INTRODUCTION

Migraine, both with (MA) and without aura (MOA), is well recognized as being recurrent in families, although the exact mode of inheritance is unclear. There are abundant examples of migraine families whose pattern of affliction suggests a simple “monogenic” or mendelian genetic disorder (1). However, the vast majority of “sporadic” migraineurs cannot be consistently categorized by segregation analysis (2,3) and instead present with the multigenic, multifactorial features of complex diseases. Similarly, while twin studies indicate the possible role of a genetic component, concordance rates suggest the influence of other, probably environmental factors. An early family study highlighted a 2.5 times greater tendency for maternal transmission of migraine, which is compatible with cytoplasmic inheritance.

A rare form of migraine, familial hemiplegic migraine (FHM), is a subtype of MA that is autosomal dominant and highly penetrant, and thus the only migraine type with a definite mendelian inheritance pattern (4). 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 re-
recent mapping of another FHM locus on chromosome 1 (locus FHM2) (5) confirms the genetic heterogeneity in FHM. Evidence is growing that the chromosome 19 FHM locus contributes in some way to the more common types of migraine. Since FHM is considered 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 gene/s) has a major effect or whether, instead, it is one of several additive gene effects that is responsible for the genetic component in regular migraineurs. Almost certainly, multiple genes and multiple environmental triggers/factors interact to produce migraine and hence we can expect variability and some degree of overlapping in the migraine phenotypes (the clinical manifestations of the genetic defect). As a result of the clinical complexity and multifactorial etiology of migraine (6), epidemiologic studies have been confused by variable penetrance, environmental factors, lack of definition of the migraine syndromes, and referral bias (7).

HETEROGENEITY IN MIGRAINE

The International Headache Society (IHS) criteria (8) for migraine helped to standardize the definition of phenotypic headache syndromes and provided a reasonable point from which to start the search for eventual correlations with genotypes. It is likely that phenotypic heterogeneity, i.e., the spectrum of clinical expression associated with each genetic mutation, is wide and the same applies to the genetic components. Phenotypic and genotypic heterogeneity is quickly becoming the rule rather than the exception, as we unravel the molecular code of genetically based diseases and undermine the notion of the simple monogenic disorder.

The concept of heterogeneity characterizes migraine attacks and migraine considered as a disease (6). It is common in clinical practice to find widely varying acute migraine phenomena, attributable, for instance, to the presence or absence of the features of aura, to the degree of pain severity, to the occurrence or otherwise of neurovegetative signs and symptoms, and to the drug response in patients. Likewise, aspects of the disease itself can vary, with differences emerging in the age at onset, in the natural history, in the effectiveness of treatments, in the association with other disorders, and in the evolutive potential or outcome of the disease. The heterogeneity of migraine, considered both in terms of “attacks” and as a “disease”, accounts for the observation that most, but not all, of the large population of migraineurs face severe disability and social limitations in their daily lives. Additionally, the phenotypic expression may vary over time. The importance of this phenotypical heterochronia (6) emerges from a simple observation of the natural history of migraine in an individual’s lifetime: in some patients, the phenotypic manifestations remain unchanged over time, whereas in others the clinical picture becomes more complicated, and may include arterial hypertension (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 chronic daily headache forms (“transformed migraine”). The reciprocal links between migraine and the associated diseases remain obscure (9), and the factors affecting the evolution of the clinical picture are also largely unknown. However, it has been clearly observed that migrainous women under 35 years of age have an increased risk of stroke (10) and that the association between migraine and mood disorders becomes closer with age (11).

Additional factors, including environmental and personal 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 found to be significantly higher in all proband subgroups vs unaffected relatives when the probands were categorised by seizure type, age at onset, etiology of epilepsy, and histo-
ry of epilepsy in first-degree relatives. Age-specific incidence of migraine among probands was higher after onset of epilepsy than before. These results indicate that migraine and epilepsy are strongly associated, and that 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 the latter may be allelic or due to closely linked genetic traits. This notion is reinforced by the overlap between FHM and hereditary forms of basilar migraine. Some FHM2 family members have seizures during or around the time of migraine attacks (12). A study of 20 families with benign essential tremor reported that 26% of affected members also co-segregated with migraine with aura (13). 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. Reasonably, this phenotypic heterogeneity is due to the presence of modifier genes as well as environmental influences. Recent and future association studies will aim at identifying the role of the less frequent genes in the more common migraine types.

