Pathophysiology of Migraine

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ABSTRACT

Our understanding of migraine pathophysiology is a work in progress. As more is learned about migraine, it seems that the probability of identifying a single unifying explanation for this common disorder becomes less and less. Although the neuroanatomy and elements of pain physiology underlying migraine attacks are probably shared pathophysiologic elements, the emerging complexity of migraine genetics suggests that the acute attack may be the final common expression of more than one type of initiating abnormality. After a brief summary of the neuroanatomic structures involved in the generation of migraine attacks and the traditional theories of migraine, the author focuses on the current understanding of migraine genetics and reviews recent data from the neuroimaging and the neurophysiology of migraine.

KEYWORDS: Migraine, pathophysiology, aura, central sensitization

WHAT IS MIGRAINE?

Migraine is a common neurologic syndrome the typical features of which include a moderate to severe, recurrent, unilateral or bilateral, throbbing headache lasting hours to days, which is usually accompanied by nausea, photophobia, and phonophobia and worsened by routine physical exertion.[1] Up to 25% of migraine sufferers experience transient focal neurologic symptoms, including visual disturbance, unilateral paresthesias, motor symptoms, and language disturbance.

Migraine sufferers differ from the rest of the population in that they are susceptible to recurrent activations of the trigeminovascular and upper cervical pain systems causing headaches that are not based on an identifiable pathologic process such as infection, inflammation, a tumor, or other structural abnormality, or exogenous toxins. When migraine occurs infrequently, the pain systems themselves appear to be functioning normally. In fact, many of the clinical features that we use to identify migraine, such as nausea or photophobia, are fairly nonspecific and may occur with head pain of any cause. However, as the frequency of the headache increases and the disorder becomes chronic, it may be that changes occur in the pain systems themselves or in their activation thresholds.

In the following pages, the neuroanatomic structures involved in migraine attacks, the traditional theories of migraine that serve as the foundation for current research, and the important findings from current migraine genetic and pathophysiological research will be reviewed. For organizational clarity, the information will be divided into (1) sections related to the brain events initiating a migraine attack, (2) those sections examining the mechanisms of activation and transmission within trigeminal afferent neurons, and (3) sections focused on the modulation of nociceptive trigeminal input within the central nervous system and the effect of migraine attacks on the brain.

Neuroanatomic Structures that Underlie Headache

Studies performed in conscious patients in the 1930s revealed that though the brain itself is largely insensate,

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the dura mater, the intracranial segments of the trigeminal, the vagus, and glossopharyngeal nerves, and the proximal portions of the large intracranial vessels including the basilar, vertebral, and carotid branches,[2,3] are highly pain-sensitive structures. Depolarization of small caliber pseudounipolar neurons projecting from the trigeminal ganglion, which invest these meningeal structures and cerebral vessels,[4] results in activation of second-order neurons within the brainstem areas of the medullary trigeminal nucleus caudalis (TNC) and the dorsal horn of upper cervical spinal cord segments.[5] Stimulation of trigeminal nociceptive neurons results in activation patterns, organized somatotopically along the rostrocaudal axis of the brainstem[6] in a pattern consistent with the classical "onionskin" distribution seen in the sensory deficits experienced in patients after trigeminal tractotomy. Once activated, second-order neurons in the TNC and cervical dorsal horn are modulated by projections from the nucleus raphe magnus, periaqueductal gray,[7] rostral trigeminal nuclei,[8] and descending cortical inhibitory systems.[9] These activated second-order neurons project to other brainstem nuclei,[10,11] as well as the contralateral dorsomedial and ventroposteromedial nuclei of the thalamus.[6] Trigeminal pain is also associated with activation in several cortical areas, including the insular cortex, anterior cingulate cortex, and somatosensory cortex.[12] In the primary somatosensory cortex, trigeminal painful stimulation results in a laminar configuration similar to that observed within the brainstem trigeminal nuclei with V1 more caudal, V2 more rostral, and V3 medial, abutting the area of activation observed after stimulation of the thumb.[6]

