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Migraine comorbidity: from genotype to phenotype

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Abstract In this paper, we review the "current" and "ancient" concepts of comorbidity in migraine attack and disease. We emphasize the role of migraine as a complex disease and stress the appropriate consideration that genetic determinants require in modern taxonomy of migraine headaches. Novel attempts to revise migraine nosography should consider the complexity of genotype-phenotype-environment interactions in order to identify more rational approaches to treatment.

Key words Channelopathy • Comorbidity • Genotype • Heterogeneity • Migraine • Phenotype

Introduction

The familial tendency for migraine with aura (MA) and without aura (MOA) is well recognized, even though the exact nature of inheritance has been elusive. Previously favored theories regarding mode of inheritance include an autosomal dominant pattern with higher penetrance in women, or a sex-determined, autosomal recessive pattern, or both [1]. There are abundant examples of migraine families whose pattern of affliction supports the notion of a simple "monogenic" or mendelian genetic disorder [2]. However, the majority of smaller migraine families and single "sporadic" migraine patients cannot be consistently categorized by segregation analysis [3, 4] and instead fit the multigenic, multifactorial features of complex diseases. Likewise, twin studies strongly support the notion of a genetic component, yet monozygotic female concordance rates, which are well below 100% (0.32–0.44), predict the influence of other factors. Hormonal influences have long been implicated and correlate with a 2:1 female to male ratio of migraineurs noted in several of epidemiologic surveys. An early family study pointed out a 2.5-times greater tendency for maternal transmission of migraine, which is compatible with cytoplasmic, mitochondrial inheritance.

A rare form of migraine, familial hemiplegic migraine (FHM), is a subtype of MA which is autosomal dominant and highly penetrant, and thus the only migraine type with a definite mendelian inheritance pattern [5]. Some FHM families were found to have missense mutations in a brain P/Q voltage-gated calcium channel (CACNL1A4) located on chromosome 19 (locus FHM1). The recent mapping of

another FHM locus on chromosome 1 (locus FHM2) [6] confirms the genetic heterogeneity of FHM disorders. Evidence is growing for some contribution of the chromosome 19 FHM locus to the more common types of migraine. Patients with FHM may also have attacks of "non-hemiplegic" migraine, and FHM families sometimes have either individuals with typical FHM or individuals with non-hemiplegic migraine [7]. Since FHM is considered to be part of the migraine spectrum, it can serve as a model to study the complex genetics of typical migraine. However, it remains to be seen whether the mutated gene (and other FHM genes) will have a major effect or whether it will contribute one of several additive gene effects responsible for the genetic component of MA and MOA.

Almost certainly, multiple genes and multiple environmental triggers and factors interact to produce migraine. Hence, we can expect variability and some degree of overlap in the migraine phenotypes (the clinical manifestation of the genetic defect). Given the complexity of clinical expression and multifactorial etiology [8], family and epidemiologic studies have been confused by gender-dependent, age-related, and variable penetrance, environmental factors, lack of definition of the migraine syndromes, and referral bias [9]. Furthermore, the diagnosis of migraine and other headache disorders relies almost entirely on the clinical history with no definitive clinical signs or markers of disease being available, especially interictally [10, 11].

The concept of migraine heterogeneity

The International Headache Society (IHS) criteria [12] for migraine helped standardize the definition of phenotypic syndromes and provided a reasonable starting point for the eventual correlation with genotypes (the genetic marker for a specific gene mutation). There will likely be significant *phenotypic heterogeneity* or a spectrum of clinical expressions associated with each genetic mutation. There also will be significant *genetic heterogeneity* or more than one gene resulting in similar clinical expressions. Phenotypic and genotypic heterogeneity is quickly becoming the rule rather than the exception, as we continue to unravel the molecular code of genetically based diseases and undermine the notion of a simple monogenic disorder.

The concept of heterogeneity characterizes migraine in terms of both attacks and disease [8]. With regard to the former, it is a common observation that acute migraine phenomena can vary considerably, according, for instance, to the presence or absence of the aura and its peculiar features, to the degree of pain severity, to the presence or absence of neurovegetative signs and symptoms, and to the response to symptomatic drugs. Similarly, there are variable aspects which belong to the disease itself, such as the differences in age at onset, the frequency of clinical disturbances, the natural history of disease, the pattern of response to various neurobiological tests, the effectiveness of treatments, the association with other disorders, and the evolutive potential or outcome of disease. The heterogeneity of migraine, both as attacks and as a disease, accounts for the observation that alongside the large population of migraine sufferers living an almost normal life exists a group of patients with serious disability, who face social, affective and occupational limitations of varying degrees of severity.

