The Migraine Aura

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ABSTRACT

PURPOSE OF REVIEW: This article discusses the basic mechanisms of migraine aura and its clinical significance based upon evidence from human studies and animal models.

RECENT FINDINGS: Prospective clinical studies have reinforced the understanding that migraine aura is highly variable from one individual to the next as well as from attack to attack in an individual. While migraine with aura clearly has a higher heritability than migraine without aura, population studies have not identified specific genes that underlie this heritability for typical migraine with aura. Imaging studies reveal hypoperfusion associated with migraine aura, although the timing and distribution of this hypoperfusion is not strictly correlated with migraine symptoms. Mapping of migraine visual aura symptoms onto the visual cortex suggests that the mechanisms underlying the aura propagate in a linear fashion along gyri or sulci rather than as a concentric wave and also suggests that aura may propagate in the absence of clinical symptoms. Cortical spreading depression in animal models continues to be a translational model for migraine, and the study of spreading depolarizations in the injured human brain has provided new insight into potential mechanisms of cortical spreading depression in migraine. Migraine with aura has multiple comorbidities including patent foramen ovale, stroke, and psychiatric disorders; the shared mechanisms underlying these comorbidities remains a topic of active investigation.

SUMMARY: Although it occurs in the minority of patients with migraine, aura may have much to teach us about basic mechanisms of migraine. In addition, its occurrence may influence clinical management regarding comorbid conditions and acute and preventive therapy.

INTRODUCTION

The aura is a remarkably complex and variable feature of migraine that has significant implications regarding pathophysiology, comorbidities, and therapy. While it has been recorded in detail for centuries, the understanding of migraine aura continues to evolve. This article describes the classification of migraine aura, its clinical features, its basic mechanisms, and its relevance to clinical management.

Migraine aura is described in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) as "recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache

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RELATIONSHIP DISCLOSURE:
Dr Charles receives personal compensation for serving on the advisory boards of Alder BioPharmaceuticals, Inc; Biohaven Pharmaceutical; Eli Lilly and Company; and eNeura Inc. Dr Charles receives personal compensation for serving as associate editor of *Cephalalgia*; as CME program speaker of Medicom and Medlearning Group; and as a consultant for Amgen Inc. Dr Charles has served as an expert witness in legal proceedings for Milano & Wanat LLC.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Charles discusses the unlabeled/investigational use of ketamine for the treatment for migraine aura.

and associated migraine symptoms."[1] Refer to TABLE 2-1 for detailed *ICHD-3* diagnostic criteria of migraine with aura.

CLINICAL FEATURES OF MIGRAINE AURA

A key point regarding the definition of migraine aura is its gradual onset and progression in contrast to the abrupt onset of symptoms that is typical of brain ischemia or hemorrhage. Also, unlike with ischemia, positive visual and sensory symptoms (eg, flashing lights, paresthesia) are more common than negative ones.[2,3] These symptoms reflect an underlying physiologic phenomenon that begins slowly and spreads slowly (CASE 2-1).

The clinical features of migraine aura are remarkably variable both from one individual to the next as well as from attack to attack in an individual.[2,3] Visual aura symptoms are by far the most common, occurring in 90% or more of patients, followed by sensory, language, and motor symptoms.[3] When sensory, language, or motor aura symptoms do occur, they most commonly occur in conjunction with visual symptoms, although nonvisual aura symptoms occasionally occur in isolation.[2,3] In some but not all patients, a consistent temporal progression from visual symptoms to other aura symptoms occurs.[3] The basis for the propensity of migraine aura to involve the visual cortex remains unclear. It has been speculated that the higher neuron-to-astrocyte ratio in the

TABLE 2-1 ***ICHD-3* Diagnostic Criteria for Migraine With Aura**[a]

A At least two attacks fulfilling criteria B and C

B One or more of the following fully reversible aura symptoms

1 Visual
2 Sensory
3 Speech and/or language
4 Motor
5 Brainstem
6 Retinal

C At least three of the following six characteristics

1 At least one aura symptom spreads gradually over ≥5 minutes
2 Two or more aura symptoms occur in succession
3 Each individual aura symptom lasts 5 to 60 minutes
4 At least one aura symptom is unilateral
5 At least one aura symptom is positive
6 The aura is accompanied, or followed within 60 minutes, by headache

D Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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visual cortex could be involved or that the distinct columnar organization of the cortex could play a role.

