Migraine - The New Understanding

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Introduction

Headache is one of the commonest of medical complaints and accounts for approximately 25% of a general neurologist’s out-patient practice. Of all the disorders that present to the clinician with headache, migraine is the commonest and also the most burdensome. Most often, migraine diagnosis is easy and treatment straightforward but, in a small number, it can be complex and debilitating. In some, migraine can progress from being an episodic disorder to a chronic form, when it can be more difficult to manage. Although there are still many unanswered questions, much more is now known now about the pathophysiology of migraine, there are newer drug options and newer treatment strategies. As a result, we need to conceptualize migraine differently and modify our attitude and approach. This review will highlight some aspects of this new understanding and emphasize the need to look at migraine from the right perspective.

Epidemiology

Migraine is one of the most disabling of neurological disorders. The World Health Organization (WHO) has identified migraine among the world’s top 20 leading causes of disability. Migraine is estimated to account for 2.0% years of life lost due to a disability in women of all ages. In both sexes of all ages, migraine is responsible for 1.4% of total years of life lost due to a disability. These findings will have an impact not only on individual sufferers but also on their families and on society itself.

Estimates of migraine prevalence vary, mainly because of differences in study methodology. There are no population-based studies from India. Based on large epidemiologic studies from around the world, the prevalence of migraine was about 18% in women and 6% in men. Migraine is an illness of long duration and the prevalence is highest from the ages of 25 years to 55 years. Migraine can occur at all ages and usually begins before the age of 20 in 50%. The overall prevalence of headache increases from preschool age children to mild adolescents. Before puberty, migraine prevalence is higher in boys than in girls. As adolescence approaches, incidence and prevalence increases until approximately age 40, after which it declines.

Migraine prevalence also varies by race and geographic region. A meta-analysis has shown that prevalence was lowest in Africa and Asia and highest in North America. If these conclusions differ from the real picture seen in practice, it may be because similarly designed epidemiological studies are often lacking from Asian countries.

Migraine also impacts society through direct and indirect costs. Headache accounts for about one third of analgesic use across the counter. Indirect costs include the cost of absenteeism and reduced productivity at work. Hu and colleagues estimated that productivity losses caused by migraine cost American employers 13 billion dollars per year. Migraine is comorbid with a number of other illnesses and these have been discussed in detail elsewhere in this issue.

Migraine – Pathophysiology

There is now enough evidence to confirm that migraine is a genetically inherited vulnerability. Numerous studies have reported a positive family history. With the characterization of mutations in 3 different genes responsible for Familial Hemiplegic Migraine - FHM1, FHM2 and FHM3, it is clear that alterations in cellular excitability are capable of generating a phenotype of FHM. The search for a gene for common migraine still continues to elude us and in fact there may be multiple genes involved. Experimental evidence suggests that in migraine, the cerebral cortex is hyperexcitable and exhibits enhanced responsiveness to external stimuli. Genetic mutations may contribute to this hyperexcitability.

Based on current theories, our understanding of the pathophysiology of migraine has evolved from the concept of a vascular disorder to a neurologic disorder. The vascular theory was brought to the forefront by Wolff and he explained the pain of migraine on the basis of dilation of cranial vessels. Typically, migraine attacks are characterized by moderate to severe, throbbing head pain, sensitivity to sound (phonophobia) and sensitivity to light (photophobia), nausea, vomiting and the pain is exacerbated by movement. Intracranial vasodilatation may explain only the throbbing pain but does not explain the numerous other accompaniments of migraine. With the demonstration of alternative sites and mechanisms of action for migraine-specific drugs such as ergotamine and triptans which were once thought to work by vasoconstriction, it is now convincingly proven that alteration in vascular tone alone is not responsible for the clinical features of migraine. Migraine is therefore now labeled a ‘Neurovascular disorder’ and is thought to arise from a primary dysfunction of the brain and the brainstem. This leads to activation and further sensitization of the trigemino-vascular system (TGVS). The TGVS includes the neurons within the trigeminal ganglion, their peripheral projections to the meninges and their central projections to second- order neurons in the brainstem.

