paresthesias or a “feeling of needles and pins” are usually the first sensory symptoms, leaving numbness in their wake,⁶⁴ although auras which consist of numbness primarily also occur. Russell and Olesen, in a study of 51 patients with sensory aura, reported that the hand (96% of cases) and face (67%) were the body parts most commonly affected, whereas the leg (24%) and torso (18%) were much less likely to be involved. The sensory symptoms, recorded in Russell and Olesen’s series of individuals, progressed for less than 30 minutes (82%). The unilateral symptoms of sensory aura are frequently quite distressing for patients, especially at their first appearance, because of their similarity to those of stroke or transient ischemic attack. Although the presence of migraine aura does, in fact, seem to be an independent risk factor of ischemic stroke in women who have a low level of other cardiovascular risk factors,⁶⁵ the overall increase in absolute risk attributable to migraine with aura when compared with other factors is modest. There are clinical features that help to distinguish sensory aura from stroke. The spread of paresthesias across the face and into the mouth to affect half the tongue is a classical feature of migraine sensory aura and is rarely seen in cases of cerebrovascular ischemia.⁶⁶

Language System Aura Dysfunction

Because it is relatively uncommon, language disturbance during migraine aura may be overlooked in the history unless the patient is specifically asked about it. While speech disturbance may result from numbness and tingling in the mouth or tongue, as the sensory aura gradually migrates intraorally, this is distinct from language aura. In language aura, patients have impaired language comprehension, marked word-finding difficulties, and a decreased ability to read or write—implying more than just a pure sensory or proprioceptive disturbance. Interestingly, language aura seems to occur with a higher frequency in patients with hemiplegic migraine than in those with typical aura only (approximately 20% in typical aura versus 47% in hemiplegic migraine).⁶⁷ In another series of patients with language aura, 76% had paraphasic errors, 72% had other production problems and 38% had impaired comprehension.⁴ Fortunately, the very distressing symptoms of language disturbance tend to persist for less than 30 minutes in most patients.⁴ A recent questionnaire based on case series reported other instances of symptomatic cortical dysfunction including proper name anomia, ideational apraxia, and proposagnosia.¹⁰

PATHOPHYSIOLOGY OF MIGRAINE AURA

The aura has figured prominently in migraine pathophysiological research. Until the 1980s, the vasogenic theory of migraine was used to explain the aura. It postulated that the aura occurred as the consequence of an initial vasoconstrictive phase in the

migraine attack. However, as early as the 1940s, proponents of the neurogenic theory of migraine hypothesized that the aura was the clinical manifestation of a spreading abnormality which moved over the visual cortex at a rate of 3 to 5 mm per minute. This spreading abnormality was believed to be atypical for ischemia. Around the same time, Leao,⁶⁸ a neurophysiologist, described an electrophysiological phenomenon, characterized by cortical hyperexcitation followed by suppression, which originated and migrated over areas of contiguous cortex in experimental animals at a slow rate of 3 to 4 mm per minute, after chemical or mechanical stimulations. This phenomenon, which Leao called cortical spreading depression (CSD), has been proposed as the cause of migraine aura, based on its slow rate of cortical spread which is similar to that extrapolated for migraine aura across visual cortex.⁶⁹ The fact that both CSD and aura move across neurovascular boundaries strengthens this hypothesis. The neurogenic theory proposes that the drops in blood flow observed during migraine aura are the direct consequence of reduced metabolic demand in abnormally functioning neurons, rather than the vasoconstriction. Evidence from functional imaging techniques, applied during the aura phase in humans, has increasingly supported the neurogenic theory.

