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MIGRAINE (R COWAN, SECTION EDITOR)

Our Evolving Understanding of Migraine with Aura

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Abstract Migraine aura consists of fully reversible focal neurologic symptoms that may precede or coexist with headache in a significant minority of migraine patients. Typical aura symptoms include visual, sensory, and language disturbances. The most recent International Classification of Headache Disorders, 3rd edition (beta version) has added other aura types such as brainstem localizing symptoms, lateralizing weakness, and monocular visual loss. Currently available data from animal models and functional neuroimaging in humans implicate cortical spreading depression (CSD) as the phenomenon underlying migraine aura. Ongoing study suggests that susceptibility to migraine aura and CSD may be genetically mediated. CSD appears to be a potential target for future development of migraine-specific preventive therapies.

Keywords Migraine · Aura · Focal neurologic symptoms · Cortical spreading depression

Introduction

Migraine is a common disorder of the central nervous system that affects around 12 % of the general population [1]. Between a quarter and a third of migraine patients report that they have experienced focal neurologic symptoms before or during at least some of their headaches [2, 3]. In the International Classification of Headache Disorders, 3rd edition (ICHD-3 beta), migraine aura is defined as fully reversible neurologic dysfunction that precedes or accompanies a headache, with gradual onset, progression of 5 minutes or more and duration for each aura symptom of 5–60 minutes. If more than 1 aura symptom occurs, they generally proceed in succession. Under the latest proposed criteria, migraine with aura not only includes visual, sensory, language/speech symptoms (typical aura) but motor, brainstem or retinal symptoms as well [4••] (Table 1). Of these, visual aura is the most common.

The importance of recognizing migraine aura cannot be overstated. Generally thought to be a benign event, migraine aura may sometimes be mistaken for stroke or transient ischemic attack. Thus, differentiating aura from an ischemic event may be necessary. Female migraineurs with aura do indeed have a modestly higher stroke risk [5]. In addition, woman who have migraine with aura and are also taking estrogen supplementation are at an even higher risk of stroke [5], and recognition of migraine aura may be important when risk stratifying a patient's vascular risk [6]. Furthermore, classifying the patient appropriately may also help guide management and provide reassurance. In many instances, the symptoms of migraine aura are quite distressing or may be temporarily disabling to the patient. There are several characteristics that help differentiate migraine aura from cerebral ischemia. These include a slowly spreading or migratory pattern of symptoms that often cross the boundaries of cerebrovascular supply; a bimodal pattern in which positive symptoms (visual scintillations or kaleidoscopic visual hallucinations) are followed by negative ones (scotoma); the characteristic spread of the sensory aura into the mouth to unilaterally affect the buccal mucosa or tongue; and the typical duration of aura symptoms with complete resolution generally (except in the case of motor aura) within an hour [7].

Historical Perspective

Migraine aura has been thoroughly described by scientific observers and clinicians in the medical literature since the 18th century [7]. In 1870, Hubert Airy provided a most

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Table 1 ICHD-3 beta criteria for migraine with aura

A. At least 2 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 2 of the following 4 characteristics:

1. at least 1 aura symptom spreads gradually over greater than or equal to 5 m, and/or or more symptoms occur in succession
2. each individual aura symptom lasts 5–60 m
3. at least 1 aura symptom is unilateral
4. the aura is accompanied, or followed within 60 m, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

Notes

1. When, for example, 3 symptoms occur during an aura, the acceptable maximal duration is 3×60 m. Motor symptoms may last up to 72 h.

2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

detailed description of his own migraine auras. He noted the gradual progression of visual aura with the characteristic features of scintillation, blind spots, hemifield involvement, bright flashing colors, and gradual recovery [8]. He also first used the term "teichopsia" [9] referring to the geometric patterns in visual aura, which often resemble the fortifications of medieval castles. The cause of aura was disputed throughout much of the 20th century with the debate centered on the competing vasogenic and neurogenic theories [10]. The vasogenic theory, which was largely accepted until the 1980s, held that migraine aura was caused by recurrent episodes of vasospasm within cerebral vessels causing transient drops in blood flow and resultant neurologic symptoms. Proponents of the vasogenic theory argued that the headaches occurred as a result of rebound vasodilation, which caused mechanical activation of nociceptive neurons within and around cerebral vessels. However, the neurogenic theory as proposed by Karl Lashley in the 1940s and others supposed that the cause of aura was due to a wave of hyper-excitation that was spread across areas of contiguous cortex at a rate of 3 mm per minute [11]. Within a few years, Aristides Leão performed electrophysiologic studies on the brains of rabbits and noted that after the cortex was mechanically or chemically stimulated, a wave of spreading electrical excitation followed by depression occurred and propagated at a rate of 3 mm per minute [12]. This phenomenon was termed cortical spreading depression (CSD). Based on functional neuroimaging and blood flow studies in humans with migraine in the 1980s and 1990s (see further details below), CSD is currently thought to be the most likely pathophysiologic process underlying migraine aura [13].