Although the scintillating scotoma is the classically described visual aura phenomenon, flashing lights is a more commonly reported visual disturbance.[2] Isolated scotomas and other distortions of vision are also common. When the scintillating scotoma of migraine does occur, it typically begins at the center of the visual field and expands outward, but it can also begin peripherally and propagate toward the center. Individual patients may have multiple sites of migraine aura initiation in the visual cortex. The visual aura percept may propagate throughout an entire visual field or may remain spatially limited.[4] Some patients may simply report blurred vision, but no consensus exists about whether blurred vision should be considered an aura symptom. Sensory symptoms are typically paresthesia of the hand and face, although numbness may also occur, and the distribution may spread to involve the trunk and lower extremity in some patients.[3] The most common language symptom is

CASE 2-1

A 27-year-old woman with a history of episodic headache presented for evaluation of new transient visual, sensory, and language symptoms. She reported that 2 days ago she had an episode consisting of "flashing lights" that gradually spread to involve most of the right side of her vision. She had difficulty focusing her vision while this occurred. While the visual symptoms were occurring, she noticed a mild global headache and light sensitivity. About 5 minutes after the visual disturbance began, she experienced a tingling sensation on the right side of her face and her right hand, and at some point after this, she noticed that she was having difficulty speaking. She also noticed that her right arm felt "clumsy." The visual symptoms and difficulty speaking resolved after approximately 30 minutes, but she continued to feel some tingling of her face and had mild impairment of coordination of her right hand for several hours. She had moderate bilateral headache for the next 24 hours, after which all her symptoms had resolved completely. She had not been taking any medications until 2 weeks prior to this episode, when she had started on an oral contraceptive preparation. Her neurologic examination was entirely normal.

COMMENT

This case describes a typical presentation of a migraine aura. The gradual onset and progression of symptoms is reassuring, indicating that her symptoms are likely not due to cerebral ischemia. Although visual symptoms are most common, sensory, language, and motor symptoms may occur. "Flashing lights" are a common migraine visual aura description; aura symptoms may vary from attack to attack in a given individual. Typically, but not always, visual symptoms precede other aura symptoms. Other migraine symptoms including headache and light sensitivity may accompany rather than follow aura or may not occur at all. New onset of aura may happen in patients with migraine in times of hormonal change, particularly during pregnancy or following the initiation of hormonal therapies.

word-finding difficulty, but a variety of dysphasic language disturbances may occur.[3] The typical duration of aura is 30 minutes; however, in some cases, the aura may last only a few minutes and, in others, it may last more than 4 hours.[3]

Dizziness and vertigo during migraine attacks may be more commonly associated with migraine with aura, although these symptoms may also occur in migraine without aura.[5] Symptoms including vertigo, dysarthria, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness are now included as part of the diagnosis of migraine with brainstem aura (TABLE 2-2).[1] The diagnosis of migraine with brainstem aura has replaced the diagnosis of basilar migraine in the *ICHD-3*, reflecting an understanding that the symptoms included in this diagnosis do not necessarily reflect changes in perfusion through the basilar artery. The evidence that these symptoms arise from aura mechanisms involving the brainstem is not strong, and peripheral vestibular or cochlear dysfunction could also be involved in producing symptoms of dizziness, vertigo, tinnitus, and hearing impairment.

The duration and severity of the headache of migraine with aura has been reported to be less than with those without aura, but the severity of pain associated with aura varies widely. Migraine aura without headache is common, whereas, conversely, some patients report that their attacks that include aura are associated with their most severe headache.[3] As discussed below, the variable relationship between migraine aura and headache occurrence and severity raises questions regarding the relationship between the mechanisms of aura and those that cause pain.

INCIDENCE AND PREVALENCE OF MIGRAINE AURA

In population studies, the prevalence of migraine with aura among individuals with migraine has been reported to range from approximately 20% to 40%.[6] The

TABLE 2-2 ***ICHD-3* Diagnostic Criteria for Migraine With Brainstem Aura**[a]

A Attacks fulfilling criteria for migraine with aura and criterion B below

B Aura with both of the following:

1 At least two of the following fully reversible brainstem symptoms:

- a Dysarthria
- b Vertigo
- c Tinnitus
- d Hypacusis
- e Diplopia
- f Ataxia not attributable to sensory deficit
- g Decreased level of consciousness (Glasgow Coma Scale ≤13)

2 No motor or retinal symptoms

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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relative prevalence of migraine with aura compared with migraine without aura is approximately the same in women and men.[6] Of those who have attacks of migraine with aura, the majority also have attacks of migraine without aura.[3] This variability is a potential confounding factor in clinical studies, in which patients are commonly binned in a binary fashion as having either migraine with or without aura when, in fact, many have both.