Functional Neuroimaging and the Migraine Aura

Beginning in the early 1980s, various functional imaging techniques^{70–72} employed during aura symptoms have supported a CSD or CSD-like phenomenon as the underlying mechanism of the migraine aura. One of the most recent of these studies applied blood-oxygen-level-dependent (BOLD) imaging, to aura. BOLD imaging is based on known increases in MRI signal intensity that occur in response to decreases in local deoxyhemoglobin concentration.⁷³ In this study, BOLD imaging was performed before, during and after exercise-induced visual auras.⁷⁴ BOLD imaging was also performed during aura symptoms in two spontaneous auras. During visual aura there was a loss of cortical activation to visual stimuli in the occipital lobe contralateral to the visual field in which a scotoma was reported by the patient. As the visual symptoms resolved, cortical activation within the affected occipital lobe returned to normal. In the study of the induced aura, BOLD imaging was initiated after exercise but before the onset of symptoms, was performed continuously during the visual symptoms, and was continued well into the headache phase after complete resolution of the visual symptoms. With the onset of the aura symptoms, loss of cortical activation to visual stimulation was observed first in V3a, an area of visual association cortex, rather than in the primary visual cortex. Over the next 30 to 40 minutes, the portion of visual cortex which was unresponsive to visual stimulation expanded to involve neighboring occipital cortex at a rate of 3.5 mm per minute, eventually encompassing large areas of the ipsilateral primary visual and association cortices. The BOLD functional MRI (fMRI) findings observed during human migraine aura are very similar to those that have been seen in CSD induced in animal experiments,⁷⁵ indicating that a human process analogous to CSD might be the source of migraine visual aura. It is important to note that findings from two cases of spontaneous migraine visual aura studied with BOLD imaging were the same as those observed during later time points in the exercise-induced aura.

Findings from fMRI performed on patients experiencing prolonged or persistent aura have been inconsistent.^{15,16,76,77}

Altered Cortical Function in Migraine with Aura

There is accumulating evidence that differences in patients who experience migraine aura have altered cortical function. Such differences may account for their

susceptibility to recurrent episodes of aura. In the 1980s and 1990s,³¹ P magnetic resonance spectroscopic (MRS) studies indicated altered phosphocreatine/inorganic phosphate ratios (index of brain phosphorylation potential),^{78,79} indicating altered neuronal energy metabolism. Other MRS studies have shown low magnesium levels in the occipital cortex of migraine aura sufferers,⁸⁰ suggesting lowered thresholds for induction of a CSD or CSD-like phenomenon by way of disinhibition of NMDA receptor activity.⁸¹ Interestingly, a more recent MRS study of migraine aura revealed that patients who experienced purely visual aura had baseline elevated lactate levels which showed no changes despite prolonged visual stimulation between migraine attacks. Conversely, patients who reported experiencing episodes of visual aura symptoms plus an additional aura type (sensory, language, or motor) had levels of brain lactate which were not elevated compared with those in healthy controls, but increased rather sharply with prolonged visual stimulation.⁸² The causes of these unexpected findings are not clear.

Electrophysiological studies, which have employed various evoked potential modalities, have consistently demonstrated a decrease in habituation in the cortex of migraineurs with aura after repeated stimulation compared with normal controls. This altered habituation response has led to the hypothesis that a deficiency in habituation related to abnormal functioning in the subcortical aminergic pathways is critical in vulnerability to aura.⁸³ Other electrophysiological evidence from transcranial magnetic stimulation-based studies also indicates altered cortical excitability in migraineurs who experience aura.⁸⁴ Although all of the details of altered cortical processing in patients who experience the aura are not yet available, the body of evidence indicating that such differences exist is growing. There seems to be an increasing likelihood that such differences are important in the generation of the aura.

Genetic Factors

Currently, it is clear that the propensity to experience recurrent episodes of migraine aura are to a large extent genetically determined. Several genetic loci have been linked to typical migraine with aura (**Table 1**). This list excludes the genetic loci linked to FHM.

Table 1 Loci with reported association with migraine aura			
Chromosome/Locus	Gene/Protein	Migraine Type	Reference
1 p36	MTHF-R	MA	86
4 q24	?	MA	87
6 p12–21	?	MA MO	88
6 q25.1	Estrogen receptor 1 (ESR1)	MA & MO	89
11 q22–23	Progesterone receptor (PGR)	MA & MO	90
11 q23	Dopamine D2 (DRD2) Ncol	MA	91
11 q23	Dopamine D2 (DRD2) Ncol	MA	92
11 q24	?	MA	93
15 q11–q13	?GABA-A	MA	94
17 q11.1–q12	Human serotonin transporter (SLC6A4)	MA & MO	95

Abbreviations: MA, migraine with aura; MO, migraine without aura; MTHF-R, Methylene tetrahydrofolate reductase.

However, one should remember that patients with FHM may also experience typical auras.

