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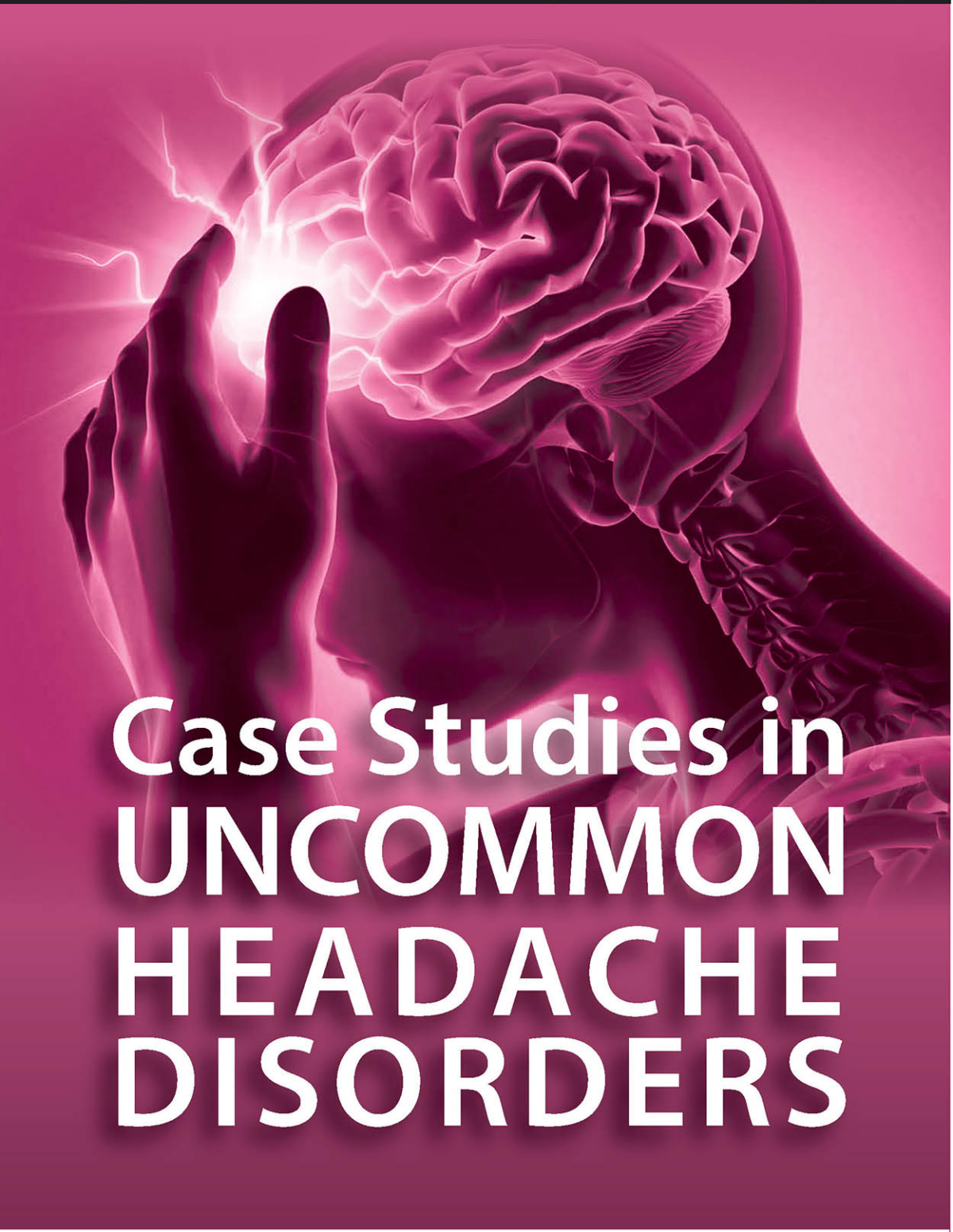

Case Studies in UNCOMMON HEADACHE DISORDERS

Ambar Chakravarty

2nd Edition

JAYPEE

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Section 1

The Migraines

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COMMENTARY 1

Chronology of Acute Migraine Attack

INTRODUCTION

According to the International Headache Society, a migraine attack can last anywhere between 4 and 72 hours. The headache is typically unilateral, pulsing, moderate-to-severe in severity, made worse by regular physical activity, and accompanied by nausea or phobic reactions to light and sound. About one-third of migraine sufferers in the west experience attacks that occasionally include an aura phase that includes visual, sensory, linguistic, or brainstem abnormalities. Four stages are involved to lead up to the acute attack, which is followed by a postdrome.

PREPARATORY STAGE

This stage defines subjects who are prone to develop acute migraine attacks because of their genetic constitution which makes their brains hyperexcitable. So, when acted upon by an attack-provoking stimulus or trigger, a cascade of events ensues leading first to an aura and then the headache.

HYPEREXCITABILITY OF THE NEURONS AND ITS GENETICS

According to neurophysiological research, the migraine brain exhibits overall neuronal hyperexcitability. Studies using evoked and event-related potentials have revealed that migraine sufferers are more excitable in reaction to a variety of stimuli, such as visual, somatosensory, and auditory stimuli, as well as brainstem reflexes in response to nociceptive stimuli. It has also been demonstrated through functional imaging studies that the migraine brain responds more strongly to sensory stimuli during the interictal phase. It is believed that the increased sensitivity to sensory stimuli observed in migraine patients during the interictal phase can be attributed to this general neuronal hyperexcitability. Additionally, it has been suggested that patients with migraines exhibit greater activation in pain-facilitating regions and decreased activation in pain-inhibiting regions both at rest and in response to painful stimuli, in contrast to healthy controls, suggesting that this hyperresponsiveness may help to develop central sensitization. The mechanism(s) underlying the generalized neuronal hyperexcitability observed in these patients may be revealed by certain

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genetic variants that have been shown to be probably related with migraine. The most important single gene migrainous disorder is familial hemiplegic migraine (FHM), an autosomal dominant disorder which may involve at least three different genetic mutations which all have been characterized and discussed in detail in the next section. All of the *FHM*-related genes have been shown to produce proteins that, in turn, alter glutamate availability at synaptic terminals and raise neuronal excitability. Twelve genetic loci, three of which increase activity in glutaminergic systems, have been linked to increased vulnerability to migraine, with or without aura, since the discovery of the *FHM* genes. This leads to increased transmission of pain signals, allodynia, and central sensitization. Numerous large-scale genome-wide association studies (GWASs) have shown genetic loci that can predict a person's susceptibility to different forms of migraine. The found susceptibility gene variations include those that may control glutamate neurotransmission (*MTDH*, *LRP1*, and *MEF2D*), as well as those that affect synaptic functioning and plasticity (*ASTN2* and *FHL5*), ion channels (*KCNK5* and *TRPM8*), ion homeostasis (*SLC24A3*, near *ITPK1*, and near *GJA1*), and ion homeostatic regulation (near *SLC24A3* and *TRPM8*). A new potassium (K^+) channel gene *TRESK* has been found to be associated with migraine with aura (MA) occurring in members of a single family only.