GENETICS OF MIGRAINE AURA

Migraine commonly runs in families, and the heritability of migraine with aura is significantly greater than that of migraine without aura. First-degree relatives of those with migraine with aura have been reported to have a nearly fourfold risk of migraine with aura but no increased risk of migraine without aura.[7] By contrast, first-degree relatives of those with migraine without aura have been reported to have a nearly twofold risk of migraine without aura and 1.4 times risk of migraine with aura.[7] Twin studies indicate heritability of 65% in patients with migraine with aura compared with 52% in patients with migraine without aura.[8] Genome-wide association population studies, however, have not revealed any clearly increased association of the verified migraine gene polymorphisms with migraine with aura as compared to migraine without aura.[9] A population study of genetic risk found a higher genetic risk for migraine in general and migraine without aura but not in migraine with aura.[9] The reasons for this apparent discrepancy between heritability studies and genome-wide association studies are unclear.

The familial hemiplegic migraine syndromes are monogenic disorders in which migraine aura is severe and often prolonged. An open question regarding the gene mutations responsible for familial hemiplegic migraine is whether their effects modulate migraine in general or rather are more specifically "aura genes," whose effects transform typical aura into more severe and widespread clinical symptoms. The frequency of migraine attacks is not necessarily higher in patients with familial hemiplegic migraine as compared with patients with typical migraine, and those with familial hemiplegic migraine may also have attacks of typical migraine.[10] Thus, familial hemiplegic migraine genes may not change the susceptibility to migraine in general but rather may change the clinical phenotype of migraine when it does occur. A mutation in the gene encoding the TRESK potassium channel (*KCNK18*), causing reduced function of the channel, was reported in a family with migraine with aura.[11] One of the two mutations in casein kinase 1 delta (*CSNK1D*) found in families with migraine and familial advanced sleep phase syndrome was associated primarily with migraine aura, although some carriers of the mutation only experienced migraine without aura.[12]

VASCULAR CHANGES WITH MIGRAINE AURA

During migraine aura, brain hypoperfusion may occur in a distribution correlated with aura symptoms as indicated by positron emission tomography (PET), MRI perfusion, and arterial spin labeling studies.[13–15] Hypoperfusion may also extend to regions of the brain beyond those related to aura symptoms or occur in patients without clinical symptoms of aura.[16] Hyperperfusion has also been reported in some cases during aura and in other cases following aura symptoms.[17,18] Neither the hypoperfusion nor the hyperperfusion are strictly correlated temporally or spatially with either aura symptoms or headache, indicating that the blood flow changes are not primarily responsible for aura

KEY POINTS

- Migraine aura symptoms include visual, sensory, language, motor, or brainstem symptoms that begin and progress gradually, which reflect a slowly propagating physiologic phenomenon in the brain.
- The symptoms of migraine aura are highly variable from person to person and may vary significantly from attack to attack in a given individual.
- Characteristics of the visual percept of the migraine aura indicate that the brain activity underlying aura can begin in different parts of the visual cortex in the same individual and that the activity spreads in a linear fashion along a sulcus or gyrus rather than as a concentric wave.
- The diagnosis of migraine with brainstem aura has replaced the diagnosis of basilar migraine in the most recent version of the *International Classification of Headache Disorders, Third Edition*, reflecting an understanding that the symptoms included in this diagnosis are not necessarily produced by changes in perfusion through the basilar artery.
- Migraine with aura has greater heritability than migraine without aura, but thus far the only genes that have been identified in association with migraine are those responsible for monogenic familial hemiplegic migraine disorders.