The genetic determinants of migraine aura probably consist of a number of loci which, based on the presence of certain polymorphisms, confer greater or lesser susceptibility to aura. Each of these potential "susceptibility genes" individually have a low-to-moderate effect.⁸⁵ It is the vector sum of these effects that determine, for a given individual, his or her overall level of susceptibility to aura and many of the clinical features of their migraine syndrome in general. It is also possible that when susceptibility conferring polymorphisms occur in the same individual, they might act synergistically to produce the migraine phenotype. Such complex genetic interactions will probably be difficult to detect by traditional single-locus linkage analysis and will probably require association studies performed in very large samples.

SUMMARY

Neurologic symptoms that accompany migraine in about one quarter of migraine patients are classically transient and occur as the result of cortical phenomena. Visual symptoms of migraine aura are by far the most common type. The visual aura may include positive and negative symptoms which occur within the homonymous visual field and characteristically last in the range of 30 minutes. Persistent migraine visual aura is uncommon and may be a distinct entity from primary persistent visual disturbance (visual snow). Transient monocular visual symptoms associated with migraine (often referred to as "retinal migraine") may be less frequent than originally suggested. Migraine has rarely been associated with fixed visual loss (most commonly from stroke, ischemic optic neuropathy, or retinal vascular occlusion), but evidence for a cause-and-effect mechanism remains somewhat limited. Other aura symptoms include unilateral sensory symptoms and language disturbance. Until recently, motor symptoms were included as an aura type. However, because of increasing genetic information as to the origin of motor aura, it has been reclassified as an integral part of a distinct migraine subtype known as hemiplegic migraine. Although patients with hemiplegic migraine also generally experience more typical visual, sensory, and language auras, the motor symptoms are of longer duration and it is unclear whether they arise from an analogous phenomenon. Recent data from functional neuroimaging suggest that the more common aura symptoms may arise from a cortical spreading depression-like process. The tendency for aura appears to be influenced by complex genetic factors and the overall susceptibility is likely to be based on polymorphisms at multiple loci and may be modulated by epigenetic factors.

REFERENCES

1. International classification of headache disorders, 2nd edition. *Cephalalgia* 2004;24:1-160.
2. Eriksen MK, Thomsen LL, Olesen J. Sensitivity and specificity of the new international diagnostic criteria for migraine with aura. *J Neurol Neurosurg Psychiatr* 2005;76(2):212-7.
3. Cutrer FM, Huerter K. Migraine aura. *Neurologist* 2007;13(3):118-25.
4. Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. *Brain* 1996;119:335-61.
5. Russell MB, Iversen HK, Olesen J. Improved description of the migraine aura by a diagnostic aura diary. *Cephalalgia* 1994;14:107-17.
6. Carlow TJ. Oculomotor ophthalmoplegic migraine: is it really migraine? *J Neuroophthalmol* 2002;22(3):215-21.