A further aspect of migraine heterogeneity which appears to be extremely relevant to clinical research is that the phenotypical expression may vary over time. The importance of this *phenotypical heterochronia* [8] stems from the simple observation of the natural history of migraine in an individual's lifetime: in some patients, the phenotypical manifestations remain unchanged over the years. By contrast, in other patients the clinical picture becomes more complicated, and may include arterial hypertension (which is itself a risk factor for cerebrovascular accidents) and/or anxiety and mood disturbances. On the other hand, it is well known that the presence of hypertension and psychiatric disorders often facilitates changes in the migraine pattern, resulting in forms of chronic daily headaches ("transformed migraine"). The reciprocal links between migraine and the associated diseases remain obscure [13], but while the factors affecting the evolution of the clinical picture are largely unknown, it is likely that age itself and gender are among the critical ones. This is suggested by the reported observations that the risk for stroke is increased in young migrainous women under 35 years [14] and that the association of migraine and mood disorders gets closer with age [15]. Presumably, phenotypic heterogeneity is due to the presence of modifier genes as well as environmental influences. Recent and future association studies will aim at recognizing the role of the lesser susceptibility genes for the common migraine types.

Despite the complexity of migraine genetics, the future is bright for genetics to provide a more precise understanding of what causes headache and possible new routes to a rational and effective therapy. This process has already begun: as the first headache gene has been identified, those patients with defined mutations are now being removed from the heterogeneous pool of migraineurs. This obviously facilitates subsequent genetic studies.

Comorbidity: migraine associated with other disorders

Some disorders generally considered as being "acquired" have been associated with migrainous or vascular type

headache. Comorbidity of migraine with other disorders raises tantalizing questions about the underlying pathophysiology and the possibility of shared pathways. Migrainous symptoms, with or without an associated aura, can occur with a variety of acquired or structural brain disorders, such as infectious or inflammatory central nervous system (CNS) conditions, vascular malformations [16], and symptomatic epilepsy [17]. Though the observation was made long ago, the association of migraine and epilepsy remains controversial based on prevalence studies [18]. Also, when assessed in relatives of probands with migraine versus those without migraine, the risk of epilepsy in relatives was not associated with the proband's history of migraine, with the exception of one subgroup (sons of female probands). Nonetheless, patients with MA, menstrually related epilepsy, and basilar migraine are most at risk for migraine-induced seizures, and an association of MA and epilepsy was found in 3% of 395 adults. A large epidemiologic study recently found that patients with epilepsy were 2.5-times as likely to develop migraine as their relatives without migraine. A subset of patients with basilar migraine (up to 20%) have persistent electroencephalographic (EEG) abnormalities interictally and they have been suggested to suffer from a separate disorder [19].

Additional factors, including environmental and indivually related ones, may play a role in this comorbid relationship. For example, migraine risk was highest in probands with epilepsy due to head trauma, but it was significantly higher in every subgroup of probands than in unaffected relatives when probands were stratified by seizure type, age at onset, etiology of epilepsy, and history of epilepsy in first-degree relatives. Age-specific incidence of migraine among probands was increased to a greater extent after onset of epilepsy than before, but it was also significantly increased more than 5 years and 1–5 years before onset. These results indicate that migraine and epilepsy are strongly associated, and this association is independent of seizure type, etiology, age at onset, or family history of epilepsy.

Other disorders with convincing familial recurrence have also been shown to co-segregate with migraine in some families. The comorbidity of migraine with these inherited disorders is even more intriguing, since they may be allelic (different mutations in the same gene resulting in different diseases) or due to closely linked genes which therefore represent possible candidate genes. This notion is reinforced by the occurrence of overlap between FHM and hereditary forms of basilar migraine. FHM has been associated with benign infantile epileptic syndrome. Some FHM2 family members have seizures during or around the time of migraine attacks [6, 20]. Also, familial types of epilepsy associated with migraine include benign occipital epilepsy [21] and benign rolandic epilepsy, though neither have yet been localized genetically. The possibility that migraine might be related to a channelopathy in view of the chromosome 19 FHM calcium channel gene mutations makes the idea of shared pathophysiology with primary epilepsies particularly appealing, given their paroxysmal nature [22].