Although currently viewed as a disorder of brain hyperexcitability, the first neurologic event is still debatable and we still are not certain of the sequence of events that trigger a migraine attack. Some neurologic events that have been proposed are (i) cortical spreading depression (CSD) and (ii) brainstem dysfunction. CSD is a slowly propagated wave of altered brain depolarization followed by neural suppression. CSD was first described by Leao in 1944. CSD propagates over the cortex slowly at the rate of 2-6 mm/min over the cortex. Secondary to these changes in neuronal activity there are changes in cerebral blood flow. Olsen et al. have shown that the headache begins during the cortical hyperperfusion phase and may end before the hyperperfusion resolves. Other patients who were investigated by PET also demonstrated cortical hyperperfusion during the pain phase of migraine. When the TGVS is activated, neuropeptides such as calcitonin gene related peptide (CGRP) and substance P are released from peripheral nerve endings.

CGRP is a key neuropeptide in the pathophysiology of
migraine. A marked increase in plasma levels of CGRP is seen during the migraine attack. CGRP levels correlate with the degree of headache pain and CGRP plays an important role in the transmission of meningeal inputs to the brain. Substance P is not released during migraine attacks. For pain generation in migraine there are central as well as peripheral events. The peripheral events include meningeal inflammation, vasodilation, plasma protein extravasations, once the trigeminal system is activated, the central trigeminal nucleus caudalis in the brainstem is activated. CGRP and glutamate are the neurotransmitters involved here. During a migraine attack, the second order neurons of the TGVS are activated and become sensitized. This process is called central sensitization. Central sensitization is important for the key clinical manifestations of migraine viz. cutaneous allodynia and for chronic migraine. Glutamate acting through the NMDA receptor also plays an important role in central sensitization.

In summary therefore, cortical hyperexcitability facilitates triggering of CSD, followed by TGVS activation, brainstem dysfunction and onset of migraine. The mediators that are released following TGVS stimulation perpetuate the pain. CGRP and glutamate are important for the transmission of nociceptive impulses. Both these are also involved in central sensitization. An understanding of this new pathophysiology is crucial to understand the way newer specific drugs work in migraine.

In addition to head pain, migraine patients are sensitive to light, sound, smell and touch. Burstein et al noted that migraine is characterized by a derangement of sensory function. They reported gradual development of cutaneous allodynia during a migraine attack and noted that its occurrence is correlated with reduced responsiveness to triptan therapy. Whether the presence of allodynia predicts the responsiveness to triptans is still a debatable issue. Central sensitization may not necessarily be a consequence of peripheral sensitization.

Migraine – The Clinical Heterogeneity

A migraine attack is a complex brain event that produces a wide range of neurological, autonomic and systemic symptoms of which headache is the most prominent. Underdiagnosis in migraine occurs mainly on account of fixed notions about the clinical presentation. Features of the migraine attack can vary from patient to patient and even between attacks in the same patient. It is therefore necessary to recognize the heterogenous nature of migraine.

Migraine headache is unilateral in 60% but can be bilateral. The pain is generally more intense in the frontotemporal and periorbital regions but could involve any region of the head or face. Up to 50% of migraineurs may describe non-throbbing headache. Neck pain occurs in up to 75% of migraineurs. Nausea, vomiting, photophobia, phonophobia may accompany the head pain.

Attacks may be preceeded by a prodrome which manifests with mood change, fatigue and neck stiffness. Severe migraine can occasionally be accompanied by parasympathetic activation (lacrimation, redness, eyelid edema, nasal congestion, rhinorrhea ) because of which it may sometimes be confused with the trigemino-autonomic cephalgias or sinus-associated headache. A variety of visual, sensory and cognitive auras may precede, accompany or follow the headache. Pitfalls in the diagnosis and migraine variants have been discussed elsewhere in this issue.

The revised headache classification ICHD2 (2004) specifies minimum criteria as essential for Migraine with and without aura. Most migraineurs with aura also have migraine without aura. Migraine with typical aura is a recurrent condition characterized by reversible neurologic symptoms, which typically develop over 5 to 20 minutes and resolve within 60 minutes. The total duration of the aura is typically less than 1 hour. If the aura lasts more than 1 hour but less than 1 week, then it is termed ‘migraine with prolonged aura’. Visual symptoms are the most common manifestations of migraine with aura. The classic form of visual aura is the fortification spectra. There can also be visual field defects that last 20 to 30 minutes. Sensory aura is present in about 30% of those with migraine with aura. Speech and language disturbances may occur in some. When two or more aura symptoms are present, they almost always occur in succession and do not occur simultaneously.