Epidemiology

The lifetime prevalence of migraine with aura is around 5 % compared with migraine without aura, which is about 8 % [14]. A recent population based study from Denmark showed a 1-year prevalence of 4.1 % for migraine with aura compared with 8.2 % for migraine without aura [15]. The 1-year period prevalence for migraine with aura in females has been estimated to be 5.3 % and 1.9 % in males [16] whereas the lifetime prevalence of migraine with aura is reported to be 7 % of women and 4 % of men [17]. When looking at the sum total of population studies worldwide, aura occurs in about 28 % of migraineurs [18].

Migraine with aura may not be present with every migraine attack. One report noted that only 19 % of migraine with aura patients had aura symptoms with every headache attack. The onset of migraine without aura may precede attacks of migraine with aura [19] and vice versa [20]. Visual aura is the most common form of aura with 1 large study showing 99 % of migraine with aura patients confirming this symptom [21]. Other published studies suggest that sensory is the next most frequent aura symptom (up to 54 %) [22] and language aura is the least common typical aura (32 %) [23].

Based on our Headache Registry Database here at Mayo Clinic, we have found that 1750/2030 (86 %) of migraine with aura patients had symptoms of visual aura. Interestingly, language aura was reported by 730/2030 migraine with aura patients (35 %) and sensory aura in 693/2030 (34 %) of migraine with aura patients, which differs from prior reports. Motor aura (or hemiplegic aura) was the least frequent aura type in our population with 210/2030 patients reporting this symptom (10 %). As would be expected in a clinic based cohort, migraine with aura was over-represented and was seen in 43 % of our migraine patients, whereas migraine without aura was present in 62 % of our migraine patients. The total over 100 % is accounted for by patients who have clearly had discrete periods where they have had one type and at the other times had the alternative type and as a result carry both diagnoses (Cutrer, unpublished data).

Pathophysiology of Migraine Aura

Based on currently available information, CSD is felt to be the phenomenon that underlies migraine aura. The CSD wave of hyper-excitation followed by suppression spreads at a speed of around 3 mm/minute across areas of contiguous parenchyma without respect to specific neurovascular boundaries of

functional cortex [24]. CSD involves a massive depolarization of neural and glial membranes with an associated disruption of ionic flow. This initial aberrant depolarization is met with a transient increase in cerebral blood flow followed by a decrease in blood flow (rCBF) as the abnormally activated cortical neurons and glia become quiescent and have a lower metabolic demand [13, 25, 26]. Although CSD can be triggered experimentally, it is unclear what triggers it spontaneously outside of a laboratory setting. CSD has been observed after head trauma, ischemic stroke, and hemorrhage [27]. The trigger(s) of CSD in the migraine population are unknown [13]. There is evidence that CSD and thus, migraine aura may be a trigger for head pain. CSD causes the release of excitatory and pro-inflammatory mediators including protons [28], nitric oxide, glutamate, eicosanoids, potassium (K+), and adenosine triphosphate (ATP) [29], which are capable of activating meningeal and perivascular nociceptive neurons. Recently, a molecular cascade of events linking CSD with headache has been characterized. In an animal model, CSD induced neuronal Pannexin1 (Panx1) mega channel opening caused caspase-1 activation followed by high-mobility group box 1 (HMGB1) release from neurons and nuclear factor κB activation in astrocytes. This cascade of molecular events resulted in prolonged trigeminovascular activation and dural mast cell degranulation, both of which are markers for activation of perivascular and meningeal nociceptive neurons in humans [30••]. Activated trigeminovascular afferent neurons release substance P, calcitonin gene-related peptide (CGRP), and neurokinin A culminating in a sterile neurogenic inflammation, which may further prolong headache pain [28, 31]. It has been experimentally demonstrated that CSD may cause oxidative stress in the trigeminal afferents also leading to pain [32].

Risk Factors for Aura

Multiple triggers for migraine with aura have been described in the literature. One questionnaire based study noted that stress, light, fumes, heavy scents, exertion, or smoke can be potent and consistent triggers for migraine with aura [33]. Another investigation, a large prospective study of 327 patients, looked at risk factors for migraine aura. In this study, menstruation and smoking were found to be the most significant risk factors for having the migraine aura. However, menstruation was also found to be a risk factor for migraine without aura and for other headaches, whereas smoking was only found to be a risk factor for migraine with aura only [34]. Assuming that CSD or a CSD-like phenomenon is the basis for migraine aura, identification of the mechanisms by which menstruation and/or smoking may trigger spontaneous CSD will be particularly informative [35].