Traditional Theories of Migraine Pathogenesis: Brain versus Vessel

Two competing theories dominated the discussion of migraine pathogenesis throughout the 20th century. The vasogenic theory, which viewed migraine as a form of vascular dysregulation and assumed that the aura was due to a transient vasoconstriction-induced hypoxemia, dominated the discussion until the 1980s. According to the vasogenic theory, migraine headache was caused by a rebound vasodilation that resulted in a mechanical depolarization of primary nociceptive neurons within the walls of engorged intra- and extracerebral vessels.[13] One of the mainstays of the vasogenic theory was the fact that it was consistent with the observed headache inducing effects of vasodilating drugs, such as nitroglycerin, and the therapeutic effects of ergotamines, which were known to be potent vasoconstrictors. Reports of no efficacy from the nonvasoconstrictive substance P antagonists in acute migraine also seemed to favor the vasogenic hypothesis.[14] However, recent imaging studies revealed that the headache induced by nitroglycerin begins well after the resolution of vasodilation when vessels are at their normal baseline caliber.[15,16] In addition, other vasodilating substances, like vasoactive intestinal peptide, do not induce migraine headache.[17]

The alternative neurogenic theory viewed migraine as a disorder of the brain in which vascular changes were the result of neuronal dysfunction. Proponents of this theory pointed to the fact that multiple neurologic symptoms often occur during a single aura that are difficult to localize within a single neurovascular territory. Also in favor of the neurogenic theory were findings from neuroimaging studies conducted during spontaneous, classical visual auras, which indicated that the decreases in cortical blood flow observed during aura are not sufficient to cause ischemia, and that subsequent vasodilation does not take place until well after the onset of headache.[18–20] In addition, multiple nonvasoconstrictive treatments are known to be effective in migraine.[21] Unfortunately, at this point in time, if viewed rigidly, neither theory alone can account for all of the clinical and treatment response characteristics of migraine.

Genetic Factors

There is accumulating evidence that migraine is a complex genetic disorder. The influence of inheritance in migraine has long been recognized. Over the past several years, investigators have identified three distinct single gene defects that may account for familial hemiplegic migraine (FHM), a rare autosomal dominantly inherited form of migraine. The first defect to be identified was for FHM type 1 and was found in a gene known as CACNA1A located on chromosome 19p13. CACNA1A codes for the α_1-subunit of a brain specific voltage-gated P/Q-type calcium channel.[22] A second defect (linked to FHM type 2) has been identified on chromosome 1q23 in the ATP1A2 gene that encodes the α_2-subunit of a $Na^+/K+$ pump.[23] More recently, a third mutation on chromosome 2q24 has been associated with FHM type 3. This mutation occurs in the voltage-gated sodium channel SCN1A.[24] At least 17 different mutations within the CACNA 1A have been linked to migraine or other related clinical syndromes. In addition to unilateral motor weakness, patients with FHM experience typical visual, sensory, and/or language auras with some attacks of FHM. Just as in the more common forms of migraine, FHM is more common in women than in men, possibly implicating hormonal shifts in migraine pathogenesis.

Linkage analysis and various association studies have implicated numerous polymorphisms in the more common forms of migraine: migraine with aura (MA) and migraine without aura (MO). It is increasingly evident that the common forms of migraine are based on complex, heterogeneic genetics (Table 1). The obvious complexity of the underlying genetics will likely be

Table 1 Genetic Sites Proposed to Be Important in the Common Forms of Migraine

Chromosome/Locus	Gene/Protein	Migraine Type	Reference
1p13.3	Glutathione S-Transferase (GST)	MO	25
1 p36	MTHF-R	MA	26
4 q24	?	MA & MO	27,28
4 q21			
4q31.2	Endothelin type A (ETA-231 A/G)	Not specified	29
6 p12–21	?	MA MO	30
6p21.3	Tumor necrosis factor α (TNFα)	Not specified	31
6p21.3	HLA-DRB1	MO	32
6q25.1	Estrogen receptor 1 (ESR1)	MA & MO	33
6q25.1	Estrogen receptor 1 (ESR1)	Not specified Females only	34
9q34	Dopamine β-hydroxylase (DBH)	Not specified	35
11 q24	?	MA	36
11 p15	DRD4	MO	37
11q22–23	Progesterone receptor (PGR)	MA & MO	38
11q23	DRD2 Allele 1 TG dinucleotide non-coding	MO	39
11q23	Dopamine D2 (DRD2) NcoI	MA	40,41
14 q21–22	?	MO	42
17q11.1-q12	Human serotonin transporter (SLC6A4)	MA & MO	43
17q23	Angiotensin converting enzyme (ACE)	MO	44
19p13.3/2	Insulin receptor INSR	Not specified	45
22q11.2	Catechol-*O*-methyltransferase (COMT)	not specified	46
X q24–28	?	MO	47

MA, migraine with aura; MO, migraine without aura.

a key factor in ongoing and future migraine pathophysiologic research.