Changes in vascular and smooth muscle function are expected to play a significant role in migraine pathogenesis, according to a meta-analysis of 22 GWAS that found several migraine-associated single nucleotide polymorphisms (SNPs) that modify both arterial and smooth muscle function. This is in line with the fact that migraines, especially those with aura, are more likely to have vascular disease (such as ischemic stroke and cardiovascular disease). This is also connected to the priority of the central neuronal mechanisms engaged in migraines in light of the close anatomical and physiological ties between the blood artery and the neuronal and glial cells within the neurovascular unit.

MIGRAINE CASCADE

Premonitory Stage: Hypothalamus, Autonomic Nervous System, and Mechanism of Triggering

Some individuals may accurately forecast the arrival of a migraine headache up to 12 hours in advance thanks to the premonitory phase of the condition, which can start as early as 3 days before a migraine headache. The involvement of the hypothalamus, brainstem, limbic system, and specific cortical regions during the early stages of an attack is suggested by common symptoms experienced during this phase, such as weariness, mood changes, food cravings, yawning, muscle discomfort, and photophobia. In addition to having a diurnal periodicity, migraine is frequently brought on by changes in homeostasis. These findings imply that chronobiological mechanisms are involved in migraine pathogenesis and have prompted research into the hypothalamus as a potential migraine attack origin site.

Studies using functional magnetic resonance imaging (fMRI) show that the hypothalamus is active during the premonitory period. The posterolateral hypothalamus, midbrain tegmental area, periaqueductal gray (PAG), dorsal pons, and various cortical areas were all activated during the premonitory phase in a positron

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emission tomography study using cerebral blood flow as a marker of neuronal activity in patients with induced migraine attacks. fMRI was employed in a second investigation during the interictal phase, which is the interval between migraine attacks.

Imaging showed stronger functional connections between the hypothalamus and regions of the brain associated with pain transmission and autonomic function in migraine patients as compared to nonmigraineous controls, which may explain some of the autonomic symptoms felt during the interictal and premonitory phases. With research suggesting that the hypothalamus is involved in the early stages of migraine, it has been hypothesized that the hypothalamus may be crucial in facilitating or enhancing pain transmission during an episode. The two primary hypotheses for how this mechanism works are one involving regulation of nociceptive signals from the trigeminal nucleus complex (TNC) to supratentorial regions involved in pain processing. The other involves increased parasympathetic tone activating meningeal nociceptors.

Numerous migraine-related symptoms, including nausea, vomiting, and thirst, as well as cranial autonomic symptoms such as lacrimation, nasal congestion, and rhinorrhea, are signs of altered autonomic function in the central nervous system (CNS). It has, therefore, been demonstrated that changes in sympathetic and parasympathetic tone can be seen from the premonitory period to the postdrome. It has been hypothesized that migraine triggers including stress, waking up, or other modifications to physiological or emotional equilibrium activate nociceptive pathways via raising parasympathetic tone. The triggering of migraines by stress may also involve additional pathways. In experimental models, it has been demonstrated that sympathetic outflow into the meninges, which involves norepinephrine release, influences the dural afferents and fibroblasts to produce pronociceptive signaling. The kappa-opioid system's activation in response to corticotropin-releasing hormone and dynorphin production brought on by stress may also contribute to stress-induced migraine. Through the release of neuropeptide transmitters from parasympathetic efferents that innervate the meninges and meningeal blood vessels, these physiological mechanisms, which involve networks that project to preganglionic parasympathetic neurons in the superior salivary nucleus, may cause peripheral nociceptor activation.

How triggers trigger an acute migraine attack—some detailing

In essence, triggers are a cerebral phenomenon. In general, triggers can be thought of as sensations—whether they are visible or invisible—and must thus be understood at the cerebral level. Triggers may enter the spinal cord by the bloodstream humorally (e.g., sex hormones, chemicals from diet), normal sensory routes (e.g., heat, head bath), or specific sensory pathways (light, sound, and smell). Reaching cortex, they might influence ionic flow across cell membranes in susceptible individuals via affecting the activation of calcium (Ca^{++}) channels or through sodium (Na^{+})-K^{+} ATPase systems. In a brain that is already very excitable, this might cause cortical spreading depression (CSD). Stress, anxiety, and sadness are examples of psychic triggers that are primarily cerebral in origin and are mediated by neurotransmitter activity. Fasting is likely a trigger produced by the hypothalamus. Although there is not much experimental evidence in support of this theory, it is remarkably similar

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to how genetically predisposed people experience epileptic episodes. Precipitating factors for epileptic seizures include lack of sleep, photic stimulation, stress, and worry. Triggers are all appreciated at cortex (consciously or unconsciously), but the information is most likely projected downstream through descending pathways to the brainstem nuclei, which include the migraine pain-modulating nuclei such as PAG, locus coeruleus (LC), and rostral ventromedial medulla (RVM).

The PAG matter and the nucleus raphe magnus (NRM) of the brainstem are thought to be the two brainstem nuclei that are directly affected by activation of cortical neurons in most migraines. This causes normal sensory input from the dura to be experienced as migraine pain as these nuclei release their ongoing descending control of dura matter sensation in the trigeminal nucleus.