Clinical Features of Typical Aura

Visual Aura

The visual aura in migraine typically begins with a small area of visual disturbance lateral to the point of visual fixation. This disturbance is often described as an area of visual loss or a bright spot. This disturbance may progress over a period of 5 minutes to 1 hour to involve a hemifield or quadrant of vision [7]. The expanding margin of the visual disturbance may have the appearance of zigzagging lines or geometric shapes known as fortification spectra or teichopsia. Positive visual phenomena may assume a C-shape or a crescent with shimmering edges (scintillations) with or without color. This shape expands to form the leading edge of an area of visual loss or scotoma [36] (Fig. 1). Simple flashes (phosphenes), specks, white dots, colored dots, bean-like forms, curved lines, bright bars of light or other geometric forms may also be seen [18, 37]. Vision returns centrally as the disturbance migrates peripherally [7].

Sensory Aura

Sensory changes in migraine aura are generally described as migrating paresthesias [37]. The classic descriptive term cheiro-oral, means that the numbness typically starts in the hand and migrates up the arm to involve the face, lips, and tongue. It may also involve the leg, foot, or hemibody as well, and has rarely been noted to progress to bilateral involvement in some people. Sensory auras most commonly follow the visual aura [21] and are only occasionally the sole aura symptom [37]. Numbness typically follows the paresthesias but rarely occur in isolation from positive symptoms [7]. In our clinical experience, what a patient sometimes calls “weakness” of an arm or leg is actually a sensation of clumsiness or lack of control of the limb due to loss of proprioception during the sensory aura. Therefore, it is very important to clarify and inquire in detail whenever a patient complains of “weakness”.

Language Aura

Language disturbance may also occur as a manifestation of migraine aura. Although generally regarded as the least common among the typical aura symptoms, we found in our large cohort that language aura was reported with a similar frequency to that of sensory aura. Language aura may consist of impaired language comprehension, marked word-finding difficulties, and/or a decreased ability to read or write. It should be noted that cheiro-oral sensory changes may lead to slurring of speech and should not be confused with language aura [38]. Word finding difficulties seem to be the most commonly encountered type of language aura symptom but impaired comprehension can definitely be seen [21]. Prosopagnosia,

Fig. 1 Appearance of a typical visual aura with scintillations and scotoma

apraxia, transient amnesia, and proper name agnosia have also been described in the literature [39]. Language disturbance noted by migraine patients may be hard to categorize [4••]. In our experience when headache patients are asked if they have any trouble thinking or talking during an attack, they may report nonspecific cognitive issues that are not suggestive of language related disturbance. These cognitive issues such as impaired attentional performance [40], lack of concentration, mental "cloudiness", or "fuzziness" and decline in overall cognitive functioning [41] may be separate from language aura and can be seen in migraine without aura (and other headache types) as well. Therefore, it is important to carefully assess the patient's language complaint in order to assign the correct diagnosis.

Duration of Typical Aura

In the most recent ICHD criteria, typical migraine aura must gradually spread over a period of 5 minutes or more and may only last 5–60 minutes for each aura symptom. If a patient has more than 1 type of typical aura, the aura symptoms generally occur in succession and not simultaneously. When an otherwise typical migraine aura lasts longer than an hour (but less than 1 week) then it should be termed probable migraine with aura [4••]. However, a recent systematic review indicated that a significant proportion of migraineurs have aura symptoms that last longer than an hour. This study found that 12 %–37 % of migraine with aura patients report attacks in which aura symptoms that lasted longer than 1 hour [42]. Furthermore, cases of aura lasting days and weeks have also been well-documented [43–46]. Previously called "complicated migraine" by some clinicians, the current ICHD criteria classify aura symptoms lasting longer than 1 week in absence of ischemic change on neuroimaging as persistent aura without infarction [4••].

Migraine Aura and Headache

The temporal relationship between aura symptoms and headache during migraine attacks is variable. The classical progression in which the aura is separate from, and followed by the headache phase [47] does not always occur. In a recent prospective study in which 201 migraine with aura patients were asked to keep a headache diary to track their symptoms starting with aura onset, 73 % of 861 attacks studied involved headache during the aura phase. In 54 % of attacks, headaches that met criteria for migraine occurred within the first 15 minutes of aura onset [48]. Many patients who have migraine with aura also report attacks of migraine without aura [49]. Migraine aura without headache may also be present in patients without a history of migraine [50–52]. A Japanese questionnaire-based study found that typical aura without headache was seen in 35/1063 patients (3.2 %) and occurred most commonly between the ages of 20–39 and 60–69 [53].

Persistent Aura

Although rare, occurrence of persistent aura is recognized by the ICHD criteria [4••]. Prolonged visual aura is the most commonly documented persistent aura type [54]. Although the cause of persistent visual aura is unknown, it is thought that it may be due to recurrent waves of CSD. It has also been

postulated that lack of recovery from visual aura symptoms may be due to NMDA-receptor hyperexcitability [55]. In a magnetoencephalography based study, Chen and colleagues showed that persistent visual aura is associated with sustained hyperexcitability of the visual cortex ictally and interictally [56]. Persistent visual aura symptoms may be described as bright colors, flickering or flashing lights, dot-like disturbances, wave-like lines, shimmering or scintillations. Persistent visual aura has been reported to occur in either 1 or both eyes. And it may involve either 1 or both hemifields of vision [54]. Cases of persistent sensory deficits tend to be reported much less commonly in the literature but have been described [45]. Persistent auras in the form of motor weakness will be described later.