INVESTIGATIONS OF MIGRAINE PATHOPHYSIOLOGY

Investigations of migraine pathophysiology can be divided into three groups based on the cascade of clinical events that occur during an acute migraine attack. These groups include (1) those investigations related to the brain events initiating a migraine attack; (2) those examining the mechanisms of activation and transmission within trigeminal afferent neurons, and (3) those focused on the modulation of and possible consequences of recurrent nociception trigeminal input within the central nervous system.

Investigations of Migraine Attack Initiation

The factors that render an individual susceptible to attack initiation arguably constitute the essential abnormality of migraine. Efforts to find a single mechanism to explain migraine are ongoing and putative sites have been suggested from the calcium channel to the rostral brainstem. However, thus far, no single convincing all-encompassing mechanism has been identified. Over the past two decades, research focusing on migraine initiation has centered on (1) changes in cortical blood flow and in activation patterns during attacks of migraine with aura, (2) altered activation thresholds within the cerebral cortex, and (3) changes that occur in the activation pattern in brainstem nuclei in migraine attacks without aura.

INVESTIGATIONS OF THE MIGRAINE AURA

The aura consists of focal neurologic symptoms that herald the acute migraine attack and occurs in up to 25% of migraine sufferers. The aura has figured prominently in attempts to study and ultimately explain migraine pathophysiology. The vasogenic theory assumed that the aura represents the consequence of an initial vasoconstrictive phase of the migraine attack.[13] However, in the 1940s Lashley, after plotting progression of his own visual scotomata, proposed that aura was due to an abnormality which spread over his visual cortex at a rate of 3 to 5 mm per minute.[48] This migratory pattern would have been atypical for an ischemic phenomenon. Around the same time, Leao, a neurophysiologist, described an electrophysiologically measurable phenomenon that appeared and migrated over the cortex of experimental animals at a slow rate of 3 to 4 mm per minute after mechanical or chemical perturbations.[49] Although this phenomenon consisted of an excitatory phase followed by a phase of depressed activity, it has been termed cortical spreading depression. Based on the slow rate spread of both phenomena and the movement across neurovascular boundaries in both, it has been proposed that the aura of migraine is caused by a human analogue to cortical

spreading depression. According to this proposed scenario, the alterations in blood flow observed during migraine aura are secondary to decreased metabolic demand in abnormally functioning neurons rather than the underlying cause of symptoms of aura. This view is increasingly supported by evidence from functional imaging techniques applied during aura in humans.

FUNCTIONAL NEUROIMAGING AND THE MIGRAINE AURA

The development of noninvasive functional neuroimaging techniques have enabled investigators to study in real time the location and progression of physiologic changes that occur in the brain during migraine and migraine-like symptoms in human patients. Almost three decades ago, Olesen, Lauritzen, and their coworkers utilized intraarterial ^{133}Xe blood flow techniques to investigate whether changes in blood flow occurred during aura-like symptoms induced during carotid angiography. They found that regional cerebral blood flow (rCBF) was reduced by 17 to 35% in the posterior parietal and occipital lobes[50,51] during visual aura-like symptoms, although hypoperfusion in the frontal cortex was also observed occasionally in combination with the posterior drops in blood flow. The decreases in rCBF persisted for up to one hour after the initial drop at the onset of the aura-like symptoms. After one hour, rCBF either normalized or remained focally decreased.[52,53] The observed decreases in blood flow[50,52] were not large enough to cause ischemia and were termed "oligemia." An anterior spread of oligemia[51] was reported in many subjects that did not respect neurovascular boundaries. Both small magnitude and spread beyond vascular territories of the rCBF tended to support a primarily neuronal origin for migraine aura. At first, Olesen's findings were controversial, and proponents of the vascular hypothesis argued that both the severity and duration of aura might correlate with the magnitude and duration of blood flow alterations,[54] suggesting that observed decreases in blood flow are sufficient to cause the neurologic symptoms of migraine aura. However, there have been patients studied during aura who showed nominal or no disturbance in cerebral blood flow in several series.[51,52,55] Others argued that Olesen's finding were flawed by the artifact of Compton's scatter[56] (to which ^{133}Xe techniques are vulnerable). They proposed that Compton's scatter was responsible for both an underestimate of CBF decrements and the apparent spreading quality of the phenomenon.