The current author amended this idea in light of the well-established theory of the spinal level pain-appreciating pathway, known as the "gate control theory," which was first introduced in 1962 by Wall and Melzack. This idea had been widely used in numerous clinical pain syndromes, and pain-relieving treatments (such as acupuncture, TENS, etc.) had been created based on this idea. The spinal dorsal horn cells, which make up the cell bodies of the second neuron channel for ascending sensory impulses, are where the "gate" is thought to be placed in the spinal pain pathway. Pain inputs would "compete" with other general sensory stimuli at the "gate" (spinal dorsal horn) to enter the CNS and proceed to the thalamus and cortex. These workers suggested that the brainstem TNC contains the second-order neuron cell bodies necessary for transmitting trigeminal pain and functions as the medullary analog of the spinal dorsal horn. The embryological idea that the spinal cord is fundamentally a component of the brainstem supports this idea. It is now possible to suggest that a gate control mechanism is also in use in this situation. According to the current author, two impulses compete at this "gate" during migraine attacks. First, the trigeminal nerve transmits an afferent pain feeling from dura matter and blood vessels (a result of CSD), as well as modulatory impulses from brainstem nuclei such as PAG, LC, and RVM/NRM via descending fibers. Descending fibers from the cortex which convey trigger sensations have an impact on the activity of brainstem nuclei, which in turn inhibits the TNC's "gate" mechanism. If the "gate" was to "open," afferent pain impulses sent by the trigeminal nerve may travel upstream to the thalamus and cortex. This then turns into the second point of action for migraine triggers (the imagined "gate" at TWC). But how does the TNC gate control system function? Of course, one needs a "gateman." The 5HT receptors, according to the current author, are the "gateman" in this situation.

Goadsby has written extensively and studied the literature on the function of 5HT IB/ID receptors in migraine. Along with 5HT 1F receptors, these receptors are widely distributed in the meninges and blood vessel walls where, during migraine attacks, they regulate the release of vasoactive peptides [vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide (CGRP)] that cause inflammation and give the trigeminal sensory nerve terminals a painful input. Triptans (5HT IB/ID agonists) alter receptor activation and manage the inflammatory response associated with CSD and migraine symptoms. The brainstem region close to the TNC23 has also been found to contain 5HT receptors. Therefore, it may be hypothesized that activation or modification of the activity of these receptors mediates the "gate control" process

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at TNC. The PAG/LC/RVM's descending fibers govern the "gate" activity that determines whether trigeminal pain impulses can pass through or not (acting thus as the gateman in reality). Thus, migraine triggers can affect the activity of the 5HT receptor-controlled "gate" at TNC by affecting the activity of the brainstem fibers that descend from the cortex to the brainstem nuclei and subsequently to the receptors. Triptans may also be effective at the medullary level, meaning they have a second site of action for stopping migraine attacks in addition to the peripheral one.

Modulation of Nociceptive Signals and Role of Cyclical Brainstem Activity

The release of excitatory and inhibitory neuropeptides/neurotransmitters from hypothalamic and brainstem neurons may alter nociceptive trigeminovascular signals that travel to the thalamus. The interaction of these neurotransmitters controls how relay trigeminovascular neurons fire. The firing of thalamic trigeminovascular neurons can switch from burst to tonic mode if the neurotransmitter is excitatory. The transition is from tonic to burst mode if the convergent inputs from the hypothalamus and brainstem neurons are inhibitory.

The high and low set points for the allostatic load in migraine patients, which measures the amount of physiological or emotional stress that the brain can handle, control whether nociceptive signals are sent to the cortex. The current circadian phase of cyclical brainstem activity may also impact whether the premonitory phase progresses into the headache phase. The threshold for nociceptive trigeminovascular signal transmission is elevated and nociceptive signals are suppressed in the presence of high levels of cyclical brainstem activity.

A migraine headache may happen if the threshold for the transmission of nociceptive signals is decreased due to low cyclical brainstem activity. This may help to partially explain why the same migraine triggers (both internal and external) may not always result in an attack. It is possible that this is due to the current state of the cyclic brainstem rhythm and the degree of modulation of the trigeminovascular nociceptive signals.

Aura Stage

Cortical Spreading Depression

Aristides Leao originally defined CSD in 1944, and it is believed to be the neurophysiological correlate of migraine. The onset and progression of aura symptoms are accompanied by a wave of depolarization in neuronal and glial cell membranes that propagates slowly (3–5 mm/min) and is followed by a suppression of cortical activity for up to 30 minutes.

Additionally, a wave of hyperemia and a protracted phase of cerebral oligemia are linked to this wave of spreading depression. Localized increases in extracellular K^+ cause persistent depolarization of neurons lasting 30–50 seconds, which causes CSD.

It has been proposed that the repetitive depolarization and repolarization of hyperexcitable neurons in the cerebral cortex cause the first accumulation of extracellular K^+, and that this accumulation of extracellular K^+ subsequently further depolarizes the cells from which it was discharged. This significant K^+ outflow is accompanied by a significant alteration of the ionic gradients in cell membranes,

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an inflow of Na^+ and Ca^{2+}, and the release of glutamate. Several theories exist; however, the transmission of CSD is still not entirely understood. Initially, it was believed that K^+ or glutamate interstitial diffusion caused CSD to spread, but more recent hypotheses contend that gap junctions between glial cells or neurons actually mediate this process. Animal research has provided more and more evidence to back up the idea that CSD can activate trigeminal nociception and hence set off headache mechanisms.

The question is: Does CSD cause the aura symptoms? Probably so. The hypoperfusion of CSD in some way induces both the positive and the negative components of the aura. The next question that arises is whether CSD occurs in subjects with migraine without aura (MO). CSD generation is an integral part of the migraine cascade and probably activates meningeal inflammation and trigeminal nociception through release of noxious chemicals. So, it must occur in subjects with MO as well. It was suggested earlier that CSD in MO principally occurs in silent or noneloquent areas of the cortex and, hence, no aura symptoms are produced. More recent thoughts are that the CSD in MO does not reach the threshold to produce focal neurological features which we call aura. Two other aspects about CSD propagation need to be considered. CSD spread does not follow vascular territory but stops at major sulci. However, it can bypass major sulcus as well by travelling deep into the depths of the sulcus and then coming back on surface travelling up along the cortex on the other side of the deep sulcus. This can explain the development of both motor and sensory symptoms in subjects with hemiplegic migraine where CSD crosses the central sulcus, involving both motor and sensory cortical areas by this mechanism.