Motor aura is rare. Until recently, motor symptoms were included as an aura. However, in ICHD-2, it has been reclassified as an integral part of a distinct migraine subtype known as hemiplegic migraine. At present, the International Headache Society recognizes motor aura as a key manifestation of hemiplegic migraine (HM).

The ICHD2 (2004) also lists the entire spectrum of presentations that are now to be included under the migraine heading. These have been listed elsewhere in this issue.

Some migraine entities that have gained importance in recent years and which are included as part of the extended migraine spectrum have been detailed below.

**Chronic Migraine**

Transformed migraine (TM), and Chronic Migraine (CM) are terms that have been used to describe a subset of migraineurs who have previously were diagnosed to have episodic migraine and then progressed to having headache on more than 15 days of the month. Since TM implies the presence of specific factors that lead to the transformation, the use of this term was not preferred. The term CM was introduced in ICHD2-2004 and the criteria were revised in 2006 and were included in the appendix, pending further evaluation and field testing. The revised criteria specify that within the 15 or more headache days, in the absence of MOH, at least 8 days should be characterized by headache that meets criteria for migraine without aura or responds to migraine-specific treatment before it can develop characteristics allowing it to meet criteria for migraine without aura.

Explanations for the transformation to chronic migraine mostly center around central sensitization as the cause for reduction in the threshold for peripheral transmission and central processing of nociceptive input. Additionally, other risk factors have been identified which include female sex, habitual snoring, lower socioeconomic status and increased caffeine consumption. Obesity has also been identified as a risk factor, especially when comorbid with depression or anxiety. Excessive consumption of analgesic medications leading to medication overuse headache (MOH) frequently can complicate the diagnosis of CM. The frequent use of analgesics may play an important role in the process of CM. Bigal and Lipton have found in their population study that while opioids and barbiturates were associated with the development of chronic migraine, triptan use was not and non-steroidal use appeared to be protective.

**Vestibular Migraine**

That migraine can present with vertigo is not so well known.
When a migraine patient presents with vertigo, clinicians must determine whether an individual patient has vertigo that is caused by migraine, dizziness or vertigo of an unrelated cause, or has one of several vestibular and nonvestibular dizziness syndromes. The term migraine associated vertigo has been used to describe this entity.

The clinical features of vestibular migraine or migraine associated vertigo have been well documented. The key to the diagnosis is the repeated occurrence of migrainous symptoms and vertigo in the presence of triggers and response of the symptoms to antimigraine prophylactics. Vestibular Migraine has to be differentiated from other cause of vertigo such as Meniere’s disease (MD), benign paroxysmal positional vertigo (BPPV), motion sickness and basilar migraine.

### Childhood Migraine

Migraine is common in children and adolescents. Diagnosing migraine in children can be a particular challenge. The clinical manifestations of migraine vary widely through childhood. Children with migraine may present with transient neurologic, autonomic, gastrointestinal, or visual symptoms and headache may not be the primary symptom.

The most frequent form is migraine without aura, characterized by attacks of frontal or bitemporal pounding and nauseating headache lasting 1 to 72 hours. The criteria for the diagnosis of migraine in children are somewhat different from those specified for adults with migraine. The attack duration is shorter and may be anywhere from 1 to 72 hours. The location of the pain may be unilateral or bilateral (bifrontal or bitemporal). The accompanying associated autonomic features may not be so prominent.

Visual aura in children may include bizarre visual illusions and children may describe distorted visual perceptions, such as micropsia, macropsia or metamorphopsia. Ophthalmoplegic migraine (OM) has been now removed from migraine into the group of cranial neuralgias’ as a result of neuroimaging evidence demonstrating an underlying demyelinating-remyelinating mechanism. But there are many instances of normal imaging findings in what clinically would fit in with the diagnostic label of ophthalmoplegic migraine. Ptoisis, limited external ocular movements are most commonly seen. Signs may persist for days or even weeks after the headache has resolved.