In the mid-1990s, Woods and coworkers fortuitously captured the onset of a spontaneous attack in a migraine sufferer undergoing blood flow measurements (^{15}O-labeled water) as a control subject in an unrelated positron emission tomography (PET) study. Woods reported a bilateral spreading drop in blood flow that appeared in the visual association cortex (Brodman areas 18 and 19) within a few minutes after the onset of bilateral occipital throbbing headache. The flow changes spread anteriorly across vascular and anatomic boundaries.[18] The patient, whose previous attacks of migraine had occurred without aura, reported no visual symptoms other than a transient difficulty focusing on the visual target during the study. This episode has been viewed as an atypical visual aura; therefore, it is difficult to be certain that the findings in this case are exactly those that would be found during classical visual aura.

At roughly the same time, functional magnetic resonance imaging (fMRI) techniques, including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and the blood oxygen level dependent (BOLD) imaging were also beginning to be used to study migraine aura. The rapid acquisition times for many fMRI techniques allowed the evaluation of metabolic as well as hemodynamic parameters within a single attack. One case series reported DWI findings during five spontaneous migraine visual auras in four patients.[19] DWI (based on detection of changes in net movement of water molecules across neuronal membranes that may result from an impairment of Na^+K^+ ATPase activity seen in ischemia[57] or cortical spreading depression (CSD)[58,59] was performed during spontaneous migraine visual aura in humans. Spreading depression induced in animal models has been associated with waves of reduced apparent diffusion coefficient (ADC), moving at a rate of 3 millimeters per minute. The decreased cortical ADC areas returned to normal levels after 30 seconds.[58] In patients suffering from spontaneous, acute migraine visual auras and in postaural scans, quantitative ADC maps were symmetric and normal.[19] This implied that CSD was in some way different from the process underlying migraine aura. However, the DWI methods used in these studies may have had insufficient sensitivity to draw firm conclusions about changes within minute brain regions.

Unlike DWI, perfusion-weighted imaging studies in the same series of spontaneous visual auras showed significant changes. PWI estimates three hemodynamic parameters: rCBF, relative cerebral blood volume (rCBV), and mean transit time (MTT) based on the decrements in signal intensity caused by the first pass of a bolus injection of a paramagnetic contrast agent (gadolinium) through the cranial vasculature. PWI is particularly sensitive to microvascular changes (capillary/arteriolar), and has higher spatial resolution than radionuclide-based techniques. rCBF and rCBV decreased, while MTT increased in gray matter of the occipital cortex contralateral to the affected visual hemifield. No detectable hemodynamic changes were seen in the thalamus, cortical areas, or brainstem during the aura. The changes in hemodynamic parameters appear to be specific to the aura. In a series of 14 attacks of migraine without aura studied from 1.5 to 11 hours after headache onset, changes in PWI parameters were not observed.[60] The PWI findings during spontaneous migraine aura using a

technique that is not susceptible to the artifact of Compton's scatter were consistent with the ^{133}Xe blood flow studies of Olesen.

BOLD imaging, based on known increases in magnetic resonance imaging (MRI) signal intensity with decreases in local deoxyhemoglobin concentration,[61] was also applied to migraine aura. In one series,[62] BOLD imaging was used to study occipital cortex activation patterns induced by visual stimulation in migraine with and without aura. In five of 12 subjects, headache or visual changes (but not classical aura) was preceded by areas of signal suppression that followed initial activation, which spread across the occipital lobe at a slow rate (3 to 6 mm per minute). In a later series by the same group studying migraine attacks (with and without aura) triggered by visual stimuli, 75% were found to have increases in BOLD signal within the red nucleus and substantia nigra prior to changes seen in occipital cortex, implicating these structures in both migraine with and without aura.[63]

