Migraine as a complex disease: heterogeneity, comorbidity and genotype-phenotype interactions

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Abstract. Migraine is a chronic illness interspersed with acute signs and symptoms, which is currently defined in terms of "attacks" according to HIS criteria. However, this should not lead us to ignore a critical point emerging from the simple observation of patients, i.e. the variability of the combinations in which the disease manifests itself in the same individual and especially in different individuals. This heterogeneity underpins both migraine "as attacks" (e.g. presence/absence of aura, different pain severity) and migraine "as a disease" (e.g. different onset, occurrence, association with other diseases, evolution, outcome). Genetic determinants are certainly at the basis of some migraine forms, and the role of genetics is now increasing due to the 1988 criteria allowing a better phenotypical characterization. In most cases, however, migraine occurs as multifactorial inherited character. The level of complexity is further increased by the effect of "modifying" genes (such as those encoding for dopamine receptors), by comorbidity (the non coincidental association with other neurological diseases), and by the fact that the expression of comorbidity varies over time (phenotypical heterochronia). The clinical-descriptive approach only allows a partial understanding of migraine, the nature of which is more complex and heterogeneous than previously thought.

Key words: channellopathy, comorbidity, genotype, heterogeneity, migraine, phenotype.

L'emicrania come malattia complessa: eterogeneità, comorbidità e interazioni genotipo-fenotipo

Riassunto. L'emicrania è un disordine cronico caratterizzato da segni e sintomi accessuali che sono definiti in termini di "attacchi" dalla vigente classificazione delle Cefalee della International Headache Society (IHS). Ciò non deve tuttavia farci ignorare un aspetto critico che emerge dalla semplice osservazione clinica dei pazienti, e cioè la variabilità con cui la malattia si manifesta nello stesso individuo e soprattutto fra individui diversi. Questo concetto di eterogeneità sottende sia l'emicrania come "attacchi" (ad esempio presenza/assenza dell'aura, differente intensità del dolore) sia l'emicrania come "malattia" (diverso esordio, variabile occorrenza delle manifestazioni, associazione con altre patologie, evoluzione, outcome). Determinanti genetici sono certamente alla base di alcune forme di emicrania, e il ruolo della genetica sta divenendo preponderante grazie alla migliore caratterizzazione fenotipica dei pazienti, resa possibile dai criteri del 1988. Nella grande maggioranza dei casi, tuttavia, l'emicrania si manifesta come patologia ereditaria multifattoriale. Questo livello di complessità è ulteriormente accresciuto dal ruolo dei cosiddetti geni modificatori (come ad esempio quelli che codificano per i recettori della dopamina), dalla comorbidità (l'associazione non casuale con altre patologie), e dal fatto che l'espressione della comorbidità possa variare nel tempo (eterocronia fenotipica). L'approccio clinico-descrittivo consente una comprensione solo parziale dell'emicrania, la cui natura è più complessa ed eterogenea di quanto finora ritenuto.

Parole chiave: emicrania, canalopatie, eterogeneità, genotipo, fenotipo.

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La migraña como enfermedad compleja: heterogeneidad, comorbilidad e interacciones genotipo-fenotipo

La migraña es un trastorno crónico caracterizado por signos y síntomas agudos que actualmente son definidos "ataques", según la clasificación internacional de cefaleas de la International Headache Society (IHS). Esto sin embrago no debería llevarnos a desconocer un aspecto crítico que surge de la simple observación clínica de los pacientes, es decir la variabilidad de las manifestaciones de esta enfermedad en el mismo indiviudo y, especialmente, en diferentes individuos. Esta heterogeneidad implica tanto la migraña como "ataques" (por ejemplo presencia/ausencia de aura, diferente intesidad del dolor), cuanto la migraña como "enfermedad" (inicio diferente, frecuencia variable de las manifestaciones, comorbilidad, evolucción, outcome). Sin duda alguna hay determinantes genéticos que dan origen a algunas formas de migraña, y el papel jugado por la genetica se está volviendo central gracias a la mejor caracterización fenotípica de los pacientes, hecha posible por los criterios del 1988. Sin embargo en la gran mayoría de los casos la migraña aparece como un trastorno hereditario multifactorial. Este nivel de complejidad aumenta aún más si se consideran los papeles jugados por los así llamados genes modificadores (por ejemplo esos genes que codifican para los receptores de la dopamina), por la comorbilidad (la asociación no casual con otras patologias), y por el hecho de que la expresión de la comorbilidad varía con el tiempo (heterocronía fenotípica). El enfoque clínico-descriptivo solo permite una comprensión parcial de la migraña, trastorno más complejo y heterogéneo de lo que se pensaba anteriormente.