Visual Snow

Visual snow is a phenomenon characterized by a continuous "static" or "snow-like" disturbance throughout the entire visual field akin to an analog television set that is not tuned properly. This disorder is felt to be separate from migraine and persistent migraine aura although it can be seen in the migraine population [57] and may be more severe in migraineurs [58]. A recent study by Schankin and colleagues noted that patients who experience visual snow often suffer from other visual complaints such as palinopsia (after images), nyctalopia (impaired night vision), and photophobia. In general, these patients have normal ophthalmologic examinations, which exclude any ocular cause [57]. Schankin and colleagues also performed positron emission tomography (PET) on patients with visual snow and found that the lingual gyrus was metabolically hyperactive. This is thought to be a unique, objective correlate further distinguishing it from migraine [58]. This disorder is often unresponsive to migraine preventive medications and may be quite difficult to treat [58, 59].

Motor Aura

Hemiplegic migraine differs from the other forms of migraine with aura in that motor weakness is present. The ICHD-3 beta criteria classify hemiplegic migraine as a form of migraine with aura [4••]. It should be noted that hemiplegic migraineurs almost always experience typical aura (visual, sensory, language) symptoms as well. The duration of the motor aura tends to be longer (typically up to 72 hours) than the typical migraine aura symptoms and is fully reversible according to the ICHD3 beta criteria [4••]. However, in some instances the weakness of motor aura has been reported to persist for weeks or even result in permanent neurologic deficit [60]. Hemiplegic migraine is quite rare as one study estimates the prevalence of this disorder to be 0.01 % [61]. Hemiplegic migraine has variable genetic penetrance [62] and there is tremendous variability of clinical phenotype [63]. The weakness of hemiplegic migraine tends to start in the hand and progress up the arm in a gradual fashion. Motor weakness is associated with at least 1 other aura symptom by criteria, with sensory disturbances being the most frequent. The weakness has been described as ranging from mild clumsiness to complete paralysis. When other aura symptoms are seen in patients with motor aura, they manifest themselves in a successive fashion. Less commonly, patients with motor aura may exhibit encephalopathy, coma, and cerebellar signs [62]. Headache typically accompanies or overlaps with the aura in hemiplegic migraine [64, 65].

Hemiplegic migraine occurs in sporadic and familial forms. In order to be diagnosed with the familial form, a first or second-degree relative must meet criteria for hemiplegic migraine as well [4••]. There are 3 recognized familial forms of familial hemiplegic migraine (FHM), each of which is associated with mutations to a specific gene. FHM 1 is caused by genetic mutations in the *CACN A1A* gene located at 19p13.1, which codes for a neuronal calcium channel [66]. A mutation in *ATP1A2*, a gene located on 1q21-q23 that encodes a subunit of a glial sodium/potassium pump, has been identified as the cause of FHM2 [67]. FHM3 has been linked to mutations in *SCN1A (chromosome locus 2q24)*, which encodes a neuronal voltage gated sodium channel subunit [68]. It has been experimentally demonstrated that gene mutations in FHM 1-3 cause neuronal hyperexcitability, which may lower the threshold for initiation of CSD [69, 70]. However, not all cases of FHM are due to the aforementioned genes [71]. For example, cases of FHM have been described due to mutations in the *PRRT2* (proline-rich transmembrane protein 2) gene, which encodes for a protein involved in exocytosis [72, 73]. Sporadic cases of FHM are diagnosed when the patient has no first- or second-degree relatives with hemiplegic migraine [4••]. However, de novo mutations of genes already implicated in FHM have been detected in sporadic hemiplegic migraine. Furthermore, some cases of sporadic hemiplegic migraine have shown inheritance of the causative genetic mutations from asymptomatic family members [74, 75].