A study of 20 families with benign essential tremor reported that 26% of affected members also co-segregated for migraine with aura [23]. Interestingly, essential tremor has been reported in some FHM1-linked families who also have cerebellar dysfunction and in another FHM family with nystagmus and ocular motility changes suggestive of brainstem-cerebellar dysfunction. FHM was also associated with deafness, retinal degeneration, ataxia, and nystagmus reminiscent of Usher's syndrome in a single complicated family. In addition, CADASIL (cerebral autosomal dominant arteriopathy and stroke with ischemic leukoencephalopathy) caused by Notch-3 gene mutations on chromosome 19p [24] and the Dutch form of hereditary cerebral amyloid angiopathy caused by a point mutation in the amyloid precursor protein gene on chromosome 21 [25] have been associated with migraine.

Psychiatric comorbidity in migraine

The comorbidity of migraine with psychiatric conditions is well established [26], though the complexity of these disorders make it difficult to estimate the impact and the usefulness to the geneticist. Two epidemiologic studies of young adults focused on the relationship between migraine and affective disorders, such as major depression, dysthymia, bipolar disorder, and cyclothymia. Through application of current definitions of migraine and psychiatric disorders in structured diagnostic interviews, data have been obtained that strongly support clinical observations on comorbidity of migraine with major depression. The findings supporting a link between migraine and bipolar disorder are presently less consistent. In particular, lifetime prevalence of major depression was approximately three-times higher in subjects with migraine and with severe headaches compared to controls. A significant bidirectional relationship was observed between major depression and migraine, with migraine predicting first-onset depression and depression predicting first-onset migraine. In contrast, persons with severe headaches had a higher incidence of first-onset major depression but major depression did not predict a significantly increased incidence of other severe headaches. The conflicting results regarding the relationship of major depression with migraine versus other severe headaches suggest that different causes may underlie the co-occurrence of major depression in migraineurs compared with other headaches sufferers.

As for affective disorders, the lifetime prevalence of major depression is 34.4% in patients with migraine and 10.4% in patients without migraine. The prevalence of bipolar I disorder is 6.8% in patients migraine with aura versus 0.9% in normal subjects. The lifetime prevalence of anxiety disorders in migraine is significantly increased versus controls in panic disorder (10.9% vs. 1.8%), generalized anxiety disorder (10.2% vs. 1.9%), obsessive-compulsive disorder (8.6% vs. 1.8%), and phobic disorder (39.8% vs. 20.6%). In addition, no psychopathological, biological or genetic explanation seems to account for this comorbid pattern. These results remain primarily descriptive, but they justify a clinical investigation of affective and anxiety disorders (and even of any suicide attempts), in all patients with migraine. They also justify the treatment of pain associated with the treatment of any coexisting affective or anxiety disorders.

It is also important to realize how migraneurs adapt to their medical condition. A recent study examined the association between migraine and personality profile, taking into account history of coexisting psychiatric disorders [27]. Data obtained from an epidemiologic study of young adults also suggested that migraine was associated with neuroticism, but not with extraversion or psychoticism, and that an excess of 25% of patients with migraine alone (uncomplicated by psychiatric comorbidity) scored in the highest quartile of neuroticism. The results suggest that migraine sufferers might be more vulnerable to psychopathology and are characterized by a poor adjustment to their medical condition. Physicians caring for patients with migraine or affective disorders should maintain diagnostic vigilance for comorbid disease and, if present, should consider comorbidity when planning treatment interventions.

The role of genetics

In an attempt to elucidate the phenomenon of heterogeneity, it has to be borne in mind that while genetic determinants are certainly at the basis of some (and probably all) clinical forms, the contribution of biological factors of various nature critically affects the clinical appearance of disease. The recent findings in the field of neurogenetics have deeply changed our approach to migraine, emphasizing the limits of the current diagnostic and nosographical system [8]. Indeed, while according to the current IHS criteria subjects who have experienced up to 4 attacks of migraine without aura or only 1 attack of migraine with aura cannot be recognized as being migraineurs, in the future the diagnosis of migraine may even be made in individuals bearing a given genetic alteration but otherwise completely asymptomatic.