Phase 3: Headache

Trigeminovascular pathway activation is commonly acknowledged as the cause of the migraine headache's distinctive throbbing discomfort. The anatomy and physiology of the trigeminovascular system are well understood, and they help to explain how migraine pain is distributed.

Trigeminovascular Pathway

From the meninges, the trigeminovascular system transmits nociceptive information to the brain's core regions, which then travels to the cortex. Meninges and significant cerebral arteries are both innervated by nociceptive fibers that come from the trigeminal ganglion. The trigeminal nerve's ocular branch is primarily responsible for this nociceptive innervation. Before connecting to second-order neurons in the trigeminal cervical complex (TCC), which includes the TNC and the dorsal horn of the upper cervical spinal cord (C1-C2), afferent projections from the trigeminal ganglion congregate with inputs from nearby skin, pericranial and paraspinal muscle, and other C1-C2 innervated tissues. The sense of referred pain in the periorbital, occipital, and cervical areas is caused by the convergence of afferent projections with neurons from extracranial tissues. Signals are sent by ascending routes from the TCC to several brainstem, thalamic, hypothalamus, and basal ganglia nuclei.

These nuclei are involved in processing the cognitive, emotional, and sensory-discriminative aspects of nociceptive signals and give rise to some of the associated

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symptoms that are characteristic of the attacks and the syndrome, such as photophobia, phonophobia, cognitive dysfunction, and retrosplenial, auditory, visual, and olfactory symptoms. These nuclei also project to multiple cortical areas, including the somatosensory, insular, motor, parietal association, and retros.

Activation of the Trigeminovascular Pathway

When nociceptive neurons that innervate the dura mater are stimulated, they release vasoactive neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PCAP) and CGRP, which cause signaling along the trigeminovascular pathway. The extent to which arterial vasodilatation, mast cell degranulation, and plasma extravasation are involved is still unknown. Some people think that CSD starts the nociceptors in the meninges from activating. It is believed that during a CSD, molecules released locally, including ATP, glutamate, K^+, hydrogen ions, CGRP, and nitrous oxide, diffuse to and activate meningeal nociceptors. It has been demonstrated that focal stimulation of the rat visual cortex causes CSD and results in persistent activation of meningeal nociceptors. This neural activation also happened roughly 14 minutes after the generated CSD, which is comparable with the interval between the development of an aura and a migraine headache. Additionally, it has been demonstrated in experimental experiments that CSD can result in sustained increases in activity in central trigeminovascular neurons in the spinal trigeminal nucleus, confirming the hypothesis that CSD causes first the peripheral and subsequently the central trigeminovascular neurons to become activated.

Preclinical data also suggests that CSD may directly activate or disinhibit central trigeminal sensory neurons by a mechanism native to the CNS. The activation of second-order trigeminovascular neurons in the TCC caused by CSD was not hampered in these trials by sensory inhibition of the trigeminal ganglion. This shows that CSD does not merely work peripherally to enhance central trigeminovascular circulation; rather, it may also do so. This would explain how migraine discomfort may develop. The development of mechanical allodynia (neck discomfort) before the onset of headache in some patients, for instance, could be explained by this, together with other clinical data.

Aura may appear after the headache phase has already started, and individuals may feel aura but not the subsequent headache. Nevertheless, the majority of migraine attacks are not preceded by clinical signs of aura. During the aura phase, many patients describe migraine symptoms as nausea, photophobia, phonophobia, and headache; some even say the headache began at the same time as the aura. Therefore, it has been proposed that physiological events occurring during the premonitory phase of a migraine attack, which occurs before aura, may be the main cause of both activation of the trigeminovascular pathway and cortical neuronal/glial activity, and that aura may instead be the result of an aberrant "brain state" that occurs in a genetically susceptible individual during a migraine attack.

Calcitonin Gene-related Peptide

The calcitonin gene (*CALCA*) encodes a 37-amino acid neuropeptide called calcitonin gene-related peptide, which is involved in sensory, digestive, and cardiovascular processes. In the central and peripheral neurological systems, the cardiovascular

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system, the gastrointestinal system, and other parts of the body, CGRP and its receptor are highly expressed. The development of neural sensitization and the production of pain, particularly in migraine, have both been linked to the somatosensory function of CGRP. There is strong evidence that CGRP, a powerful vasodilator found in afferents that innervate meningeal blood vessels, plays a significant role in migraine development. Additionally, CGRP is a neurotransmitter that can improve synaptic transmission mediated by glutamatergic signaling; during migraine attacks, CGRP levels in jugular venous blood are elevated.

Intravenous injection of CGRP does not cause migraines in healthy volunteers but does in migraine patients. There are several locations along the trigeminovascular route where CGRP is thought to act. Meningeal nociceptors may become activated and sterile inflammation may occur as a result of peripheral release of CGRP in the meninges. By boosting substance P release, CGRP indirectly causes plasma extravasation in the peripheral nervous system. CGRP has a central role in the trigeminal ganglion and may play a role in communication between these neurons. In addition, neuronal-glial cell signaling inside the trigeminal ganglion has been linked to CGRP, which may aid in the development of peripheral sensitization. By boosting the release of neurotransmitters from nearby primary afferent terminals, the release of CGRP in the TCC may promote nociceptive transmission.

Peripheral Sensitization

Peripheral trigeminovascular neurons get sensitized to dural stimuli once they have been triggered by endogenous mediators; this means that their threshold for response lowers and the strength of their response rises. The throbbing pain that is typical of migraines and the increase of discomfort when bending over or coughing are likely both caused by peripheral sensitization. This heightened sensitivity to sensory stimulation is assumed to be brought about by primary afferent fiber hyperresponsiveness and/or central neuron hyperactivity. It is still unclear, which specific inflammatory mediators encourage the activation and sensitization of peripheral trigeminovascular neurons. Dural nociceptors are permanently activated and sensitized by mast cell degranulation. Numerous studies on animals suggest that the beginning and maintenance of peripheral sensitization depend on CGRP release.

The reaction threshold to a painful mechanical stimulation was dramatically lowered after many CGRP injections into the paws of rats as a result of peripheral sensitization.