In another report, BOLD imaging performed during both spontaneous ($n = 2$) and exercise-induced visual auras[64] revealed a loss of cortical activation to visual stimuli in the occipital lobe contralateral (but not ipsilateral) to the symptomatic visual field in all patients. Activation within the affected occipital lobe returned to normal with resolution of the clinical symptoms. In the inducible subject, BOLD imaging was started after exercise but before the onset of visual symptoms. It was continued for the full duration of visual symptoms and into the headache phase after resolution of visual symptoms. When the patient reported the beginning of the aura, suppression of activation was observed first in area V3a and then expanded into the neighboring occipital cortex at a rate of 3.5 mm per minute to involve both primary visual and association areas. The area of BOLD signal change within striate cortex corresponded to the retinotopic visual disturbance. At the end of the studied auras, perfusion defects were present in the same areas that had exhibited abnormal BOLD activation. The BOLD MRI findings shared several characteristics with those seen in CSD, suggesting that a human analogue of CSD might be the source of migraine visual aura. The fMRI similarities include (1) CSD and the migraine visual aura are both characterized by an initial hyperemic phase lasting ~3 to 4.5 minutes; (2) the hyperemia in both CSD and migraine aura is followed by mild hypoperfusion lasting 1 to 2 hours; (3) the hyperemia/hypoperfusion signal spreads across the cortex at a slow rate (2 to 5 mm/min); (4) the BOLD signal complex during both aura and induced CSD in animals halt at major sulci; (5) evoked visual responses during CSD and during aura are suppressed and take ~15 minutes to recover; and (6) in CSD and migraine aura, the first affected area is the first to recover normal evoked responses. Other recent investigations have shown that CSD-like phenomena, such as intercellular calcium waves propagated in astrocytes, can modulate both neuronal and vessel function[65–67] and suggest a possible role for such phenomena in human migraine aura.

ALTERED CORTICAL FUNCTION IN MIGRAINE WITH AURA

If the migraine visual aura arises from an increased susceptibility to induction of CSD or a CSD-like phenomenon, then underlying differences in cortical reactivity or irritability should probably be detectable. There is increasing evidence suggesting that differences between the cortices of nonmigraine sufferers and patients with migraine with aura do, in fact, exist.

In the 1980s, Welch and colleagues[68,69] using ^{31}P magnetic resonance spectroscopy (MRS) reported a decrease in the phosphocreatinine/inorganic phosphate ratio (an index of brain phosphorylation potential) during headache in migraine patients who had aura, but not in normal controls or migraine sufferers without aura. This altered ratio was present in the context of normal pH, suggesting that the altered cortical function was caused by defective aerobic metabolism rather than vasospasm with ischemia. In another series, low levels of brain magnesium were present in migraine sufferers[70] possibly augmenting *N*-methyl-D-aspartate (NMDA) receptor activity and thereby lowering the threshold for CSD.[71] Thus far, spectroscopy has not been performed during typical migraine aura. Evoked potential studies employing several different modalities have indicated that a lack of habituation is the most reproducible interictal abnormality in the sensory processing of migraine sufferers. Evidence of altered cortical excitability in migraine aura comes from transcranial magnetic stimulation-based studies. A blinded study found a significantly lowered threshold for phosphene (visual sensation in the absence of light) generation in the occipital cortices of migraine sufferers with aura (42.8%) compared with normal controls (57.3%) [$p = 0.0001$].[72] However, other investigators have found reduced cortical excitability in migraine sufferers.[73] Some have suggested that an instability of regulation of cortical function rather than absolute gain or loss of function may underlie the propensity to migraine aura.[74] Although the details of the differences in cortical function in migraine sufferers are, thus far, not completely understood, the body of evidence for the existence of altered cortical function is growing. It is likely that differences in cortical processing are involved in the generation of the aura.

Investigations of Headache Activation and Evolution

The central feature of the migraine syndrome is headache; that is, the recurrent activation of the trigeminocervical pain system. In the physiologic setting, this

activation occurs when peripheral terminals of nociceptive neurons are depolarized and then, in turn, transmit the depolarization to the central terminals causing a trans-synaptic activation of second-order neurons in the medulla and cervical spinal cord. For secondary headaches in which intracranial pathology can be identified (e.g., chemical irritants during subarachnoid hemorrhage or mechanical traction as seen with intracranial tumors), there is a static cause of activation and it is easy to understand how headaches persist for hours or days. However, in migraine no ongoing cause of activation has been identified.

