ABSTRACT

Migraine is a constellation of neurological symptoms with variable disease progression. Despite the standardization of migraine diagnosis with the International Headache Society (IHS) criteria, its etiology eludes medical research because its complexity as a disease lies in the multiple factors involved in migraine onset. The study of migraine genetics is providing important clues to the pathophysiology of migraine, but the results indicate a complex interaction between numerous factors. The frequent comorbidity of migraine with several other disorders may be used to discover the mechanisms of onset as well as optimizing therapeutic strategies. This paper reviews the current hypotheses regarding migraine nature and the role of comorbidity in migraine diagnosis and management. Implications for therapeutic strategies are also discussed. (Advanced Studies in Medicine 2001;1(2):55–63)

PROCEEDINGS

PHENOTYPE-GENOTYPE INTERACTIONS IN MIGRAINE: A COMPLEX DISEASE

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Migraine is a complex, chronic disease characterized by intermittent attacks of severe headache and autonomic and neurological symptoms. It is a very common disorder with a wide range of clinical presentations. The diagnostic classification criteria published by the International Headache Society (IHS) have been of inestimable value in identifying and diagnosing migraine and in the differential diagnosis of other primary headache disorders. However, the complexity of migraine as a disease lies in the multiple factors involved in its pathophysiology. These factors include gender, psychosocial factors/life events, genetics, and comorbidity with other diseases. Thus, while we appear to understand migraine on the surface based on its nosology, there are many aspects of its pathophysiology that remain under investigation. The disease mechanisms result in myriad clinical presentations, and our lack of understanding potentially limits our ability to optimally treat migraine patients.

The IHS criteria help define migraine in terms of attack (ie, the duration, the pain characteristics, the presence of nausea or vomiting, and the presence of photophobia or phonophobia as well as prodromes), while migraine is also characterized by other variable factors, such as association with other diseases and different ages of onset, response to provocative tests, response to prophylaxis, evolution, and outcome. Heterogeneity (in both attacks and disease) is referred to as the “migraine complex” and is the rule rather than the exception. Migraine heterogeneity must be considered in decisions regarding diagnosis and therapeutic approaches.
PROCEEDINGS

MIGRAINE AND COMORBIDITY

Comorbidity is thought of as the simultaneous presence (more frequent than by chance) of 2 illnesses. Several conditions are comorbid with migraine including neurologic (epilepsy, ataxia, mitochondrial diseases), psychiatric (depression, mania, panic disorder, anxiety disorders), cardio- and cerebrovascular (hypertension, mitral valve prolapse, angina/myocardial infarction, stroke), and immunologic (asthma, allergies) diseases. Interestingly, migraine shares similar characteristics with some of these diseases. Stroke and migraine both produce headache and focal neurological deficits.1 Epilepsy and migraine both produce paroxysmal neurological attacks and headache.2 Depression and migraine both result in head pain and mood changes.3,4

As noted by Lipton and Silberstein, the study of comorbid migraine conditions has diagnostic, therapeutic, and etiological implications. For example, when migraine is known to be comorbid with certain conditions, the presence of 1 disorder should increase, not reduce, the suspicion that the other one may be present.5 The treatment of migraine and the presence of a comorbid illness can offer therapeutic advantages. For example, patients with comorbid depression can be treated successfully with tricyclic antidepressants. Beta-blockers and calcium channel blockers may be effective in treating both hypertension and migraine. For patients with migraine and epilepsy, antiepileptic drugs can be effective. Conversely, comorbid conditions also pose certain therapeutic complications. For example, beta-blockers are not recommended for patients with comorbid migraine and depression, and tricyclic antidepressants or neuroleptics may lower the seizure threshold in a patient with migraine and epilepsy.6