7. Hupp SL, Kline LB, Corbett JJ. Visual disturbances of migraine. *Surv Ophthalmol* 1989;33(4):221–36.
8. Spector RH. Migraine. *Surv Ophthalmol* 1984;29(3):193–207.
9. Evans RW, Rolak LA. The Alice in Wonderland syndrome. *Headache* 2004;44(6):624–5.
10. Vincent MB, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. *Cephalalgia* 2007;27(12):1368–77.
11. Schott GD. Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration. *Brain* 2007;130(Pt 6):1690–703.
12. Liu GT, Schatz NJ, Galetta SL, et al. Persistent positive visual phenomena in migraine. *Neurology* 1995;45(4):664–8.
13. San-Juan OD, Zermeno PF. Migraine with persistent aura in a Mexican patient: case report and review of the literature. *Cephalalgia* 2007;27(5):456–60.
14. Cupini LM, Stipa E. Migraine aura status and hyperhomocysteinaemia. *Cephalalgia* 2007;27(7):847–9.
15. Jager HR, Giffin NJ, Goadsby PJ. Diffusion- and perfusion-weighted MR imaging in persistent migrainous visual disturbances. *Cephalalgia* 2005;25(5):323–32.
16. Relja G, Granato A, Ukmar M, et al. Persistent aura without infarction: description of the first case studied with both brain SPECT and perfusion MRI. *Cephalalgia* 2005;25(1):56–9.
17. Berezcki D, Kollar J, Kozak N, et al. Cortical spreading edema in persistent visual migraine aura. *Headache* 2008;48(8):1226–9.
18. Rothrock JF. Successful treatment of persistent migraine aura with divalproex sodium. *Neurology* 1997;48(1):261–2.
19. Chen WT, Fuh JL, Lu SR, et al. Persistent migrainous visual phenomena might be responsive to lamotrigine. *Headache* 2001;41(8):823–5.
20. Narita AS, Elder JE. Ocular migraine in an eight-year-old girl. *Aust N Z J Ophthalmol* 1994;22(4):275–7.
21. Katz B. Bilateral sequential migrainous ischemic optic neuropathy. *Am J Ophthalmol* 1985;99(4):489.
22. Katz B, Bamford CR. Migrainous ischemic optic neuropathy. *Neurology* 1985;35(1):112–4.
23. O'Hara M, O'Connor PS. Migrainous optic neuropathy. *J Clin Neuroophthalmol* 1984;4(2):85–90.
24. McDonald WI, Sanders MD. Migraine complicated by ischaemic papillopathy. *Lancet* 1971;2(7723):521–3.
25. Weinstein JM, Feman SS. Ischemic optic neuropathy in migraine. *Arch Ophthalmol* 1982;100(7):1097–100.
26. Lana-Peixoto MA, Barbosa A. Anterior ischaemic optic neuropathy in a child with AS haemoglobinopathy and migraine. *Br J Ophthalmol* 1998;82(2):199–200.
27. Lee AG, Brazis PW, Miller NR. Posterior ischemic optic neuropathy associated with migraine. *Headache* 1996;36(8):506–10.
28. Foroozan R, Marx DP, Evans RW. Posterior ischemic optic neuropathy associated with migraine. *Headache* 2008;48(7):1135–9.
29. Chiari M, Manzoni GC, Van de Geijn EJ. Ischemic optic neuropathy after sumatriptan in a migraine with aura patient. *Headache* 1994;34(4):237–8.
30. Sommer S, Delemazure B, Wagner M, et al. [Bilateral ischemic optic neuropathy secondary to acute ergotism]. *J Fr Ophtalmol* 1998;21(2):123–5.
31. Wollensak J, Grajewski O. [Bilateral vascular papillitis following ergotamin medication]. [author's transl]. *Klin Monatsbl Augenheilkd* 1978;173(5):731–7.