Brainstem Aura

Migraine with brainstem aura is a syndrome previously known as basilar artery migraine, basilar migraine, or basilar-type migraine. This name change is appropriate given the fact that changes in the caliber of the basilar artery are not felt to be causative of the aura symptoms. In migraine with brainstem aura, symptoms that localize to the brainstem occur. These include diplopia, vertigo, tinnitus, dysarthria, hypoacusis, ataxia, or impaired consciousness. In order to make this diagnosis, at least 2 brainstem symptoms must

occur in the absence of motor symptoms. Typical aura symptoms almost always also occur however, they are not required for the diagnosis [4••]. One study from 2006 measured the prevalence of migraine with brainstem aura in families with migraine with aura in Denmark. Migraine with brainstem aura was found in 38/362 (10 %) patients with migraine with aura. Furthermore, 36/38 of patients with migraine with brainstem aura also had migraine with typical aura as well [76]. The most typical brainstem symptom seen in this Danish study was vertigo (61 %) followed by dysarthria (53 %), tinnitus (45 %), diplopia (45 %), bilateral visual symptoms (40 %), bilateral paresthesias (24 %), impaired consciousness (24 %), and hypoacusis (21 %). Of the typical aura symptoms, visual aura is the most common in the migraine with brainstem aura population [77]. The typical aura length in migraine with brainstem aura is around 60 minutes [76]. Individuals reporting migraine with brainstem aura have been found to carry mutations in the *CACN A1A* or *ATP1A2* genes in some cases [78, 79]. However, thus far, no causative mutation has been found across all subjects [76].

Retinal Aura

The aura of retinal migraine is described as repeated attacks of a reversible monocular visual disturbance including scintillations, scotoma, or blindness that appear gradually over a period of 5 minutes or longer and last 5–60 minutes, associated with a migraine headache and in the absence of other causes such as carotid disease [4••]. In a 2006 case series of 6 new patients and literature review of 40 additional patients with retinal migraine, half of the patients from the literature and 4 out of the 6 case series patients had a history of migraine with aura prior to their retinal migraine [80]. Twenty-one (46 %) patients in this series eventually developed permanent monocular visual loss. Given this, the authors recommended aggressive migraine preventive therapy despite a lack of evidence for the efficacy of migraine prophylactic treatments in this specific entity [80]. However, the view that migraine in any form may lead to permanent visual loss is controversial and it should be remembered that retinal migraine is a rare form of aura and may mimic other ocular disease. Some cases reported by patients as retinal aura may not be true monocular visual disturbance but rather homonymous hemianopia. Even when patients have homonymous hemianopia, they may sense a greater disturbance in 1 eye, especially when the disturbance affects the temporal field as it is larger than the nasal field [81].

The proposed pathophysiology of retinal aura has historically involved theories of retinal vasospasm versus retinal spreading depression. Retinal spreading depression has, thus far, not been documented in mammals [82]. However, documented cases of vasospasm in patients with "retinal migraine" have been reported [81, 83–85]. At present, the understanding of retinal migraine and its pathophysiology is incomplete.

Functional Imaging and Aura

Studies over the past 3 decades have laid the groundwork for our understanding of migraine aura and its relationship to CSD. In the 1980s, studies utilizing intra-arterial injection of ^{133}Xe in patients undergoing carotid catheterization who experienced evoked migraine with aura symptoms demonstrated reductions of regional cerebral blood flow (rCBF) in the parietal and occipital lobes during the induced aura symptoms. The blood flow reductions were not of sufficient magnitude to cause ischemia and were termed oligemia. An anterior spread of oligemia was also noted (even frontal cortex oligemia was seen) that did not respect any vascular distribution. This perturbation in cerebral blood flow, which coincided with aura symptoms, lasted up to 1 hour and after such a time, flow normalized or remained in its reduced state [25, 26, 86, 87]. These initial imaging insights were very important and implicated CSD in the neuronal dysfunction of migraine aura.

Hemodynamic alterations in patients with spontaneous and physiologically evoked migraine auras have also been demonstrated by multimodal MRI techniques including perfusion-weighted imaging (PWI) and blood oxygen level dependent (BOLD) imaging. These techniques are not susceptible to the same artifact issues as the ^{133}Xe studies [7] and provided, in spontaneous migraine attacks, confirmation of the findings of the earlier studies [88]. In 1 early MRI study published in 1998, PWI and diffusion-weighted imaging (DWI) was carried out in 4 patients during spontaneous attacks of migraine with aura. This study demonstrated that the DWI was negative during migraine aura and that the blood flow decrements seen on PWI were smaller than those required for cerebral ischemia. These findings, which were consistent with the earlier ^{133}Xe studies, were observed in the occipital cortex contralateral to the symptomatic visual field [89]. Larger follow-up studies have confirmed perfusion deficits in migraine with aura patients that do not respect a specific vascular territory and that are insufficient to cause ischemia [90].

BOLD imaging is based on the flow-related deoxyhemoglobin content and corresponding changes in MRI signal. This method has been widely used to derive functional brain activation maps [91]. One BOLD study looked at visually-triggered headache attacks in 10 patients with migraine with aura and in 2 patients with migraine without aura. In 5 of the patients, headache and/or visual change was preceded by a spreading depression (at a rate of 3–6 mm/min) and increased occipital cortex oxygenation [92]. A different BOLD study looked at 2 patients with spontaneous visual aura and 1 patient with exercise-triggered visual aura with near-continuous recording throughout the course of the

aura. This study showed that all subjects had loss of activation of the affected occipital cortex (contralateral to the affected visual field). The ipsilateral occipital cortex was normal in all individuals. This study also demonstrated in the patient with exercise-induced aura that the visual aura coincided with suppressed activation, which first appeared in the extrastriate cortical (visual association cortex) area V3a, with subsequent CSD-like propagation at a rate of 3.5 mm/min to involve other areas of cortex [93]. These studies demonstrated convincing evidence for CSD or a CSD-like phenomenon as the basis for migraine aura [94] and strongly correlate objective BOLD changes in the visual cortex with the reported aura symptoms [88].