Many clinical researchers are using the comorbidity of migraine with other disorders to understand the pathophysiology of migraine. However, there are several possibilities for the causal relationship between migraine and other illnesses, adding to the concept of the migraine complex. Lipton and Silberstein discussed these relationships as 4 possible scenarios (Figure 1).7 First, the disorders may not really be associated but rather are selected for unintentionally. For example, patients with migraine and depression are typically more difficult to treat and therefore more likely to be referred to a headache specialist. In clinic-based studies, the association between migraine and depression may therefore be overestimated. So, to establish comorbidity as something occurring more frequently than by chance, population-based studies are preferred. Secondly, 1 condition can cause the other. For example, perhaps migraine triggers epilepsy by causing focal neurological damage to the brain, resulting in an epileptic focus. Conversely, epileptic seizures might cause migraine by altering the trigeminal vascular system and lowering the threshold for migraine. It is a unidirectional causal hypothesis but it can go either way. The third situation can arise when both conditions share an environmental or genetic risk factor. For example, a common genetic dysfunction of excitatory neurotransmitter systems has been linked to epilepsy and migraine.6-9 Similarly, disruption of serotonergic systems may explain the occurrence of both migraine and depression. Finally, a more complicated scenario involves...
independent genetic and environmental risk factors producing a "brain state" that predisposes to migraine and a comorbid condition. The comorbidity of migraine and epilepsy, for example, has been attributed to neuronal hyperexcitability in the brain. This may be the result of a genetic predisposition (to be discussed later) or an environmental insult such as head trauma.

**MIGRAINE AS A GENETIC DISORDER**

The putative role of genetics in migraine pathophysiology is gaining increasing acceptance. Certain types of migraine show strong familial aggregation but the number of genes involved is not known. Also, the comorbidity of migraine with so many other disorders suggests that several genes may be involved.

Familial hemiplegic migraine (FHM) is a rare subtype of migraine with aura characterized by hemiparesis during migraine attack, a young age of onset, and ataxia in some patients. FHM has been linked to loci on chromosomes 1 and 19. However, FHM itself appears to be heterogeneous. The association of the chromosome 1 and 19 loci was found in only some of the families tested and penetrance of the chromosome 19 locus is incomplete. One associated gene, which codes for alpha-1A subunit of voltage-dependent P/Q-type calcium channels (now referred to as the CACNA1A gene), has been identified on chromosome 19. Mutations in CACNA1A are autosomal-dominantly inherited and several recent studies have shown an increasing number of CACNA1A mutations on chromosome 19p13 in migraineurs. However, these data do not unequivocally show that migraine is due to CACNA1A mutations, and other studies contradict a widespread role of CACNA1A in common forms of migraine.

FHM also appears to be susceptible to genotype-phenotype interactions. Patients with involvement of the chromosome 19 locus may experience cerebellar signs, including essential tremor, whereas patients with involvement of the chromosome 1 locus may experience epilepsy and febrile convulsions. Similarly, at least 18 CACNA1A mutations have been identified with variable clinical expression.

<table>
<thead>
<tr>
<th>Table 1. Channelopathies with Known Genetic Alterations</th>
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<tbody>
<tr>
<td>Gene Locus</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Familial hemiplegic migraine (FHM)*</td>
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<tr>
<td>Episodic ataxia type 2 (EA2)</td>
</tr>
<tr>
<td>Spino-cerebellar ataxia type 5 (SCA6)*</td>
</tr>
<tr>
<td>Benign neonatal epilepsy type 1 (BNE-1)</td>
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<tr>
<td>Congenital myotonia (Thomsen)</td>
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<tr>
<td>Hypokalemic periodic paralysis type 2</td>
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<tr>
<td>Long QT syndrome</td>
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</tbody>
</table>

*Forms associated with migraine.

Finally, 50% of migraine cases remain sporadic, so genetics of FHM do not account for the whole story. For example, the higher prevalence in females may be explained by genetic determinants recently discovered on chromosome Xq24-28.24