### Menstrual Migraine

Menstrual Migraine (MM) develops most frequently in the second decade of life, around the onset of menarche, and prevalence peaks around age forty. ‘Pure menstrual migraine’ affects 10% to 14% of women with migraine and refers to attacks occurring exclusively on days 1± 2 (ie, days -2 to +3 of menstruation in at least two out of three cycles and at no other time of the month. Close to 60% of women with migraine experience menstrual related migraines. ‘Menstrually related migraine’ affects over 50% of women who have migraine and by definition migraines occur not only in the perimenstrual periods as described, but also at other times of the month.

It is important to distinguish premenstrual headache from MM. Premenstrual headache occurs earlier in the cycle, typically 2 to 7 days before the onset of menses and may be part of premenstrual syndrome (PMS). Migraine attacks may occur before, during, or after menstruation, but attacks associated with menstruation are often more severe, of longer duration, and less responsive to both acute and prophylactic treatment than migraine occurring at other times of the cycle. Menstrual migraine is usually migraine without aura. Whereas MM begins around the onset of menses, headache associated with PMS usually resolves with the onset of menstruation.

### Migraine and White Matter Abnormalities on Imaging

White matter abnormalities (WMA) are foci of hyperintensity on proton density and T2-weighted images in the deep and pericentral white matter resulting from interstitial edema or perivascular demyelination. WMA are easily detected on MRI but are not seen on CT scans. MRI studies have investigated WMA on scans of patients who had migraine.

Kruit and coworkers obtained MRI scans in a population – based sample of Dutch adults, ages 30 to 60, who had migraine with aura (n=161) or migraine without aura (n=134) and in well – matched controls (=140). In the cerebellar region of the posterior circulation territory, however, patients who had migraine had a higher prevalence of infract than controls (5.4% versus 0.7%). Kruit and colleagues further reported the brainstem and cerebellar hyperintense lesions found in their same migraine population. Those who had infratentorial hyperintensities also had supratentorial white matter lesions more often. The cause may be small-vessel disease (arteriosclerosis), perfusion deficits, or both. The presence of antiphospholipid antibodies might be another risk factor for WMA in migraine.

A subgroup of migraineurs may have a genetic predisposition for white matter lesions on MRI scans. Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) is a familial genetic disease with migraine as a common symptom and severe WMA on MRI as a consistent neuroimaging finding.

### Migraine- New Treatment Options

**Occipital nerve blockade**

Pharmacological treatment options have been discussed elsewhere. Greater occipital nerve blockade (GONB) has been shown to be effective for treating primary headache disorders such as chronic migraine and chronic cluster headache. The mechanism of action is thought to be the result of the anatomic overlap of the trigeminal nucleus caudalis and the C2 nerve roots that supply the greater occipital nerves.

Asghar and colleagues investigated the response of 54 chronic migraineurs to greater occipital nerve blockade with 3 mL of 2% lidocaine and 80 mg of methylprednisolone. Ashkenazi and colleagues conducted a study where patients who had TM were randomized to receive GONB with 2% lidocaine and 0.5% bupivacaine and either saline or triamcinolone. There were no statistically significant differences between the two groups with regard to reduction in pain severity or reduction in number of headache days after 4 weeks.

**Occipital nerve stimulation**

Greater occipital nerve stimulation (ONS) may exert some benefit in chronic migraine that is refractory to pharmacologic treatment. Stimulation of the greater occipital nerve is thought to suppress nociceptive input. Centrally mediated antinoiceptive mechanisms may be responsible for the efficacy of ONS in CM. Schwedt and colleagues have reported a series of 15 patients, consisting of eight patients with CM who were treated with ONS. This feasibility study suggests that ONS may be a promising treatment for some patients who have medically refractory CM.
but further randomized controlled trials are required.\(^{32}\)

**Vagal nerve stimulation**

Vagus Nerve Stimulation might play a role in treatment of medically refractive headache.\(^{33}\) VNS is thought to exert its influence on the parasympathetic dysfunction as well as by suppressing nociceptive input that is thought to occur in primary headache disorders. This treatment modality, however, has not undergone formal randomized studies.

**In Conclusion**

Migraine treatment needs a balanced approach with pharmacologic and non-pharmacologic measures. With all the current options, it is easier now to recognize and treat migraine optimally. Treatment decisions must be based on headache prevalence, by race. Neurology 1996;47(1):52-9

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