Genetics and Migraine with Aura

The heritability of migraine has been recognized for some time [95]. Genetic influences are especially pronounced in patients with migraine with aura. One study estimated that the relative risk of migraine with aura was increased 4-fold in the first degree relatives of a proband with migraine aura as compared with a 1.9 increased risk of migraine in the first degree relatives of a patient with migraine without aura [96]. Much of what we know about migraine genetics comes from the study of the familial hemiplegic migraine subtypes (FHM 1, 2, 3). All 3 FHM types include aura as an element of their phenotype (discussed above). There are numerous reports of candidate gene variants with modest association with migraine with aura (Table 2). However, the inheritance of typical migraine is complex with no single Mendelian pattern yet identified [88]. In terms of migraine with aura, genome-wide association studies (GWAS) have identified some possible loci of interest. A GWAS from 2010 reported that the single nucleotide polymorphism (SNP) rs1835740 on chromosome 8q22.1 was associated with migraine with aura [112•]. This SNP was found to be in a region that is implicated in glutamate homeostasis, suggesting a possible link between migraine aura and glutamate regulation [113]. Another GWAS published in 2011 reported that SNPs rs2651899 (1p36.32, *PRDM 16*), rs10166942 (2q37.1, *TRPM8*), and rs11172113 (12q13.3, *LRP1*) were associated with migraine. However, these associations were not specific for migraine with aura [114].

A candidate gene study published in 2010 linked a dominant-negative mutation in the TWIK-related spinal cord potassium channel (TRESK) to migraine with aura. The implicated gene in this study, *KCNK18*, codes for TRESK. This gene was studied in a large family pedigree and a frameshift mutation was noted only in affected individuals with migraine with aura. This mutation led to an alteration in function of TRESK, possibly altering neuronal thresholds for CSD. The authors also noted that TRESK was abundantly expressed in the trigeminal ganglion [106•]. Other polymorphisms have been linked to migraine with aura. The 677TT polymorphism for methylenetetrahydrofolate reductase gene (1p36.3, *MTHF-R*) was associated with a migraine with aura (OR 2.05) [115] as was the angiotensin-I converting enzyme (D/D genotype) [116]. It is also interesting to note that certain monogenetic syndromes, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) are intimately associated specifically with migraine with aura [69]. The causative *NOTCH3* mutation in this instance has been demonstrated to increase susceptibility to CSD [117]. Despite the importance of discoveries thus far, the details of genetic inheritance in migraine with aura remain incomplete and further work is ongoing (see Table 2 for a summary of the mutations thus far found in migraine with aura).

Vascular Risk and Aura

Migraine aura has been associated with an increased risk of ischemic stroke for some time. A meta-analysis of published data by Schurks, in 2009 showed that migraine with aura increased the risk of ischemic stroke by a factor or more than 2 (RR 2.16). In addition, this study also found that in women who had migraine with aura, the risk of stroke was additively increased further by other factors such as smoking, oral contraceptive use, and age under 45 [5]. A later study, part of the American Migraine Prevalence and Prevention (AMPP) study, looked at 6102 migraineurs and 5243 controls utilizing a questionnaire-based format. This study showed that while migraine with aura was associated with ischemic stroke (OR 3.14), there was no association between migraine without aura and stroke (OR 0.89) [118]. Migraine with aura has also been associated with cardiovascular disease. In 1 study from 2006, Kurth and colleagues found that the risk of cardiovascular disease, myocardial infarction, and death from ischemic cardiovascular disease was increased in patients with migraine with aura. Once again, risk was not increased in patients with migraine without aura [119].

Migraine with aura has also been associated with the appearance of clinically-silent white matter hyperintensities and infarct-like brain lesions. Kruit and colleagues published a cross-sectional study in 2004, which showed that migraine with aura patients had 7 times the risk of infarct-like lesions in the cerebellum compared with migraine without aura patients [120]. A subsequent study, the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study showed a higher prevalence of subclinical infarct-like lesions in the distribution of the posterior circulation with an odds ratio (OR) of 13.7. This study also showed a higher preponderance of white matter hyperintensities in female migraineurs irrespective of migraine type [121]. In another