Thus far, a single mechanism of trigeminal activation common to all migraine sufferers has not been identified. Although direct activation of the trigeminal system by dysfunction within central areas of pain processing cannot be excluded, there is more direct evidence that activation of peripheral nociceptors may occur during acute migraine attacks, at least in some individuals. For example, sumatriptan (the prototype of the highly effective "triptan" class of migraine abortive agents) does not avidly cross the blood–brain barrier suggesting that it acts at peripheral sites. Furthermore, during acute migraine attacks, levels of calcitonin-gene-related peptide (CGRP) which is known to be released from the peripheral terminals of activated peripheral nociceptive c-fibers, rise in external jugular blood.[75]

ACTIVATION DURING ATTACKS OF MIGRAINE WITH AURA

In migraine sufferers who experience the aura, there is increasing evidence to suggest that the cortical events responsible for the aura symptoms may also be capable of activating trigeminal nociceptors. Bolay and coworkers[76] have reported experimental data from animal models that demonstrate that induced spreading depression can cause vasodilation in meningeal vessels by a reflex dependent on intact trigeminal and parasympathetic neurons. These findings link events intrinsic to the cerebral cortex to changes within pain-sensitive meningeal vascular structures. This link further implicates CSD as a potentially important pain generating mechanism in migraine with aura. In addition, induced CSD within the brains of experimental animals was shown in the mid-1990s to result in the expression of the immediate early gene *c-fos*, a marker for activation, within the nuclei of second order neurons in the trigeminal nucleus caudalis.[77] Experimentally induced CSD is associated with the release of factors (H^+ ions, K^+ ions, NO, and arachidonic acid metabolites),[78–80] which when present in sufficient concentrations are capable of activating perivascular nociceptive neurons.

One might ask, how do such factors cross the boundaries of normal brain compartments to gain access to the trigeminal fibers? One possibility is the activation of matrix metalloproteinases (MMP). Preliminary data[81] indicate that levels of MMP9 increase as early as 15 minutes after a single CSD within ipsilateral cortex, which is separated from the site of CSD initiation enough to make activation due to the initiating stimulus unlikely. The increases are quite large by 3 to 6 hours and persist for 48 hours. Activation of MMP activity results in decreases in laminin and other markers of intact compartmental barriers. The findings suggest the possibility that CSD may initiate activation of trigeminal nociception.

A recent study in which two of the known mutations for FHM1 were "knocked in" to genetically modified mice reveals a strong correlation between the clinical manifestations of the mutation and the characteristics of induced CSD.[82] One of the groups of experimental mice had the R192Q mutation, which is associated with a milder form of FHM1 in humans. The other group had the S218L, a severe, sometimes lethal form of the FHM1 mutation in humans. When compared with the wild-type mice (those without any inserted mutation) both experimental groups of mice exhibited prolonged hemiparesis analogous to that seen in human FHM after induced CSD. In addition, the mice with the FHM1 mutations showed increased propagation speed for CSD, increased CSD frequency, and enhanced corticostriatal propagation of induced CSDs. In the experiment groups, susceptibility to CSD was modulated by allele dosage (homozygotes had more susceptibility than heterozygotes), mutation type (S219L mutants had more susceptibility than those with R192Q), and gender (as in human FHM, females were more susceptible to CSD induction than males). The findings are consistent with a strong correlation between CSD and FHM1.

Activation in Migraine without Aura

The mechanisms by which trigeminal and cervical nociceptive neurons are activated during migraine without aura are not well understood. The possibility that a CSD-like phenomenon may occur in noneloquent areas of cortex during migraine without aura cannot at this point be excluded; however, evidence from PWI does not support this view.[60] There may be one or (perhaps, more likely) several mechanisms of activation in migraine without aura that remain to be detected and elucidated.

BRAINSTEM ACTIVATION DURING MIGRAINE WITHOUT AURA

One possible mechanism of activation during migraine without aura was suggested in the mid-1990s by a positron emission tomography- (PET-) based study that measured blood flow changes in the brains of nine patients during spontaneous attacks of migraine without aura.[12] Increases in rCBF of 11% were measured in the medial brainstem contralateral to the headache. Effective

treatment of the headache with subcutaneous sumatriptan did not reduce the midbrain CBF change, although it did reverse increases in flow observed in other cortical sites (insula and anterior cingulate gyrus). Based on these findings, it has been proposed that migraine attacks are initiated by a brainstem generator either through direct abnormal activation or through a failure of inhibition. Similar findings of pontine and midbrain activation during migraine attacks have been reported in two subsequent studies.[20,83] Brainstem activations were not observed during a headache-free interval nor were they observed in another study in which pain in the forehead was elicited by subcutaneous capsaicin injection.[84] It is unclear whether or not a generator in rostral brainstem is responsible for acute migraine attacks or whether these findings reflect brainstem modulation of pain. Nevertheless, these findings suggest that in some individuals or in some attacks, the head pain may be driven by derangements in central areas of pain processing without recourse to peripheral nociceptive activation.