Central Sensitization

Cephalic and extracephalic allodynia is caused by sensitization of central trigeminovascular neurons in the TCC and thalamic nuclei. Increased spontaneous neural activity and a more intense reaction to harmless cephalic and extracephalic stimuli are symptoms of sensitization. The symptoms of cephalic allodynia, which is caused by sensitization in the spinal trigeminal nucleus, include discomfort in the scalp and the cephalic muscles as well as aversion to touch. After around 2–4 hours, thalamic sensitization emerges and is the cause of extracephalic allodynia. There is proof that cutaneous allodynia could contribute to the development of migraines.

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The central trigeminovascular pathways may be repeatedly activated and sensitized, leading to permanent central sensitization, to cause this, according to theory. This mechanism may be involved in the genesis of chronic migraine.

Boxes 1 to 9, Figures 1 to 6, and Flowchart 1 summarize the essential components in the genesis of acute migraine attack.

BOX 1 Key points.

- *Migraine pain much alike neuropathic/nociceptive pain*: Difference if any? Integrity of neuraxis migraine-like solid visceral pain—sensory endings in capsule
- *Brain capsule*: Meninges and meningeal vessels
- Three-neuron pathway
- *Core features*: Genes, migraine brain, CSD generation by triggers, central and peripheral sensitization—normal neuraxis reacts abnormally to even subnoxious stimuli
- Vascular change—an epiphenomenon—a byproduct of a primarily neural pathology

(CSD: cortical spreading depression)

BOX 2 Migraine: Why not vascular in origin?

- Vasodilatory headaches are not migraine
- *GTN headache*: Starts after vasodilatation when vessel caliber normal
- *VIP potent vasodilator*: No migraine
- *PCAP infusion vasodilation*: No migraine
- Degree of ↓CBF during aura insufficient to cause ischemia
- CSD and hypoperfusion do not follow vascular territory
- *Triptans and CGRP antagonists:* No vasoconstriction

(CBF: cerebral blood flow; CGRP: calcitonin gene-related peptide; CSD: cortical spreading depression; GTN: glyceryl trinitrate; VIP: vasoactive intestinal polypeptide)

BOX 3 Noxious substances released during CSD.

- H^+, K^+ NO, and arachidonic acid metabolites
- Activation of MMP9 → ↓ Laminin → Break down of B–B barrier
- Unknown factors activating NV sensory endings

(CSD: cortical spreading depression; MMP: matrix metalloproteinase; NV: fifth cranial nerve)

BOX 4 What noxious substances do?

- Release proinflammatory cytokines at NV terminals
  (SP, NKA, CGRP) Blocker: CGRP-R antagonist (Gepants)
- Crosses GAP through channels to meningeal blood vessels
- Causes vasodilatation in meningeal arteries and veins—*A secondary event*
- Mast cell activation and membrane disruption—perpetuation of sensory nerve stimulation for long: *Peripheral sensitization*
- Responsible for intolerance for subnoxious stimulation in migraineurs (i.e., bright light)
- Role of 5-HT receptors at this site doubted (action of triptans at periphery ??)

(CGRP: calcitonin gene-related peptide; NKA: neurokinin A; SP: substance P)

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BOX 5 Proof of peripheral and central sensitization.

cFOS expression at TG and TNC (also thalamus) during and in-between attacks of headache (or aura)

(TG: trigeminal ganglion; TNC: trigeminal nucleus complex)

BOX 6 Significance of vascular changes?

Summary of studies with rCBF, PET, PWI, BOLD, and fMRI:

- ↓rCBF in 30%—longer lasting than aura
- Hypoperfusion not amounting to ischemia
- Hypoperfusion secondary to ↓neuronal activity (depression)
- ↓rCBF occurs bilaterally—starts posteriorly and spreads anteriorly
- Does not follow vascular territory—rather stops at major sulci hence not related to any focal neuro feature (aura)

Vascular changes bear little relevance to basic migraine pathophysiology

(BOLD: blood oxygenation level dependent; fMRI: functional magnetic resonance imaging; PET: positron emission tomography; PWI: perfusion-weighted imaging; rCBF: regional cerebral blood flow)

BOX 7 Beyond first-order neuron.

- Activation of TNC (2nd-order neuron)
- Axons ascend along brainstem to thalamus
  (3rd-order neuron) Central sensitization
  Twig to SSN→pregang→SPG→postgang to vessels

A secondary event:

- Modulation of TNC activity by descending projections from RVN, LC, PAG, post-hyponeuron (orexin pathway)
- *Receptors*: $5HT_{1B\,ID\,IF}$ (? gate control mechanism) *Site of action of Triptans;* Dopamine receptors (D2)
- Thalamocortical path: Receptor: β-adrenoreceptors
  (? Site of action of β-blockers) (also Triptans)
- CGRP antagonists inhibit nociceptive neurons in VPM thalamus

(CGRP: calcitonin gene-related peptide; LC: locus coeruleus; PAG: periaqueductal gray; TNC: trigeminal nucleus complex; RVN: rostral ventral nucleus; SSN: superior salivary nucleus; SPG: Sphenopalatine ganglion; VPM: ventral posteromedial)

BOX 8 Final conclusion: Is migraine a disease?

- Migraine is a phenomenon of the *brain—a disorder of sensory processing—not of blood vessels!*
- Migraine, an example of genetically determined adaptive behavioral response to internal or external stresses orchestrated by a threatened brain. *The migraine attack itself may not be categorized as a disease,* i.e., a deviation from or interruption of the normal structure or function of the brain but it may turn into a disease in an allostatic perspective, when *repeated attacks start maladaptive mechanisms that resulted in a chronic pain of the brain*

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BOX 9 How does a migraine attack stop?