symptoms.[13] It is extremely rare for the hypoperfusion associated with migraine aura to reach the threshold for ischemia, which is consistent with the rarity of migrainous infarction. Interestingly, however, patients with migraine aura have been reported to have increased recruitment of ischemic tissue into the infarct with acute stroke and possibly a larger infarct size.[19] Thus, it appears that while migraine aura itself does not result in stroke, migraine aura mechanisms may worsen stroke when it occurs because of causes other than migraine (see the discussion of spreading depolarizations below). Changes in vascular permeability have also been reported with migraine with prolonged aura and hemiplegic migraine,[20] although such changes may not occur with typical aura.[18]

CORTICAL SPREADING DEPRESSION IN ANIMAL MODELS

The phenomenon of cortical spreading depression, originally described by Leão in the 1940s, is generally assumed to be the physiologic mechanism responsible for the migraine aura. Leão described a slowly propagated depolarization, followed by suppression of electrographic activity, that spreads from a focal site of initiation to involve the majority of one hemisphere of the lissencephalic (lacking sulci or gyri) cortex in different animal models. Cortical spreading depression in animals can be triggered by mechanical perturbation of the cortex, local application of potassium, excessive electrical stimulation, administration of endothelin (which may cause local ischemia), and application of the sodium-potassium ATPase inhibitor ouabain.[21] Cortical spreading depression results in the massive release of neurotransmitters including glutamate, dopamine, and ATP, as well as large changes in the concentrations of extracellular and intracellular ions including sodium, potassium, chloride, and calcium.[21]

Cortical spreading depression in animal models also results in dramatic changes in the vasculature. In mice, the propagating cortical spreading depression wave is accompanied by the marked constriction of cortical surface arteries followed by recovery and, in some cases, transient slight vasodilation.[22] In the 60 minutes following a single cortical spreading depression event, sustained vasoconstriction occurs in the face of ongoing depolarization and neuronal firing, consistent with an uncoupling of the normal relationship between brain activity and blood flow.[22] It is possible that this sustained neurovascular uncoupling could play a role in the consequences of cortical spreading depression, including pain, via release of nociceptive messengers such as ATP and calcitonin gene-related peptide (CGRP).

Studies in rodent models indicate that cortical spreading depression activates peripheral and central trigeminal pain pathways. This may occur via trigeminal afferents that innervate the dura[23] or via direct descending central pathways.[24] Potential nociceptive messengers include glutamate, ATP, and high mobility group box 1 (HMGB1).[25,26] A recent study found that monoclonal antibodies targeting CGRP inhibited the firing of nociceptive neurons in the brainstem, consistent with CGRP as a mechanism by which cortical spreading depression could cause pain.[27]

Mice expressing migraine-associated genes have a higher susceptibility to cortical spreading depression.[21] Female mice have also been reported to have a higher susceptibility to cortical spreading depression.[28] Estrogen has been found to increase the susceptibility to cortical spreading depression, whereas testosterone has been reported to have the opposite effect.[29] Migraine preventive medications with known efficacy in humans (including those that treat migraine

with and without aura) generally inhibit cortical spreading depression in rodents, such that this model has been used to predict the efficacy of medications in development for migraine.[30] Acute and preventive neuromodulation approaches including transcranial magnetic stimulation also inhibit cortical spreading depression.[31] Thus, cortical spreading depression in animal models appears to be a reasonable translational model for studying migraine.

CORTICAL SPREADING DEPRESSION IN HUMAN BRAIN INJURY

Spreading depolarizations that are very similar in nearly all characteristics to cortical spreading depression in animal models have been described in detail in humans with brain injury. Repetitive spreading depolarizations emanating from sites of injury have been characterized with electrocorticography in patients with traumatic brain injury and ischemic and hemorrhagic stroke.[32] These events typically propagate along a single sulcus or gyrus and can be associated with either vasodilation or paradoxical vasoconstriction, similar to what is observed in mice. In some cases, spreading depression events are believed to exacerbate underlying brain injury.[32]

CORTICAL SPREADING DEPRESSION AND MIGRAINE AURA

Despite its nearly universal acceptance as the pathophysiologic mechanism underlying the migraine aura, cortical spreading depression has, in fact, never been definitively demonstrated in conjunction with aura in humans. This may be, in part, because most EEG recordings are not configured to measure direct current changes such as those that occur in conjunction with the cortical spreading depression wave, or they may not have the spatial resolution to detect an event that may occur in a relatively small area of cortex. Slowly propagated waves of reduced blood flow over broad areas of the cortex have been reported in both migraine with and without aura, and it has been widely assumed that this propagated hypoperfusion is related to cortical spreading depression.[13,16] Indeed, the occurrence of cortical spreading depression related to migraine aura is commonly depicted as a broad concentric wave traversing multiple gyri and sulci. However, mapping of the percept of the migraine aura onto the visual cortex suggests that the mechanism underlying aura travels in a much more spatially restricted manner along a single gyrus or sulcus,[4] similar to what has been observed in humans in the setting of brain injury. It is therefore possible that most surface EEG recordings have not had the resolution to detect such a spatially restricted event.