Despite the complexity of migraine genetics, the future is likely 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: now that the first headache gene has been identified, patients with defined mutations are being removed from the heterogeneous pool of migraineurs: this obviously facilitates subsequent genetic studies.

DOES GENETICS PLAY A ROLE?

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 kinds critically affects the clinical appearance of disease. Recent findings in the field of neurogenetics have deeply changed our approach to migraine, emphasizing the limits of the current diagnostic and nosographic system (8). Indeed, while according to the current IHS criteria subjects who have experienced up to 4 attacks of MOA or only 1 attack of MA cannot be recognized as migraineurs, in the near future, migraine diagnoses may even be made in individuals bearing a given genetic alteration but who are otherwise completely asymptomatic.

The discovery that some migraine forms are characterized by well defined genetic changes is leading to a revision of the pathogenetic hypotheses originally developed on the basis of the psychobiology of interactions between the individual and the environment. In this respect, the concept, developed in the early ’80s, 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”) (7), has been regarded as a reliable model for a number of years. But since the introduction of new criteria for a better phenotypic characterization of migraineurs, the importance of the role of genetics in the mechanisms of migraine has been increasing. There are certainly several aspects to be further elucidated: first, genetic factors do not themselves account for all the clinical forms, migraine remaining a sporadic disease in >50% of cases. Uncertainty also surrounds the mode of inheritance of the familial forms. FHM, for instance, is inherited as an autosomal dominant trait but the presence of genetic determinants on chromosome X may explain the unbalanced females-to-males ratio observed within the same family (14). In most cases, however, migraine occurs as a multifactorial inherited character (15); 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, etc.), generating different clinical forms of the disease. The level of complexity is further increased by the effects of various “modifying” genes (effects that are usually small but significant), of other possible interactions between major genes, and of the preferential expression of the encoded proteins in given cells or systems. Along with environmental determinants, these phenomena may represent the molecular core of the variable clinical expression of migraine, and can be better evaluated in population studies. Such population based association studies must be large, they are subject to the usual biases, and generally test for the contribution of “minor” genes. And the additive effects of these “minor” genes could, conceivably, be important in highly prevalent disorders, such as migraine. Furthermore, the pathogenetic role of candidate gene “polymorphisms” in a particular disorder, which are identified by association studies, must also be established. 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 that can be evaluated using nonparametric methods. Biochemical and pharmacological studies of migraine have long focused on neurotransmitters, neuropeptides and receptors, with much attention being paid to serotonin and vasoactive substances, including neurokinins and nitric oxide. Dopamine may also play a role in the acute migraine attack (16), since many of the prodromal and vegetative symptoms associated with attacks can be reproduced by the administration of exogenous dopamine. Therefore, it seems reasonable to test for genes encoding dopamine receptor subtypes. Similarly, association studies must be performed to evaluate the different genetic components of other stages in migraine pathophysiology (i.e., the role of polymorphisms in ion channels, changes in genetic determinants of the mitochondrial energy producing machinery as well as the various aspects of comorbidity, for example, the affective profile of migraineurs influenced by polymorphisms in the WFS1 gene) etc. It may thus be possible to include migraine among the polygenic diseases identified over recent years.

CONCLUDING REMARKS

Given the recognition of the concept of genetic heterogeneity, it would now appear to be appropriate to speak in terms of common neurobiological mechanisms influencing the full expression of the clinical phenotype. These mechanisms can be identified as deranged brain oxidative metabolism (particularly in cortical-subcortical regions) (17), as abnormal neuronal excitability due to altered membrane ion channels (18), or as 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 (e.g., weather changes, lifestyle) produces a spectrum of manifestations, of which pain and neurovegetative signs and symptoms (typical of the migraine attack) together represent only one aspect, i.e. the tip of the iceberg. In this light, it is not so 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.

It would therefore appear that the clinical-descriptive approach to the patient, requested by the current diagnostic criteria, is based only on a partial understanding of migraine, whose nature is in fact more complex and heterogeneous than previously believed (6). Migraine continues to be a puzzling disease, and any attempt to understand it should always embrace the study of genotype-phenotype-environment interactions:
this will help identify more rational approaches to the management of this disorder and thus wiser therapies.

REFERENCES

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