Modulation of the Nociceptive Input: Peripheral and Central Sensitization

Thus far, the aura is the only well-characterized part of a migraine attack that precedes the headache. Although the longer prodromal phase is well described, it is widely variable in its duration and clinical features, making it difficult to study. When aura occurs, it generally persists for an hour or less and usually resolves before the headache is fully developed. If the initial activation of the trigeminal system may be transient and relatively brief (as may occur during the aura), then how does the headache persist and intensify long after the inciting activation has passed? Investigations of somatic pain suggest that two processes may be important: (1) *peripheral sensitization* of the primary afferent neuron, and (2) *central sensitization* of higher-order neurons within the brain and spinal cord.

PERIPHERAL SENSITIZATION

In experimental terms, peripheral sensitization develops when there is increased excitability of primary afferent neurons to mechanical stimulation after exposure to chemical/inflammatory irritation. The process may cause spontaneous firing of irritable primary afferent neurons as well. The result is that second-order neurons are bombarded with an abnormal number of impulses from the primary afferent fibers. In animal studies, Strassman and colleagues[85] recorded activity from primary afferent neurons in the trigeminal ganglion during mechanical stimulation of dural venous sinuses. Chemical stimulation of the dural receptive fields by inflammatory mediators not only directly excited axons, but also enhanced their mechanical sensitivity. After chemical stimulation, the primary afferent neurons became strongly activated by mechanical stimuli that were innocuous previously. These findings suggest that chemosensitivity and sensitization within meningeal primary afferent fibers may contribute to the hypersensitivity of migraine sufferers to small changes in intracranial pressure and to the throbbing quality of a migraine headache. It is known that, upon activation, trigeminal nociceptive fibers release proinflammatory vasoactive neuropeptides from their peripheral terminals in animal models (SP, NKA, and CGRP)[86] and during acute migraine in humans (CGRP).[75] The resulting vasodilation, mast cell activation, and membrane disruption may contribute to the peripheral sensitization of the trigeminal primary afferent neurons.[87]

CENTRAL SENSITIZATION

Upon receiving increased input from sensitized primary afferent neurons, there is evidence that second-order neurons within TNC and the dorsal horn become sensitized and begin to respond to mild stimuli that did not previously activate them.[88] Experimental studies by Burstein and coworkers[88] have shown that chemical irritants applied to the meninges lower the electrophysiologic threshold of second-order neurons to previously subthreshold low-intensity mechanical and thermal stimuli. That this electrophysiologic change correlates with pain is borne out by the fact that noxious chemical stimulation of the dura lowers the threshold for generation of cardiovascular responses (blood pressure elevation) by previously innocuous skin stimulation.[89] As central neurons receive convergent input from both intracranial meningeal/vascular structures and cutaneous structures,[88] changes in extracranial sensation (facial skin) would be expected if central sensitization occurs in migraine. The occurrence of central sensitization in humans during migraine was confirmed by a study in which 42 patients underwent repeated measurement of mechanical and thermal pain thresholds in periorbital and forearm skin during and in between attacks.[90] Seventy-nine percent of subjects exhibited cutaneous allodynia during the acute migraine attack. In a single well-studied case of migraine with aura, the development of allodynia occurred sequentially throughout the course of the attack. Allodynia was not present when testing was performed in the absence of a migraine attack but developed on ipsilateral face within one hour after the onset of headache and expanded to also involve contralateral head and ipsilateral arm at 2 hours after headache onset. Allodynia intensified further within a similar distribution at 4 hours.[91] Taken together, these findings suggest that hypersensitivity within second-order neurons may, in turn, result in sensitization at third- and higher-order levels. However, one recent study reported thermal pain thresholds dropped prior to the onset of migraine.[92]