- Triggers of termination?
- How sleep and vomiting stop migraine attack?
- Migraine cessation an active process rather than a passive one
- Structures involved in migraine are part of feedforward and feedback loops that modulate sensory inputs
- Sensory cortical and insular neurons feedback on to TNC and thalamus
- Nested ANS loops in brainstem capable of both generating and terminating headaches

(TNC: trigeminal nucleus complex)

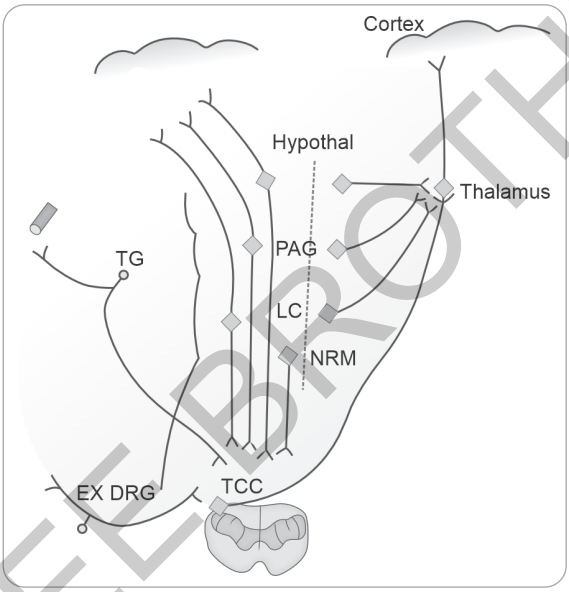

FIG. 1: Neural pathway of migraine pain generation and appreciation-1.

(LC: locus coeruleus; PAG: periaqueductal gray; NRM: nucleus raphe magnus; TCC: trigeminal cervical complex)

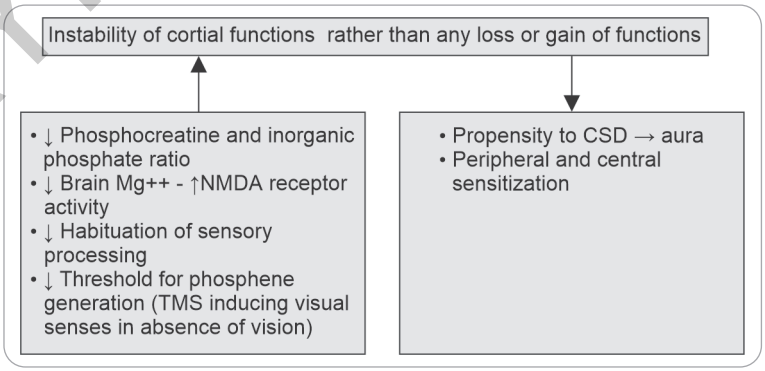

FIG. 2: Concept of migraine brain.

(CSD: cortical spreading depression; NMDA: N-methyl-D-aspartate; TMS: transcranial magnetic stimulation)

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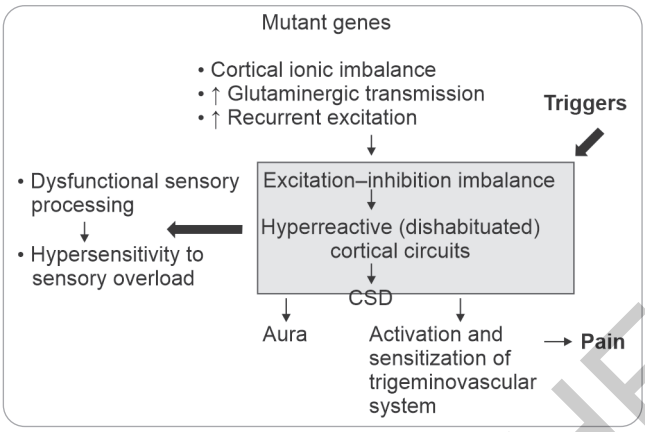

FIG. 3: What do the genes do?

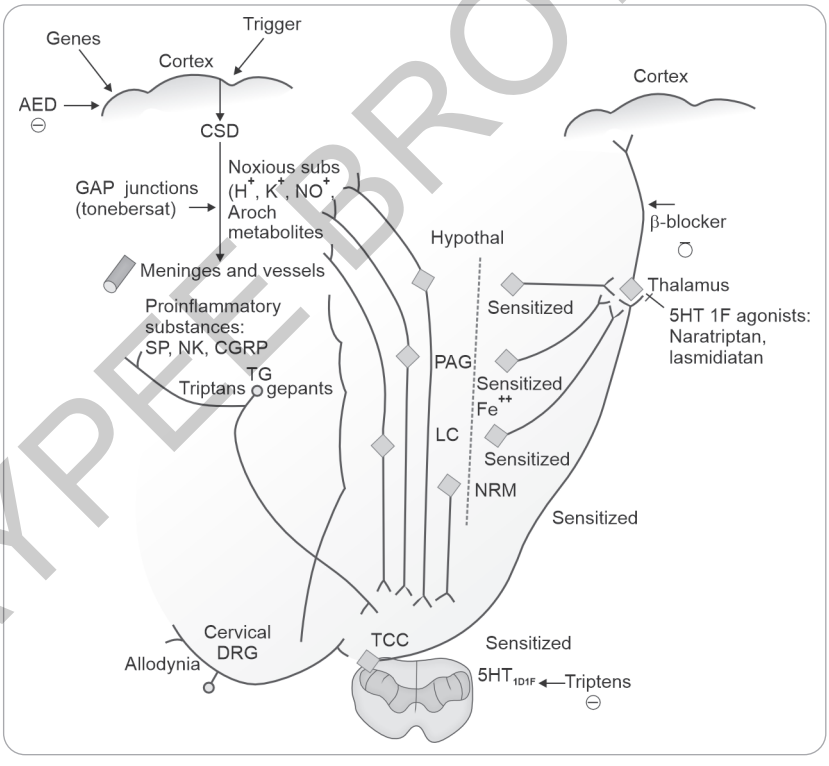

FIG. 4: Neural mechanism of migraine pain production and sites of therapeutic interventions.