The discovery that some migraine forms are characterized by well-defined genetic changes is leading to a revision of the pathogenetical hypotheses originally derived from the psychobiology of interactions between the individual and the environment. In this respect, for several years we have considered as a reliable model the concept, developed in the early 1980s, that migraine is the result of the integrated effects of different factors, some of which are intrinsic to the individual (migrainous "trait") and some to the environment "precipitating factors") [10]. With the introduction of new diagnostic criteria allowing for a better phenotypical characterization of the patients, the importance of the role of genetics in the mechanisms of migraine is now increasing. There are certainly several aspects deserving further elucidation: in the first instance, the genetic factors do not themselves account for all the clinical forms, as migraine remains a sporadic disease in over 50% of cases. Uncertainty also exists on the mode of inheritance of the familial forms, which may themselves be considerably different. FHM, for instance, is inherited as an autosomal dominant trait, according to the classical mendelian rules [5]. In addition, the presence of genetic determinants on chromosome X may explain the unbalanced ratio of females to males observed within the same family [28]. In most cases, however, migraine occurs as a multifactorial inherited character [29]. Therefore, different genes or loci may interact with factors intrinsic to the individual (e.g. the hormonal milieu) and/or with exogenous factors (e.g. psychosocial stressors related to the family or to working environment, geoclimatic changes), generating different clinical forms of disease. The level of complexity is further increased by the effects of "modifying" genes, of other possible interactions between major genes, and of the preferential expression of the encoded proteins in given cells or systems. All these phenomena, along with environmental determinants, may represent the molecular substrate of the variable clinical expression of migraine, and can be better evaluated in population studies. Such population-based association studies must be large, are subject to the usual biases, and generally test for the contribution of "minor" genes. The additive effects of these minor genes, however, can conceivably be important in a highly prevalent disorder such as migraine.

Which and how many genes?

The pathogenetic role of candidate gene polymorphisms in a particular disorder must also be established as they are identified by association studies. Given what we know about the biochemical pathways of the common forms of migraine and the calcium channel in hemiplegic migraine, there are many possible candidate loci which can be evalu-

ated using nonparametric methods. Biochemical and pharmacological studies of migraine have long focused on neurotransmitters, neuropeptides and receptors, with much attention given to serotonin and vasoactive substances such as neurokinins, calcitonin gene-related peptide, nitric oxide, and substance P. Following vessel dilatation, subsequent pain fiber stimulation along trigeminovascular pathways is presumably enhanced by the perivascular inflammation resulting from release of these substances. Dopamine may also have a role in the acute migraine attack [30], since many of the prodromal and vegetative symptoms associated with attacks can be reproduced by the administration of exogenous dopamine. In addition, a subgroup of migraineurs, especially those with migraine with aura, are especially prone to suffering an attack when given dopamine or dopamine agonists, and dopamine antagonists have long been used alone or in combination with other drugs to treat acute migraine.

It seems therefore reasonable to test for genes encoding dopamine receptor subtypes. Two studies have, indeed, suggested a link with the DRD2 dopamine receptor. In an association study, Peroutka et al. [31] showed that in 250 unrelated individuals a DRD2 polymorphism was more frequent among migraineurs with aura ($p = 0.005$). In a family association study from Sardinia [32], significantly more DRD2 gene alleles were shared among a subgroup of "dopaminergic" migraineurs without aura ($p = 0.004$) from 50 nuclear families using the transmission disequilibrium test. This dopaminergic group reported symptoms such as yawning and nausea with their headaches. Similarly, association studies must be performed to test different genetic components of other migraine pathophysiological steps (i.e. the role of polymorphisms in ion channels, changes in genetic determinants of the mitochondrial energy producing machinery [33] as well as the various aspects of comorbidity (for example, the affective profile of migraneurs). Migraine may thus be included among the polygenic diseases identified over the last years.

Conclusions

Based on the recognition of genetic heterogeneity, it now appears more appropriate to speak in terms of common neurobiological mechanisms influencing the full expression of the clinical phenotype. These mechanisms can be alternatively identified with deranged brain oxidative metabolism (particularly in cortical-subcortical regions) [34], with abnormal neuronal excitability due to altered membrane ion channels [35], or with functional changes in receptor components. The interaction of these phenomena with factors intrinsic to the individual (such as age, gender, neuroendocrine reactivity) or environmental factors (occupational aspects, weather changes, lifestyle) produces a spectrum or continuum of manifestations, of which pain and neurovegetative signs and symptoms (typical of the migraine attack) represent only one aspect, i.e. the tip of the iceberg. In this scenario, it is not surprising that other acute, paroxysmal phenomena of the central nervous system characterized by excess depolarization of cell membranes with variable alterations of the ion channel conductance and hence modified balance between excitatory and inhibitory phenomena - such as epilepsy - have been associated with migraine. For some of the acute disorders due to functional changes of neuronal ion channels (channelopathies) [22], a significant association with migraine has also been reported. Other clinical forms occurring episodically have also been considered part of the clinical spectrum.

It therefore appears that the clinico-descriptive approach to the patient, requested by the current diagnostic criteria, only allows for a partial understanding of migraine, whose nature is more complex and heterogeneous than previously thought [8]. Migraine remains a puzzling disease, and any nosographic revision should always consider the study of genotype-phenotype-environment interactions: this will help identify more rational approaches to the management of this disorder.

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