Palabras clave: migraña, heterogeneidad, canalopatias, genotipo, fenotipo.

Introduction

Migraine is an extremely common disorder, characterised by the recurrence of painful and non painful episodic phenomena and a wide variety of neurological manifestations. Nosographically, therefore, it is a chronic illness (migraine seen as a "disease") interspersed with acute signs and symptoms (migraine seen as an "attack"). Insights over the past decade have made it possible to depict migraine as an iceberg (Fig. 1). The "tip" of the structure represents the aspects immediately perceived by both the patient and the physician, i.e. the clinical expression (primarily the signs and symptoms of the attack), while the part lying below the surface, certainly much greater than previously thought, denotes those aspects of migraine which are still largely unknown in depth. The mechanisms underlying migraine appear to be increasingly complicated; hence the use of the terms *complex disease* to define the nature of the illness, and *migraine complex* to describe the whole breadth of the clinical (overt) and subclinical (latent) aspects that it encompasses.

The concept of migraine heterogeneity

As a result of strict diagnostic limitations deriving from the criteria established by the International Headache Society (IHS) in 1988 (1), migraine is defined, on the basis of certain fundamental clinical fea-

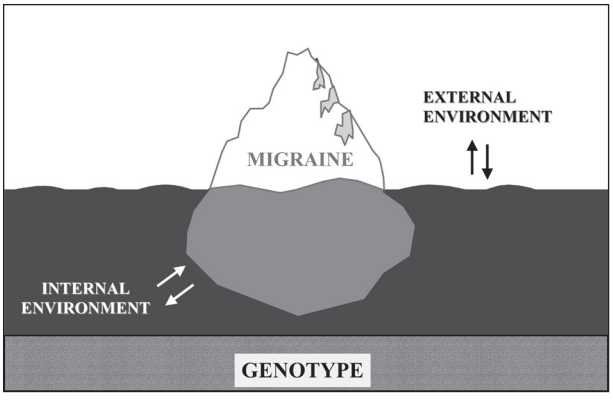

Figure 1. Schematic representation of the concept of the "migraine complex": the tip of the iceberg is made of the clinical phenomena of the migraine attack, whereas the part lying below the surface includes subclinical aspects, most of which are more complex than previously thought and still unknown in depth. The roles of the internal and external environment and that of genotype in affecting the clinical expression of migraine is also reported.

tures, in terms of "attacks". However, this should not lead us to ignore a critical point emerging from the simple observation of patients (clinical phenomenology), i.e. the variability of the combinations in which the disease manifests itself in the same individual and especially in different individuals. This multiplicity of the clinical expression of migraine, or *heterogeneity*, must be borne in mind not only with regard to diagnostic and therapeutic approaches, but also to allow the extension of our knowledge in the field of pathogenetic mechanisms.

The concept of heterogeneity underpins migraine, whether it is regarded in terms of attacks or as a disease. 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, the presence or absence of neurovegetative signs and symptoms, and the response to symptomatic drugs. Similarly, there are variable aspects which characterise migraine *per se*, such as the differences (which may at times be considerable) in the age at migraine onset, in the frequency of clinical disturbances, and in the natural history. Additionally, the pattern of response to various neurobiological tests, the effectiveness of pharmacological and non pharmacological treatments, the association with other disorders, and the evolutionary potential and outcome of disease may be quite variable.

This marked heterogeneity of migraine (of migraine attacks and of migraine as a "disease"), accounts for the observation that the large population of migraine sufferers includes patients living an almost normal life and patients complaining of serious disability (2), i.e. facing social, affective and occupational limitations of varying degrees of severity.

The novel role of genetics

In attempts to elucidate the phenomenon of heterogeneity it must 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 migraine. Recent findings in the field of neurogenetics have altered deeply our approach to migraine, emphasising the limits of the current diagnostic and nosographic system. Indeed, while the current IHS criteria do not allow subjects who have experienced up to 4 attacks of migraine without aura or only 1 attack of migraine with aura to be recognised as migraineurs, in the near future migraine may even be diagnosed in individuals bearing a given genetic alteration who are otherwise completely asymptomatic.