(AED: antiepileptic drug; CSD: cortical spreading depression; CGRP: calcitonin gene-related peptide; DRG: dorsal root ganglion; LC: locus coeruleus; PAG: periaqueductal gray; NRM: nucleus raphe magnus)

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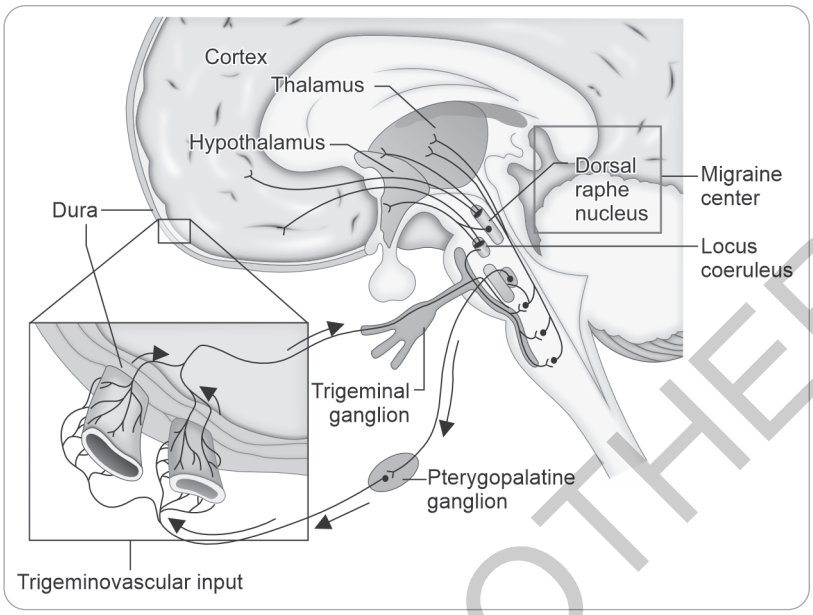

FIG. 5: Neural pathway of migraine pain generation and appreciation-2.

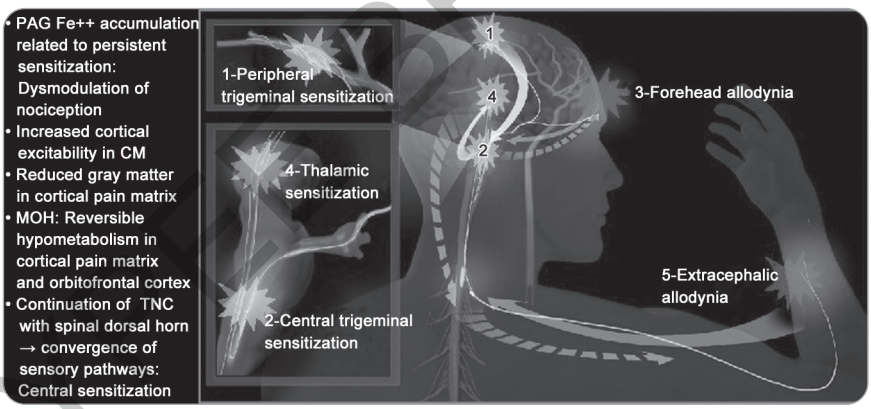

FIG. 6: Migraine chronicity and allodynia.
(CM: chronic migraine; PAG: periaqueductal gray; TNC: trigeminal nucleus complex)

Migraine Postdrome

Nonheadache symptoms may persist for 1–2 days after the headache has resolved in the postdrome or recovery phase. Postdromal symptoms, identified by retrospective recall of typical experiences, include tiredness, impaired concentration, and reduced mood. The postdrome, while disabling for many patients, has not been prospectively

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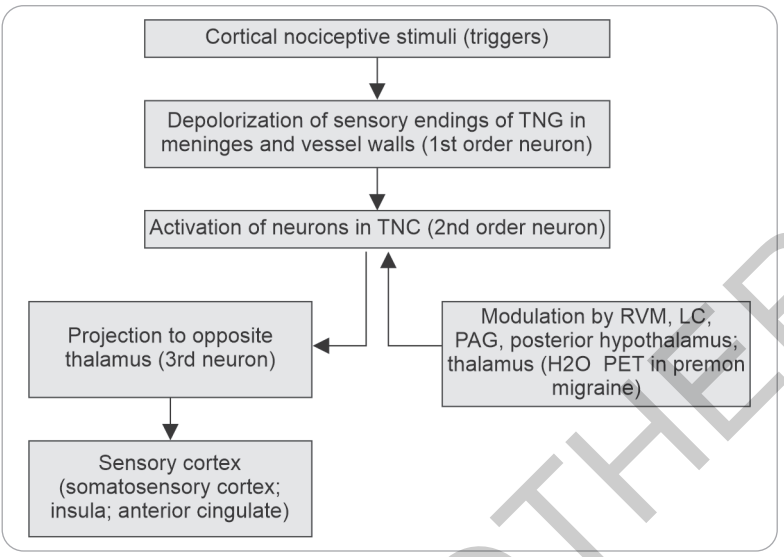

FLOWCHART 1: How pain produced?

(LC: locus coeruleus; PAG: periaqueductal gray; RVM: rostral ventromedial medulla; TNC: trigeminal nucleus complex)

documented and is not defined in the International Classification of Headache Disorders (ICHD). The persistence of nonheadache symptoms throughout all phases of the migraine attack supports the hypothesis of persistent brain changes in the attack. An altered functional state may develop during the premonitory period and persist throughout the headache phase into the postdrome.

CONCLUDING REMARKS

An underlying condition of heightened cortical and subcortical network responsiveness that amplifies the intensity of sensory stimuli in genetically predisposed people is what defines migraine as an inherited neurological ailment. Some such genetic aberrations have been identified and probably account for the neuronal hyperexcitable state which can be identified by electrophysiological means. This constitutes the preparatory stage. A premonitory, painful headache, postdromal phase, and in certain cases, reversible visual, sensory, and linguistic symptoms (aura phase) are all characteristics of migraine episodes. The hypothalamus and its functional linkages to particular brainstem nuclei and cortical regions appear to be involved in the premonitory phase, whereas migraine headache pain entails enhanced sensory processing within peripheral and central trigeminovascular pathways.

In the present authors' opinion, it is unwise to discuss migraine pathophysiology purely as a vascular or neural phenomenon, it is indeed a neurovascular act played on the backdrop of a genetically determined hyperexcitable cerebral cortical state. It is worth noting that one of the key players in this act, CGRP, is indeed a potent vasodilator. This certainly is going to be the major target for therapeutic intervention in future.

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CASE 1 A Young Boy with Recurrent Headaches and Visual Loss

CASE HISTORY

A 16-year-old boy was seen in 2001 with 15 days history of recurrent blurring of vision in both eyes lasting 10–15 minutes followed by moderately severe holocranial throbbing headache associated with photo- and phonophobia and nausea, no vomiting but some unsteadiness in walking. All symptoms would subside in about 3 hours time. He felt very sleepy afterward. He had a total of six attacks at presentation.