If the pathophysiologic mechanism of the migraine aura is indeed traveling in a more linear fashion along a gyrus or sulcus, this raises multiple other interesting issues. First, it is not clear by what path it could travel from the occipital cortex to the sensory cortex to the motor cortex. Second, the blood flow changes that have been observed in migraine may be much more extensive than changes in brain parenchymal activity that are responsible for aura symptoms. Finally, if migraine aura mechanisms do indeed contribute to pain, then it is clear that the distribution of headache is not correlated with the spatially limited location of the changes in brain activity that cause aura.

MIGRAINE AURA AND HEADACHE

Because migraine aura typically occurs at the beginning of the headache phase of an attack, and because cortical spreading depression has been shown to

KEY POINTS

- Although migrainous infarction is rare, migraine aura mechanisms occurring in response to ischemia may worsen stroke when it does occur.
- Cortical spreading depression has long been assumed to be the physiologic phenomenon underlying the migraine aura, and cortical spreading depression in animal models appears to be a valid translational model for migraine, but it has never been definitively demonstrated with migraine aura in humans.

activate trigeminal nociceptive pathways in animal models, it has been hypothesized that migraine aura contributes to headache. One problem with this hypothesis is the clinical observation that migraine aura commonly occurs without headache, and the majority of migraine attacks are not associated with aura. Further, in attacks in which aura and headache both occur, the headache may accompany aura rather than follow it, and occasionally migraine aura occurs well after headache begins. Thus, an obligate relationship does not exist between the occurrence of aura and the occurrence of headache, nor does a completely consistent temporal relationship exist between the two.[3,33]

THE CONCEPT OF SILENT AURA

Proponents of the hypothesis that aura plays a primary role in a migraine attack have suggested that aura mechanisms could be occurring in patients who do not have symptoms of aura—the so-called "silent aura." As with other migraine mechanisms, it is certainly possible that clinically silent changes may occur in the nervous system during migraine. In the case of a single patient who carefully recorded symptoms of visual aura, there were multiple minutes of recording when he did not experience symptoms, despite the apparent propagation of the aura mechanism in the visual cortex based on retinotopic extrapolation of the aura percept on to the cortex.[4] These observations reinforce the possibility that propagation of aura mechanisms through noneloquent cortex could be occurring in migraine, even in the absence of correlated clinical symptoms.

SEX HORMONE EFFECTS ON MIGRAINE AURA

Migraine with aura is not more prevalent relative to migraine without aura in women as compared to men. Nonetheless, the menstrual cycle and female sex hormones may have significant effects on migraine aura. Migraine associated with the menstrual period is more common without aura, and peak estrogen levels have been reported to be higher in women with a diagnosis of migraine with aura as compared to those without aura.[34] These observations have led to the hypothesis that the occurrence of aura is associated with higher levels of endogenous estrogen. In support of this hypothesis, new onset of migraine aura or worsening of migraine with aura may occur with initiation of oral contraceptive or hormone-replacement therapy or with pregnancy.[34] On the other hand, low-dose continuous estrogen therapy has been reported to reduce aura in a small retrospective case series, possibly because of suppression of normal fluctuations in estrogen or other hormone levels.[35]

PATENT FORAMEN OVALE AND MIGRAINE AURA

Numerous studies have reported an association between migraine with aura and patent foramen ovale, particularly large patent foramen ovale with significant right-to-left shunt.[36] In a randomized controlled trial, closure of patent foramen ovale did not result in a significant difference compared with sham control (with regard to the primary end point of a 50% reduction in migraine attacks), but exploratory analysis revealed that patients for whom aura occurred with a majority of attacks had significant benefit from patent foramen ovale closure.[37] A study of patent foramen ovale closure in patients with migraine