32. Auw-Haedrich C, Staubach F, Witschel H. Optic disk drusen. *Surv Ophthalmol* 2002;47(6):515–32.
33. Wilkins JM, Pomeranz HD. Visual manifestations of visible and buried optic disc drusen. *J Neuroophthalmol* 2004;24(2):125–9.
34. Gaynes PM, Towle PA. Hemorrhage in hyaline bodies (drusen) of the optic disc during an attack of migraine. *Am J Ophthalmol* 1967;63(6):1693–6.
35. Ramirez H, Blatt ES, Hibri NS. Computed tomographic identification of calcified optic nerve drusen. *Radiology* 1983;148(1):137–9.
36. Newman NJ, Lessell S, Brandt EM. Bilateral central retinal artery occlusions, disk drusen, and migraine. *Am J Ophthalmol* 1989;107(3):236–40.
37. Bousser MG, Baron JC, Iba-Zizen MT, et al. Migrainous cerebral infarction: a tomographic study of cerebral blood flow and oxygen extraction fraction with the oxygen-15 inhalation technique. *Stroke* 1980;11(2):145–53.
38. Robinson BE. Permanent homonymous migraine scotomata. *AMA Arch Ophthalmol* 1954;53(4):566–7.
39. Wakakura M, Ichibe Y. Permanent homonymous hemianopias following migraine. *J Clin Neuroophthalmol* 1992;12(3):198–202.
40. Carroll D. Retinal migraine. *Headache* 1970;10(1):9–13.
41. Lepore FE. Retinal migraine. *J Neuroophthalmol* 2007;27(3):242–3, author reply 4–5.
42. Evans RW, Grosberg BM. Retinal migraine associated with monocular visual symptoms. *Headache* 2008;48(1):142–5.
43. Grosberg BM, Solomon S, Friedman DI, et al. Retinal migraine reappraised. *Cephalalgia* 2006;26(11):1275–86.
44. Doyle E, Vote BJ, Casswell AG. Retinal migraine: caught in the act. *Br J Ophthalmol* 2004;88(2):301–2.
45. Glenn AM, Shaw PJ, Howe JW, et al. Complicated migraine resulting in blindness due to bilateral retinal infarction. *Br J Ophthalmol* 1992;76(3):189–90.
46. Pandit JC, Fritsche P. Permanent monocular blindness and ocular migraine. *J R Soc Med* 1997;90(12):691–2.
47. Grosberg BM, Solomon S. Retinal migraine: two cases of prolonged but reversible monocular visual defects. *Cephalalgia* 2006;26(6):754–7.
48. Solomon S, Grosberg BM, Friedman DI, et al. Retinal migraine. *J Neuroophthalmol* 2007;27(3):243–4, author reply 4–5.
49. Winterkorn JM. “Retinal migraine” is an oxymoron. *J Neuroophthalmol* 2007;27(1):1–2.
50. Daroff RB. Retinal migraine. *J Neuroophthalmol* 2007;27(1):83.
51. Hill DL, Daroff RB, Ducros A, et al. Most cases labeled as “retinal migraine” are not migraine. *J Neuroophthalmol* 2007;27(1):3–8.
52. Winterkorn JM, Kupersmith MJ, Wirtschafter JD, et al. Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 1993;329(6):396–8.
53. Robertson DM. I am a retinal migraineur. *J Neuroophthalmol* 2008;28(1):81–2.
54. Ebner R. Visual field examination during transient migrainous visual loss. *J Clin Neuroophthalmol* 1991;11(2):114–7.
55. McKendrick AM, Vingrys AJ, Badcock DR, et al. Visual dysfunction between migraine events. *Invest Ophthalmol Vis Sci* 2001;42(3):626–33.
56. Lewis RA, Vijayan N, Watson C, et al. Visual field loss in migraine. *Ophthalmology* 1989;96(3):321–6.
57. McKendrick AM, Vingrys AJ, Badcock DR, et al. Visual field losses in subjects with migraine headaches. *Invest Ophthalmol Vis Sci* 2000;41(5):1239–47.

58. Drummond PD, Anderson M. Visual field loss after attacks of migraine with aura. *Cephalalgia* 1992;12(6):349–52.
59. McKendrick AM, Badcock DR. Decreased visual field sensitivity measured 1 day, then 1 week, after migraine. *Invest Ophthalmol Vis Sci* 2004a;45(4):1061–70.
60. McKendrick AM, Badcock DR. An analysis of the factors associated with visual field deficits measured with flickering stimuli in between migraine. *Cephalalgia* 2004;24(5):389–97.
61. Yenice O, Temel A, Incili B, et al. Short-wavelength automated perimetry in patients with migraine. *Graefes Arch Clin Exp Ophthalmol* 2006;244(5):589–95.
62. Tibber MS, Shepherd AJ. Transient tritanopia in migraine: evidence for a large-field retinal abnormality in blue-yellow opponent pathways. *Invest Ophthalmol Vis Sci* 2006;47(11):5125–31.
63. Corbett JJ, Phelps CD, Eslinger P, et al. The neurologic evaluation of patients with low-tension glaucoma. *Invest Ophthalmol Vis Sci* 1985;26(8):1101–4.
64. Lord GDA. Clinical characteristics of the migrainous aura. In: Amery WK, Wauquier A, editors. *The prelude to the migraine attack*. London: Baillière Tindall; 1986. p. 87–98.
65. Kurth T, Schürks M, Logroscino G, et al. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. *BMJ* 2008;337:a636.
66. Fisher CM. Late-life migraine accompaniments: further experience. *Stroke* 1986;17:1033–42.
67. Bradshaw P, Parsons M. Hemiplegic migraine, a clinical study. *QJM* 1965;34:3465–85.
68. Leao AAP. Spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1944;7:359–90.
69. Milner P. Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao. *Electroencephalogr Clin Neurophysiol* 1958;10:705.
70. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. *Ann Neurol* 1981;9:344–52.
71. Lauritzen M, Skyhoj Olsen T, Lassen NA, et al. Changes of regional cerebral blood flow during the course of classical migraine attacks. *Ann Neurol* 1983;13:633–41.
72. Cutrer FM, Sorensen AG, Weisskoff RM, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. *Ann Neurol* 1998;43(1):25–31.
73. Sorensen AG, Rosen BR. Functional MRI of the brain. In: Atlas S, editor. *Magnetic resonance imaging of the brain and spine*. 2nd edition. Philadelphia: Lippcott-Raven Publishers; 1996.
74. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A* 2001;98(8):4687–92.
75. James MF, Smith MI, Bockhorst KH, et al. Cortical spreading depression in the gyrencephalic feline brain studied by magnetic resonance imaging. *J Physiol* 1999;519(Pt 2):415–25.
76. Smith M, Cros D, Sheen V. Hyperperfusion with vasogenic leakage by fMRI in migraine with prolonged aura. *Neurology* 2002;58(8):1308–10.
77. Gekeler F, Holtmannspotter M, Straube A, et al. Diffusion-weighted magnetic resonance imaging during the aura of pseudomigraine with temporary neurologic symptoms and lymphocytic pleocytosis. *Headache* 2002;42(4):294–6.