Another study indicates that the β-1-adrenergic antagonists, propranolol and atenolol, inhibit firing of third-order thalamocortical neurons to dural (sagittal sinus) stimulation and L-glutamate injection suggesting that these drugs, which are of known efficacy in migraine, might act to negatively modulate and perhaps suppress the tendency toward central sensitization in higher-order neurons.[93] Other interesting data indicate that in recurrent migraine there is deposition of non-heme iron within areas of periaqueductal gray that directly correlates with the total duration of illness.[94] It has been suggested that these changes result from repeated attacks. These findings have recently been confirmed in migraine sufferers under the age of 50 in a large population-based cohort (migraine cases $n = 178$ and controls $n = 75$).[95] When stratified by age, subjects under the age of 50 ($n = 50$) had lower T2 values on MR imaging suggesting iron deposition in the putamen ($p = 0.02$), globus pallidus ($p = 0.03$), and red nucleus ($p = 0.03$). When subjects over the age of 50 were included, no differences were seen. However, whether these findings of apparent iron accumulation represent injury in response to repeated activation of the pain system and its modulation in periaqueductal gray or alternatively represent the cause of dysfunctional control within the trigeminovascular nociceptive system is unclear. In a similar vein, a subsequent PET-based study[96] has suggested altered brainstem function in patients with chronic migraine.

White Matter Changes in Migraine Patients

Over the past few years, there has been increased interest in an apparent increased occurrence of small foci T2 signal on MRI (presumed infarctions) and in white matter lesions in migraine patients compared with the nonmigrainous population. In a large study of randomly selected, age- and gender-matched patients with migraine with aura ($n = 161$), migraine without aura ($n = 134$), and controls ($n = 140$), the investigators found no significant difference between patients with migraine and controls in overall infarct prevalence (8.1% vs. 5.0%). However, in the cerebellar region of the posterior circulation territory, they found that patients with migraine had a higher prevalence of infarct than controls (5.4% vs. 0.7%; P =.02). The adjusted odds ratios (ORs) for posterior infarction varied based on migraine subtype and attack frequency. Patients with migraine with aura and those with greater that one attack per month had the highest risk of infarct compared with controls. Among women, the risk of deep white matter lesions (DWML) was increased in patients with migraine compared with controls (OR 2.1; 95% confidence interval [CI] 1.0–4.1); this risk increased with attack frequency (highest in those with ≥one attack per month: OR 2.6; 95% CI 1.2–5.7), but was similar in patients with migraine with or without aura. In men, controls and patients with migraine did not differ in the prevalence of DWMLs. None of the cerebellar lesions correlated with clinical symptoms.[97,98] The cause of the lesions remains unclear, although ischemia resulting from the recurrent periods of hypoperfusion during aura has been suggested. However, one report suggests that these lesions may be transient,[99] which would be unexpected were ischemia to be their underlying cause.

Another proposed explanation is that the subclinical lesions observed in the posterior circulation of migraine sufferers might result from recurrent microemboli that gain access to cerebral circulation through a patent foramen ovale (PFO). An increased prevalence of PFO in migraine with aura sufferers has been reported by several investigators,[100] and several uncontrolled trials have suggested that PFO closure resulted in a decrease in migraine attack frequency.[101,102] However, the MIST study, the first controlled trial, did not meet its primary efficacy endpoint.[103] Other controlled trials are currently underway. A recent study in migraine patients which used transcranial Doppler techniques to detect gaseous microemboli arising from right to left shunts due to PFO concluded that the presence of right-to-left shunt does not increase white matter lesion load in patients who have migraine with aura.[104]

CONCLUSIONS

The past two decades have seen a significant increase in our understanding of several important aspects of migraine pathophysiology. However, attempts to identify a single unifying theory that encompasses and accounts for all that we know about migraine continue to be unsuccessful. The increasing evidence of genetic heterogeneity which underpins migraine, combined with the wide clinical variation seen in the disorder argues for a syndromic approach to migraine. A syndromic approach recognizes an acute migraine attack as a clinical "final common pathway" reflecting a recurrent maladaptive activation of the trigeminocervical pain apparatus which may arise from more than one initiating process. Research based on a syndromic view of migraine may ultimately aid in the identification of clinically and perhaps genetically definable subgroups that may allow for more effective, individualized therapy for this very common, disabling disorder.

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