One attack was witnessed by the resident. His visual acuity was down to perception of light and projection of rays only. Pupils were of normal size and reactive. However, he could read looking through a pinhole of 2-mm diameter. His fundi were normal. Tandem walking was abnormal.

His routine investigations were normal. Magnetic resonance imaging (MRI) of brain and MR angiography were normal.

QUESTIONS

1. What was the headache diagnosis according to ICHD-3?
2. Why did he have blurring of vision in both eyes and what was the localization?
3. Why he could read through a pinhole?
4. What are the uses of the pinhole test?
5. What are the different types of visual auras encountered in migraine?
6. How does cortical spreading depression (CSD) create visual symptoms? Does CSD occur in both migraine without aura (MO) and with aura (MA)?
7. Is CSD a unilateral or bilateral phenomenon?

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DISCUSSION

This young boy had half a dozen episodes of holocranial pulsatile headaches associated with photo- and phonophobia with nausea. Clearly, he had new-onset attacks of migraine. All these episodes were preceded by blurring of vision in both eyes and unsteadiness in gait. Clearly, he had associated focal anatomically localizable transient neurological phenomena and, hence, he certainly had MA. On the single episode when he could be examined during an episode, his pupillary reaction and fundi were normal when he had the visual blurring, suggesting that he had transient bilateral occipital cortical dysfunction. Furthermore, although his acuity was down to perception of light and projection of rays, he could clearly read through a pinhole. Reading through a pinhole of 2-mm diameter tests the macular, i.e., central vision which localizes in the macular area of the cortex which lies on the lips of the calcarine sulcus in the occipital pole. This is classical of macular sparing due to hypoperfusion or ischemia of the bilateral occipital cortices, which are supplied by the two posterior cerebral arteries, terminal branches of the basilar arteries. The macular area, on the other hand, is supplied from a posterior branch of the middle cerebral artery (MCA). The pinhole test has great utility in ophthalmology. Correction of acuity on reading through a pinhole suggests a defect in the ocular media, e.g., from refractive error. Secondly, as already stated, it can test central vision, i.e., macular vision. Thirdly in uniocular diplopia, persistence of diplopia on looking through a pinhole with the other eye closed suggests either a psychogenic diplopia or a rare parietal lobe disorder called cerebral polyopia. Coming back to the case, in addition to the visual disturbance, the boy had unsteadiness of gait suggesting brainstem–cerebellar dysfunction.

In all, preceding his migrainous headache, he had posterior (basilar) circulation hypoperfusion-related visual disturbance and ataxia—a possible brainstem–cerebellar dysfunction. Originally described by Bickerstaff in 1961 as *basilar artery migraine*, the current ICHD-3 terminology for the condition is migraine with brainstem aura and the "diagnostic criteria" include:

"A. Attacks fulfilling criteria for 1.2 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:
   - Dysarthria
   - Vertigo
   - Tinnitus
   - Hypoacusis
   - Diplopia
   - Ataxia not attributable to sensory deficit
   - Decreased level of consciousness (GCS < 13)
2. No motor or retinal symptoms."

Criterion 1.2 includes visual disturbance in addition to many other focal neurological phenomena. What then had been the pathophysiology of his transient visual loss, macular sparing, and "ataxia of gait".

Spreading cortical depression which the boy certainly had caused hypoperfusion of both occipital (visual) cortices causing bilateral transient visual blurring. The CSD

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here involved the posterior cerebral artery (branches of basilar artery) which does not supply the macular area in the lips of the calcarine sulcus causing macular sparing of vision and enabling the boy to read through the pinhole. Hypoperfusion in the brainstem–cerebellar pathway would cause ataxia.

While this explanation seems sound, it is important to remember that CSD does not follow vascular territories; hence, the vascular sparing hypothesis of macular area sparing may not be appropriate. CSD, of course, stops at places of major sulci. The calcarine sulcus, being a major sulcus, probably stopped the CSD short of this sulcus preventing hypoperfusion of the macular area and saving the area and protecting central macular vision.

Positive or negative visual events may make up the unilateral (70%) or bilateral (30%) visual aura. It frequently starts out as a change in visual perception brought on by visual loss or the presence of bright spots in the centrolateral region of the visual field and progresses to become a small scotoma. This symptom may develop over a period of 5 minutes to 1 hour and involve a quadrant or hemifield of the visual field with an increasing margin that may resemble zigzag lines, geometric shapes like teichopsia, or fortification spectra. Positive visual phenomena can take on the form of a C-shape or a crescent with shimmering edges (scintillations), either in color or without it. It is possible to observe simple flashes (phosphenes), white or colored dots, bean-like formations, and strong light bars. Auras can be distinguished from transient ischemia events by the presence of scintillations. Negative visual phenomena including hemianopsia or quadrantanopsia, scotomas, tunnel vision, and total blindness can also happen. Other visual auras include hazy vision, seeing through water, complicated visual hallucinations, and complex visual hallucinations. As the disturbance moves to the periphery, normal central vision recovers, usually after 30 minutes, for a total of 60 minutes. Acute bilateral occipital pole lesions are frequently connected with the "Alice in Wonderland" syndrome, which commonly affects young children with micropsia and telopsia (things appear smaller and further away than they are). Migraine attacks rarely start at the same time as this disease. The primary striatal visual cortex may be where the negative visual phenomena first appeared, while other extrastriate areas such as the visual unimodal association areas may also be implicated. With the exception of phosphenes, the associative heteromodal zones in the parieto-occipital fissures, superior temporal sulci, and preoccipital notch appear to be involved in migraine positive visual events, in addition to the primary visual region. Atypical symptoms could be caused by the involvement of white matter tracts connecting the frontal lobes to the visual areas.

How is CSD linked to migraine aura?

For many years, CSD has been linked to MA, but the possibilities regarding MO have been less clear. In MO, CSD has been considered to develop in cortical “silent” areas or to simply not exist. This is not in accordance with the detection of spreading oligemia in MO and CSD preference for the occipital cortex, which is hyperexcitable in migraine and hypersusceptible to CSD in rats carrying migraine mutations. The occipital cortex, affected by CSD in migraine, is not functional on a 100% basis. It seems more logical to admit that the brain is not silent; it is CSD, which produces a

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