Table 2 Genetic variants related to migraine with aura thus far

Locus	Gene	Reference	Migraine type	Ref. SNP ID
1 p36.3	Methylenetetrahydrofolate reductase (MTHFR) C677T	Lea et al., 2004 [97]	MA	No rs[a]
5 q35	DRD1 neg.	Corominas et al., 2009 [98]	MA MO mix	
11q23 3q13.3 4p15.1-33	DRD2 + but not repl			rs2283265 rs12363125 rs1554929
9q34	.			rs2234689
22q11.2	DRD3 neg.			
5p 15-3	DRD5 neg.			
11p15.5.	DBH neg. COMT neg. SLC6A3 net Tyrosine hydroxylase TH + but not replicated in second phase dif. Pop.			rs2070762 rs6356
5 p 15-3	SLC6A3 (dopamine transporter gene DAT) DRD2	Todt et al., 2009 [99]	MWA	rs40184 rs7131056
6 q25.1	Estrogen receptor 1 (ESR1) G594A in exon 8	Colson et al., 2004 [100]	MA & MO	rs2228480
6 q25.1	Estrogen receptor (ESR1)[b] G594A (G2014A variant) negative 5 other polymorphism in linkage dysequilibrium rs6557170 rs2347867 rs6557171 rs4870062 rs1801132	Kaunisto et al., 2006 [101]	MWA	rs2228480
6 q25.1	Estrogen receptor (ESR1) negative Progesterone (Alu insertion) negative	Coromina et al., 2009 [102]	MO MA mix	rs2077642 rs1801132 rs2228480
6 q25.1	ESR1 (PvuII) negative C325G exon 4 negative	Colson et al., 2006 [103]	MO MA mix	rs2234693 rs1801132
9 q34	Dopamine beta-hydroxylase(DBH)	Todt et al., 2009 [99]	MA	rs2097629
9 q34	Dopamine beta-hydroxylase (DBH)	Fernandez et al., 2009 [104]	MA & MO	rs1611115 rs6271
9 q34	Dopamine beta-hydroxylase (DBH) Deletion/insertion (DBH2) +	Fernanadez et al., 2006 [105]	MA in males	[b]X63418
10q25.2–3[a]	KCNK18	Lafreniere et al., 2010 [106•]	MWA	[a]
17 q11.1-q12	Human serotonin transporter (SLC6A4) intron 2 VTNR 16-17 bp repetitive element.	Ogilvie et al., 1998 [107]	MA and MO	No rs[a]
17 p13	TRPV3	Carreno et al., 2012 [108]	MWA	Rs7217270
17 q23.3	ACE ID	Joshi et al., 2009 [109]	MWA	rs4646994
17q25.3	Casein kinase Iδ (CKIδ)-T44A and H46R alleles	Brennan et al., 2013 [110]	MWA	No Rs
19 p13.3/2	Insulin receptor INSR Nonsign. trend for rs2860174	Netzer et al., 2008 [111]	MA MO mix	rs2860174

rs reference SNP number, *SNP* single nucleotide polymorphism

[a] no rs provided in paper

[b] non-SNP variant

population based study from France, migraine with aura related infarct-like lesions were detected in vascular distributions outside the posterior circulation [122]. There is an abundance of evidence suggesting that there is an increase in white matter lesions in patients who have migraine. However, the specific etiology of these lesions is currently unknown [123]. When the longitudinal follow-up results from the CAMERA population (in the CAMERA-2) were studied, migraine patients (with and without aura) as a whole were not at increased risk of developing new posterior circulation distribution lesions. Unexpectedly, CAMERA-2 on subgroup analysis demonstrated that the migraine with aura group did not have progression of subclinical white matter hyperintensities, whereas the migraine without aura group did show progression [124•].

The mechanism(s) by which vascular risk is increased in the migraine with aura population is unclear although numerous theories abound. One possibility is that CSD may lead to neuronal and vascular changes culminating in ischemic

damage and infarction [125]. However, migrainous infarction as defined by the ICHD criteria is very rare [126]. Patent foramen ovale (PFO) is detected more frequently in patients with migraine with aura [127] than nonmigraine controls subjects and has been put forward as another potential link between migraine aura and vascular risk. Microemboli (such as those that would be seen in patients with PFO), have been noted to trigger CSD in mouse studies. However, PFO is present in 25 %–30 % of the population [128] and even when PFO is seen in a patient with a stroke it may be incidental [129]. A recent meta-analysis echoes this sentiment and did not find a strong relationship between PFO, migraine, and stroke [130]. Endothelial dysfunction [131, 132], impaired vascular reactivity [133], platelet dysfunction [134], coagulation system abnormalities [135, 136], comorbidity with other vascular risk factors [137], and genetic predisposition/susceptibility [138] are other factors proposed to link migraine with aura and vascular risk.