**Migraine as a Channelopathy**

Migraine shares certain characteristics (episodic nature, precipitating factors, and response to therapy) with other neuromuscular disorders (such as epilepsy, episodic movement disorders, and periodic paralyses) with known defects in ligand- and voltage-gated channels (ie, “channelopathies”). These phenotypes prompted further investigation into possible related genetic mechanisms of ligand- and voltage-gated ion channels. Channelopathies are characterized by episodic excess depolarization of cell membranes producing variable ion conductance, which upsets the balance between excitatory and inhibitory neurotransmission. Table 1 lists examples of channelopathies with known genetic alterations including those associated with migraine. The alpha subunit encoded by CACNA1A is part of the voltage-dependent P/Q-type calcium channels and is the pore-forming region of 4 subunits that constitute the calcium channel. Disruption of pore formation would be expected to disrupt neuronal calcium homeostasis, which is critical for normal neurotransmitter function. Because the mutations reside in the P/Q-type calcium channels, it is not surprising that the symptoms of migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6 involve significant cerebellar symptoms and that migraine and epilepsy are comorbid.25

**Migraine as a Cerebrovascular Disease**

Several pieces of evidence point to a relationship between migraine and cerebrovascular disease. In a study on stroke patients, history of migraine was more frequent in cerebral ischemia patients than in controls. In the subgroup analyses (ie, history of migraine, arterial hypertension, cigarette smoking, hypercholesterolemia, hypertriglyceridemia, low high density lipoprotein cholesterol, diabetes mellitus, obesity, alcohol misuse, oral contraceptive use), history of migraine reached the highest odds ratio and was the only significant risk factor in women below age 35 (P = 0.003).25 Nitric oxide (NO) modulates vascular smooth muscle relaxation and vascular dilation, which has positioned it among the possible etiological candidates for migraine. Migraine attacks are associated with intra- and extracranial arterial dilation.27,28 NO has been shown to trigger migraine attacks in studies using glyceryl trinitrate, an exogenous NO donor, and histamine, which causes NO formation in vascular endothelium.29 Similarly, glyceryl trinitrate induced more severe and long-lasting headache in migraineurs than in healthy subjects. The induced headache fulfilled the diagnostic criteria for migraine without aura more often compared with healthy subjects.30 Thus, migraineurs appear to be supersensitive to glyceryl trinitrate and therefore supersensitive to NO.

NO is synthesized by nitric oxide synthase (NOS), of which there are several isoforms. NOS3 produces NO for minutes per episode, in response to chemical (eg, glutamate release) or mechanical (eg, the pulsatile strain on the arterial wall) stimuli. NOS2, by contrast, can produce NO for several days under certain conditions.31 A recent study using an NOS inhibitor showed that NO may be involved in the pain mechanisms throughout the course of spontaneous migraine attacks. Patients treated with the NOS inhibitor experienced headache relief 2 hours after administration with concomitant improvement in photo- and phonophobia symptoms.32 However, mutations in the NOS gene have been proposed in the pathophysiology of atherosclerosis and hypertension as well as in cerebrovascular disorders linked with migraine (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL).33 Similarly, the gene for the angiotensin-converting enzyme (ACE), which stimulates conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, has been implicated in increased migraine attack frequency in patients with migraine without aura. Early studies showed an association between the ACE-D allele deletion polymorphism and migraine without aura.34 Recent results suggest that the ACE-D allele (ie, the DD genotype) is associated with more frequent attacks in migraine without aura patients.35 Future management strategies may use the ACE-D genotype as a diagnostic marker that would indicate the use of ACE inhibitors as therapy. Preliminary studies using lisinopril and enalapril in migraine patients with
headaches occurring more than twice a month showed some benefit.36