with aura found that patent foramen ovale closure did not meet the primary end point of significant reduction in the number of migraine days, but a secondary analysis of these results found that days with migraine with aura were significantly reduced.[38] These findings, while not supporting patent foramen ovale closure as a therapy for migraine, do raise the possibility of a causative role for right-to-left shunt in migraine aura. Other circumstantial evidence supporting such a causal role comes from observations of patients with hereditary hemorrhagic telangiectasia, a syndrome associated with pulmonary arteriovenous malformations that may cause significant right-to-left shunt. These patients have a higher prevalence of migraine with aura, and ablation of pulmonary arteriovenous malformations has been reported to reduce migraine attacks.[39] Microemboli have been reported to trigger cortical spreading depression in rodent models[40]; paradoxical emboli via right-to-left shunt could therefore be a mechanism for triggering mechanisms of aura. Alternatively, migraine aura might be triggered by deoxygenated blood traveling via right-to-left shunt. Migraine aura has been reported to be triggered by hypoxia in human studies, suggesting this as a possible mechanism underlying the association of patent foramen ovale and migraine with aura.[41]

MIGRAINE AURA AND STROKE

Several population studies have found an association between stroke and migraine with aura but not without aura and specifically in women as compared to men.[42] A hospital registry study examining the incidence of perioperative stroke found that patients with migraine were at increased risk of perioperative ischemic stroke, with the highest risk being for those with a diagnosis of migraine with aura.[43] Investigation of patients on an inpatient stroke unit found that patients with migraine with aura were overrepresented relative to migraine without aura, and those with migraine, in general, were younger and more likely to have patent foramen ovale.[44] A study of a US health care claims database from 2006 to 2012 found that there was a cumulative incidence of 11 strokes per 100,000 females aged 15 to 49 years.[45] An increased odds ratio was found for ischemic stroke among those with migraine with or without aura not using combined hormonal contraceptives (odds ratios of 2.7 and 2.2, respectively). In patients with aura, combined hormonal contraceptive use was associated with a further increase in the association with ischemic stroke (odds ratio 6.1), but this was not the case for migraine without aura (odds ratio 1.8). Issues regarding this study include the small numbers and the reliance upon diagnostic codes. A 2002 study of the relationship between stroke and migraine in women aged 20 to 44 years of age reported that among 86 cases of ischemic stroke and 214 controls, an increased risk of stroke was found in patients both with and without aura and particularly in those who had more than 12 attacks of aura per year at migraine onset, but the study found that correcting for oral contraceptive use had no effect on this association.[46]

While substantial evidence clearly exists for the association between migraine with aura and stroke, the mechanism(s) for this association remains unclear. It is often presumed that this association is because of migrainous infarction that occurs in the setting of a migraine aura, possibly related to cortical spreading depression. No evidence supports this presumption,

KEY POINTS

- Cortical spreading depression can activate trigeminal pain pathways in animal models, but the variable relationship between migraine aura and headache does not support aura as a mechanism that triggers headache.
- Migraine with aura is associated with patent foramen ovale and increased risk of stroke; patent foramen ovale could play a significant role in the increased stroke risk associated with migraine with aura.
- No evidence supports a contraindication to triptans as acute therapies in attacks of migraine that include aura.

however, and an alternative explanation is that migraine aura and stroke share a predisposition or mechanism. Patent foramen ovale is an example of such a possible predisposition; patent foramen ovale could represent a factor that is independently associated with migraine aura and stroke.

PSYCHIATRIC COMORBIDITIES ASSOCIATED WITH MIGRAINE AURA

Migraine with aura has been reported to be associated with a number of psychiatric comorbidities including depression, bipolar disorder, panic disorder, and suicidality.[47] Interestingly, however, patients with migraine aura without headache were reported to have reduced affective disorder and suicidality compared to those with headache.[48] The mechanisms underlying these associations remain unclear but could include shared pathophysiology regarding neurochemical function or cortical excitability.

IMPLICATIONS OF MIGRAINE AURA FOR CLINICAL MANAGEMENT

Attacks of migraine with aura may be less responsive to triptans than those without aura.[49] Currently, the only treatment specifically indicated for the acute treatment of migraine with aura is single-pulse transcranial magnetic stimulation.[50] This treatment is now approved for use in the United States by the US Food and Drug Administration (FDA) for the acute treatment of migraine with aura and for the prevention of migraine. Studies have provided evidence that ketamine may be helpful for migraine with prolonged aura,[51] but this approach has not been widely adopted. No treatments are specifically indicated for the prevention of migraine with aura (CASE 2-2).