78. Welch KMA, Levine SR, D'Andrea G, et al. Brain pH during migraine studied by in-vivo 31-phosphorus NMR spectroscopy. *Cephalalgia* 1988;8:273–7.
79. Welch KMA, Levine SR, D'Andrea G, et al. Preliminary observations on brain energy metabolites in migraine studied by in vivo 31-phosphorus NMR spectroscopy. *Neurology* 1989;39:538–41.
80. Welch KMA, Barkley GL, Ramadan NM, et al. NMR spectroscopic and magnetoencephalographic studies in migraine with aura: support for the spreading depression hypothesis. *Pathol Biol* 1992;40(4):349–54.
81. van Harreveld A, Fifekova E. Mechanisms involved in spreading depression. *J Neurobiol* 1973;4:375–87.
82. Sandor PS, Dydak U, Schoenen J, et al. MR-spectroscopic imaging during visual stimulation in subgroups of migraine with aura. *Cephalalgia* 2005;25(7):507–18.
83. Ambrosini A, de Noordhout AM, Sandor PS, et al. Electrophysiological studies in migraine: a comprehensive review of their interest and limitations. *Cephalalgia* 2003;23(Suppl 1):13–31.
84. Aurora SK, Welch KM, Al-Sayed F. The threshold for phosphenes is lower in migraine. *Cephalalgia* 2003;23(4):258–63.
85. Lea RA, Nyholt DR, Curtain RP, et al. A genome-wide scan provides evidence for loci influencing a severe heritable form of common migraine. *Neurogenetics* 2005;6(2):67–72.
86. Kara I, Sazci A, Ergul E, et al. Association of the C677T and A1298C polymorphisms in the 5,10 Methylene tetrahydrofolate reductase gene in patients with migraine risk. *Brain Res Mol Brain Res* 2003;111(1–2):84–90.
87. Wessman M, Kallela M, Kaunisto MA, et al. A susceptibility locus for migraine with aura, on chromosome 4q24. *Am J Hum Genet* 2002;70:652–62.
88. Carlsson A, Forsgren L, Nylander P-O, et al. Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1. *Neurology* 2002;59:1804–7.
89. Colson N, Lea R, Quinlan S, et al. The estrogen receptor 1G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. *Neurogenetics* 2004;5:129–33.
90. Colson N, Lea R, Quinlan S, et al. Investigation of hormone receptor genes in migraine. *Neurogenetics* 2005;6:17–23.
91. Peroutka SJ, Price SC, Wilhoit TL. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. *Mol Med* 1998;4(1):14–21.
92. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) NcoI alleles. *Neurology* 1997;49(1):201–6.
93. Cader ZM, Noble-Topham S, Dyment DA, et al. Significant linkage to migraine with aura on chromosome 11q24. *Hum Mol Genet* 2003;12(19):2511–7.
94. Russo L, Mariotti P, Sangiorgi E, et al. A new susceptibility locus for migraine with aura in the 15q11-q13 genomic region containing three GABA-A receptor genes. *Am J Hum Genet* 2005;76(2):327–33.
95. Ogilvie AD, Russell MB, Dhall P. Altered allelic distributions of the serotonin transporter gene in migraine without aura and migraine with aura. *Cephalalgia* 1998;18(1):23–6.