**MIGRAINE AS A MITOCHONDRIAL DISORDER**

Mitochondrial diseases are usually referred to as disorders of the respiratory chain—the final common pathway for oxidative metabolism. Of the 70 different polypeptide subunits that form the 5 enzyme complexes in the respiratory chain, 13 are formed by mitochondrial deoxyribonucleic acid (mtDNA). The remainder is formed by genomic DNA. Mitochondrial diseases suffer from the same heterogeneity as migraine and other headache disorders. Specifically, the same clinical syndrome can be caused by different genetic defects, and the same genetic defect may present as many different clinical syndromes. For example, missense mutations in the adenosine triphosphatase genes can cause subacute necrotizing encephalopathy with ataxia and brain stem signs in children (Leigh’s disease). This mutation can result in a milder phenotype (neurogenic weakness with ataxia and retinitis pigmentosa or NARP) clinically manifested later in childhood or adult life.37 Because all mitochondrial diseases affect the respiratory chain, it is not surprising that different mitochondrial DNA defects can cause a similar disorder. The differences in phenotypic expression from 1 mutation are more perplexing but several theories have been proposed. Mitochondrial DNA in a particular patient is often a mixture of mutant and wild-type DNA. Also, there are tissue-specific differences in the dependence on oxidative metabolism. Thirdly, maternal inheritance of mitochondrial DNA is not straightforward. In mammals, mitochondrial DNA is transmitted exclusively through the maternal line. Deletion mutations are rarely, if ever, transmitted from clinically affected females to their offspring—a phenomenon that is not completely understood. However, a female with both mutant (point mutations or gene duplication) and wild-type DNA can transmit a variable amount of mutant mitochondrial DNA to her offspring.37-39

The association between migraine and abnormal mitochondrial function has been suggested based on clinical similarities between migraine and certain mitochondrial diseases. For example, migraine with aura attacks with vomiting and migraine stroke are typical features of mitochondrial encephalomyopathy with lactic acidosis and stroke-like syndrome (MELAS).40 Other examples are shown in Table 2. However, these data do not show any definite relationship between the known mitochondrial disorders and migraine, with or without aura.40-42 Nonetheless, mitochondrial diseases are themselves a novel field of exploration, and a relationship cannot yet be ruled out.

**Table 2. The Place of Migraine Within Mitochondrial Diseases**

<table>
<thead>
<tr>
<th>Gene and Locus</th>
<th>Gene Product</th>
<th>Molecular Alteration</th>
<th>Altered Function</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS</td>
<td>MTTRNAl/mtDNA Transfer RNA encoding for leucine</td>
<td>Point mutation</td>
<td>Altered energy metabolism due to reduced protein synthesis</td>
<td>Stress, hyperthermia, situations of &quot;high energy demand&quot;</td>
</tr>
<tr>
<td>MERRF</td>
<td>MTTRNAK/mtDNA Transfer RNA encoding for lysine</td>
<td>Point mutation</td>
<td>Altered energy metabolism due to reduced protein synthesis</td>
<td>Stress, hyperthermia, situations of &quot;high energy demand&quot;</td>
</tr>
<tr>
<td>NARP</td>
<td>MTA6/mtDNA Respiratory chain complex V subunit</td>
<td>Point mutation</td>
<td>Reduced/at absent ATP synthesis</td>
<td>Stress, hyperthermia, situations of &quot;high energy demand&quot;</td>
</tr>
</tbody>
</table>

MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged-red fibers; NARP = neurogenic weakness with ataxia and retinitis pigmentosa; ATPase = adenosine triphosphatase.

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MIGRAINE AFFECTED BY MODIFYING DOPAMINERGIC GENES

The migraine complex also involves the effects of possible "modifying genes," most notably the dopaminergic receptor D2. Clinical and pharmacological evidence suggests that dopamine is involved in migraine. Many prodromal and accompanying migraine symptoms (eg, yawning, nausea, vomiting) are attributable to stimulation of dopamine receptors and several dopamine receptor antagonists are effective in migraine treatment. Migraine patients also show a higher incidence of dopaminergic symptoms following dopamine agonist administration compared with controls, and several researchers have argued that migraineurs may have dopamine receptor hypersensitivity.

Recent studies have identified a specific allele (NcoI C) of the DRD2 gene, which codes for D2 receptor, that is associated with migraine with aura. However, it was noted that the NcoI C allele is neither necessary nor sufficient to cause migraine with aura because not all individuals with the homozygous genotype have migraine with aura.

Peroutka et al showed that the NcoI C allele frequency was significantly higher in individuals with migraine with aura, anxiety disorders, and major depression than in individuals who have none of these disorders. These authors suggested that migraine with aura, anxiety disorders, and major depression can be components of a distinct clinical syndrome associated with allelic variations in the DRD2 gene. Studies of the D2 receptor gene as a candidate for manic-depressive psychosis treatment are in progress in our own and other laboratories.