Although multiple organizations including the World Health Organization and the American College of Obstetricians and Gynecologists recommend against the use of estrogen-containing oral contraceptives in women with migraine with aura because of increased risk of stroke, the evidence supporting this recommendation is mixed and has many confounding factors.[52,53] Many of the studies indicating increased stroke risk were based on use of estrogen doses that are significantly higher than those used presently. Further, aura diagnosis was not consistent, nor was the diagnosis of stroke consistently definitive with imaging verification, which can be problematic when aura can present with strokelike symptoms and therefore be misdiagnosed as stroke. Also, most studies did not subclassify patients based on the frequency of aura; age may be a significant factor, and correction for other stroke risk factors was inconsistent and subject to different interpretations. While multiple studies report a higher relative risk of stroke in women with migraine with aura using estrogen-containing oral contraceptives, all studies agree that the absolute risk of stroke is small.[52,53] Although clearly still a controversial issue, at this point in time, it is this author's view that compelling evidence does not support recommendations regarding the use of oral contraceptives in women with migraine with aura, except to suggest that low-dose estrogen preparations should be used whenever possible. Also, some neurologists hesitate to prescribe triptans in patients with aura based upon concerns regarding possible vasoconstrictive effects of these medications, but magnetic resonance angiography (MRA) studies indicate that triptans do not, in fact, constrict intracranial blood vessels,[54] and no evidence supports a contraindication to triptans as acute therapies in attacks of migraine with aura.

CASE 2-2

A 24-year-old woman presented for a second neurologic opinion regarding management of migraine. She had a history of episodic migraine with and without visual aura since age 13. Her attacks occurred once per month and, if treated effectively with a triptan, lasted 1 hour. If she was not able to use a triptan as acute therapy, the attacks lasted for 24 hours. She experienced aura with approximately 30% of her attacks, consisting of a slowly expanding arc of jagged lines that propagated throughout one visual field over approximately 30 minutes. On two occasions that she could remember, she experienced numbness of her face associated with the visual symptoms. On one occasion, she experienced difficulty speaking as the visual symptoms were resolving. If the aura occurred, approximately 10 minutes after the aura began, she experienced pain that started in the neck then spread to the occipital region and eventually to the retro-orbital region. The pain increased in intensity as it spread and eventually became incapacitating in severity. She had nausea with some of her attacks and consistently experienced light sensitivity. Oral sumatriptan, which was prescribed by a neurologist, was effective in relieving headache and associated symptoms for approximately 90% of attacks.

She was interested in starting an oral contraceptive, so she had asked her primary care provider about this. She had never smoked tobacco. She was told by her primary care provider that she could not take an oral contraceptive because an increased risk of stroke existed in women with migraine aura. She was also told that she should not take sumatriptan, because this could cause stroke in patients with migraine with aura. She was confused about why her neurologist would have prescribed sumatriptan if it was risky and was concerned about the risk of stroke.

COMMENT

While multiple studies indicate that oral contraceptive use is associated with an increased risk of stroke in women with migraine with aura, the evidence is mixed, and studies regarding this question have multiple confounding factors, including estrogen dose, age, the frequency of aura, definitive confirmation of stroke, and other stroke risk factors.[52,53] This is a complex issue that remains controversial, but some neurologists (including this author) believe that the evidence is not sufficient to support guidelines recommending against use of all estrogen-containing oral contraceptives (especially low-dose estrogen preparations) in women with migraine with aura. Regarding triptan use, the misconception that triptans cause significant intracranial vasoconstriction commonly leads practitioners to avoid these medications for fear of migrainous infarction. In fact, good evidence now suggests that sumatriptan does not constrict intracranial vessels, and no evidence exists whatsoever to contraindicate triptan use in patients with migraine with aura. This author would, despite contrary guidelines, endorse the use of low-dose estrogen contraception in this patient, as well as the use of sumatriptan as an acute therapy.

CONCLUSION

The migraine aura is a dramatic neurologic event with complex neural and vascular mechanisms and has potentially important implications regarding diagnostic and therapeutic management. Refined understanding of its clinical features, comorbidities, patterns of propagation in the human brain, and specific responses to therapy can add important new insight into the pathophysiology of migraine and its optimal therapy.

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