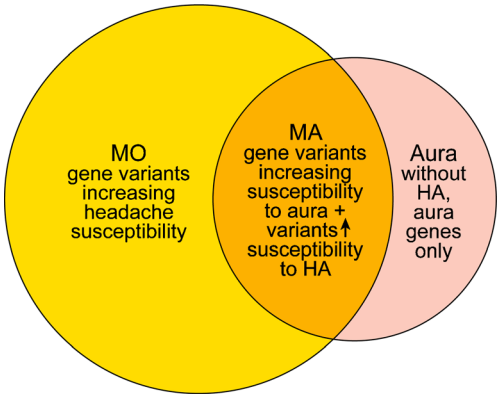

Fig. 2 Attacks of migraine with aura (MA) may occur in individuals with gene variants that render them susceptible to headaches (HA) as well as variants that increase their risk of aura. In this paradigm, migraine without aura (MO) would occur in those individuals who have genetic propensity to headache but without genetic susceptibility to aura, and recurrent aura without headache would occur in those individuals genetically predisposed to aura but less vulnerable to headaches

Aura and Targets for Therapy

The targeting of CSD in the development of prophylactic treatments in migraine with aura is a particularly attractive approach. Ayata et al. found in an animal model of CSD that several widely used migraine prophylactic treatments dose-dependently suppressed CSD frequency by 40 %– 80 % and increased the cathodal stimulation threshold for CSD [139]. If CSD is the initiating event in attacks of migraine with aura then suppressing CSD susceptibility might be a strategy to block the cascade that leads to headache activation. Thus far, the specific targeting of aura in migraine prophylactic treatment has been limited. Lamotrigine, an anticonvulsant with NMDA antagonistic properties, was found in an open label study to reduce aura frequency and duration by at least 50 % in about three-quarters of subjects studied [140]. Activation of NMDA receptors fosters propagation of CSD and NMDA (N-methyl-d-aspartate) receptor antagonists blocks CSD in experimental settings [141]. Another NMDA antagonist, ketamine was studied as a treatment for migraine aura by Afridi and colleagues in 2013. In this randomized, double blinded study, 9 patients suffering from migraine with aura patients treated with intranasal ketamine were compared with a control group of 9 migraine aura patients treated with intranasal midazolam. The patients in the ketamine treatment group reported decreased severity of their aura but did not note any reduction in aura duration [142]. Another agent, verapamil, an L-type Ca^{2+} channel antagonist is also used in the treatment of hemiplegic migraine with reported efficacy [143–145]. Acetazolamide, which has no intrinsic analgesic effect, also has some evidence of benefit in the setting of hemiplegic migraine [146]. Gap junction inhibition has been investigated for treatment of migraine with aura. Tonabersat, a novel gap junction inhibitor, yielded mixed results for treatment of migraine [147] however, 1 randomized, double blind, placebo-controlled trial showed that tonabersat 40 mg daily was effective for prevention in migraine with aura but not migraine without aura [148]. Acid Sensing Ion Channel 1 (ASIC1) [149], AMPA (α-amino-3-hydroxy-5- methyl-4-isoxazolepropionicacid), NR2B-containing NMDA, and calcitonin-gene related peptide receptors have also been shown to play a role in suppressing CSD experimentally [150] and may be future targets for migraine aura prevention.

Conclusions

Migraine aura is a group of transient focal neurologic symptoms that occur in the context of acute headache attacks in a substantial minority of migraineurs. The striking visual, sensory, language, and motor symptoms of aura are the source of significant anxiety and concern when they first occur in the lives of many migraine patients raising in them fear of stroke, intracranial tumor or other serious disorders of the nervous system. Fortunately, the presence of aura brings with it only a minor increase risk of stroke and thousands of patients experience recurrent auras throughout their lives without lasting injury. Investigations in human subjects over the past 30 years suggests that the phenomenon known as cortical spreading depression (CSD) which is, in fact, a wave of spreading cortical hyper-excitation followed by depression is the process most likely to be the underlying cause of aura. Because CSD is a measurable phenomenon and can be modelled in animals, targeting it may be one of our best hopes for the development of more effective nonempiric therapies. Migraine aura appears to be one of the more highly heritable elements of the migraine syndrome. The genetics of aura are quite complex and yet seem at this point to be ripe for investigation. Because we

have some sense of its pathophysiology, investigations of the genetic basis of the susceptibility to aura may prove to be more easily focused on the relevant molecular pathways.

The relationship of the aura to the headache in migraine patients is complicated. The majority of patients with migraine never experience the aura. Although many patients who have migraine with aura also have attacks of the migraine headache without the aura and on other occasions, the aura without the induction of a migrainous headache. Other individuals experience recurrent auras throughout their lives without ever having a single migraine headache. This combination of clinical scenarios suggests that susceptibility to the migraine aura and the migrainous headache are likely to be two genetically independent variables related by the fact that CSD, the presumed event that underlies the aura, is one means by which the migrainous headache may be activated (Fig. 2).

Compliance with Ethics Guidelines

Conflict of Interest Justin M. DeLange and F. Michael Cutrer each declare that they have no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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