THE SEROTONERGIC PATHWAYS IN MIGRAINE

The involvement of serotonin (5-hydroxytryptamine, or 5-HT) in migraine is well established but its role in migraine onset is not yet known. Migraine patients have chronically low 5-HT plasma levels intercritically with ictal increases in platelet 5-HT release. However, the release of 5-HT is thought to be an effect of a migraine attack rather than a cause.

There are 7 families of 5-HT receptors, and activation of certain types of 5-HT1 receptors results in selective constriction of cranial blood vessels and attenuation of activation of sensory afferents within the trigeminovascular system. Sumatriptan, the first of the triptans to be available, is a 5-HT1B/1D receptor agonist. Triptans have been used to successfully treat migraine attacks, and recent evidence points to their effect in reducing N-methyl D-aspartate (NMDA) receptor-evoked enhancement of NOS activity.

However, the incomplete efficacy of the triptans also suggests that the serotonergic pathways may be important in migraine but are not sufficient to cause migraine. 5-HT2 receptor activation increases inflammatory vasodilation and several drugs with potent 5-HT2 receptor-blocking activity (eg, methysergide, pizotifen) are used for migraine prophylaxis. Studies are under way to characterize any genetic determinants of altered serotonergic activity in migraine, ie, alterations in genes encoding for 5-HT receptor components.

GENOTYP-E-PHENOTYP INTERACTIONS

In addition to the complex genetics of migraine, there are numerous environmental triggers, which are critical with respect to migraine "as attacks." It has been recently stated once again that attacks occur only...
when the threshold is reduced or when the triggers are particularly strong and frequent. The threshold appears to be set by genetic factors, but it is affected by internal and external factors, such as hormonal fluctuations, fatigue, relaxation after stress, changes in weather, and substance misuse.68

**MIGRAINE HETEROCHRONIA: ANOTHER PIECE OF THE MIGRAINE COMPLEX**

One final aspect of migraine heterogeneity lies in the change in expression of comorbidity with time. Migraine prevalence peaks between the ages of 25 and 55 but it can occur up to age 65 and over.69 Comorbid disorders with migraine, however, show varying years of peak expression (Figure 2). For example, psychiatric disorders such as mood and anxiety disorders typically occur between the ages of 30 and 85, while panic disorder usually occurs between the ages of 30 and 65. Cerebrovascular disorders, by contrast, tend to occur later in life. Hypertension appears typically between the ages of 50 and 85, myocardial infarcts between the ages of 55 and 85, and stroke between the ages of 65 and 85. This phenomenon is currently referred to as “phenotypical heterochronia.”70 Interestingly, mitochondrial DNA mutations may disappear with age, as seen with MELAS mutations.21 The factors determining migraine heterochronia are under investigation but it would appear that age and gender are among the most critical ones.

**CONCLUSION**

Despite our extensive experience with diagnosing and treating migraine and other primary headache disorders, much remains unknown about the underlying pathophysiological mechanisms. Clearly, migraine is a multifactorial disorder with several genes and several internal and external environmental factors involved in its presentation. It is not surprise, therefore, that the response rates for the multitude of migraine therapies (acute and prophylactic) have been less than optimal. It is only by understanding all of the factors involved in migraine expression that true therapeutic success can be achieved given the complex interactions between genotype and phenotype. The phenotypic expression over time can be explained starting with a specific phenotype and with the addition of genetic modifiers (such as NOS, ACE, dopamine receptor, and 5HT1/2 receptor genes) to produce any one of many phenotypes. With time, other factors such as age, life events, psychosocial stress, changes in eating habits, or geography can change the phenotypic expression.

In the future, one can envision migraine patients in a broad group that may include relatively asymptomatic patients with a genetic predisposition as well as those who are incapacitated by almost daily migraine attacks with possible comorbid psychiatric or cerebrovascular disorders. Migraine therapy (including prophylaxis) will therefore be tailored to individual patients based on their external and internal factors as well as the genetic mechanisms involved.

**REFERENCES**