The discovery that some migraine forms are characterised by well defined genetic changes is leading to a revision of the pathogenetic hypotheses originally based on the psychobiological model of the 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" or "terrain") and some to the environment ("triggers" or "precipitating factors"), has been regarded for several years as a reliable model (3). It should be noted that until recently there has been a widespread tendency to overlook the genetic component of migraine, as it is often viewed as an aspect that is difficult to explore and to quantify precisely. This attitude may reflect not only the intrinsic difficulty of research in humans in general, but also the greater importance which experts in migraine phenomenology, using the observational method, generally attach to psychosocial determinants (supposed to be controllable) than to genetic factors (supposed to be non modifiable). Nevertheless, following the introduction of the current diagnostic criteria (1) allowing a better phenotypical characterisation of patients, the importance of the role of genetics in the mechanisms of migraine is now increasing. There are certainly several aspects that merit further elucidation: first, the genetic factors do not themselves account for all the clinical forms, migraine remaining a sporadic disease in over 50% of cases. Uncertainty also surrounds the mode of inheritance of the familial forms, which may present considerable variations. Familial hemiplegic migraine (FHM), for example, is inherited as an autosomal dominant trait, following the classical mendelian rules (4). In addition, the presence of genetic determinants on chromosome X may explain the unbalanced female-to-male ratio observed within the same family (5,6). In

most cases, however, migraine occurs as multifactorial inherited character (7); therefore, different genes or loci may interact with factors intrinsic to the individual (e.g. the hormone milieu) and/or with exogenous factors (e.g. psychosocial stressors related to the family or to the working environment, geoclimatic changes, food), generating different clinical forms of the 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. From this perspective, the finding of a high frequency of association of a NcoI polymorphism in the D2 dopamine receptor gene (DRD2) in migraine with aura (8), or the proposed - though as yet not demonstrated - polymorphisms of the genes encoding for NOS3 and ACE enzymes appear to be extremely relevant (9,10). Likewise, the recently observed (11) preferential expression of class A transcripts of the voltage-dependent P/Q calcium channel subunit at the level of the cerebellum (granular cells and Purkinje cells) may explain the high frequency of cerebellar symptoms in some patients with FHM.

According to the current body of genetic evidence, migraine may thus be included among the polygenic diseases identified in recent years, a representative example of which is syndrome X, i.e. the association between arterial hypertension, non insulin-dependent dibetes mellitus, obesity and dyslipidaemia. This form has been ascribed to genetic factors and to environmental factors in the respective measures of 59% and 41% (12), although some authors maintain that the genetic contribution should be played down, and the role played by environmental exposure emphasised accordingly (13).

Migraine and its comorbidity

Another important aspect of migraine heterogeneity, in close proximity to the field of genetic determinants, is the significant association between migraine and other neurological diseases (such as epilepsy, episodic ataxia, cerebrovascular disorders and stroke, and mitochondrial diseases), psychiatric illnesses (anxiety, mood and personality disorders), and cardiovascular disorders (arterial hypertension, mitral valve prolapse) (14-17). The non-coincidental association of two or more diseases, referred to as *comorbidity*, may result from different mutations in the same gene (allelic disease) or mutations in genes located in neighbouring segments of the same chromosome.

Theoretical models of migraine dating from the pre-genetic era labelled as "migraine equivalents" the areas where migraine attacks and cerebrovascular episodic phenomena (such as TIAs) overlap, and as "depressive equivalents" those conditions in which chronic migraine and mood disorders coexist (3). It would now appear more appropriate to speak in terms of common neurobiological mechanisms influencing the full expression of the clinical phenotype. These mechanisms include deranged brain oxidative metabolism (particularly in cortical-subcortical regions) (18), abnormal neuronal excitability due to altered membrane ion channels (19), or functional changes in receptor components. The interaction of these phenomena with factors intrinsic to the individual (such as sex, age, neuroendocrine reactivity) or environmental factors (occupational elements, 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. From this perspective, it is not so surprising, therefore, that other acute, paroxysmal phenomena of the central nervous system, such as epilepsy, have been associated with migraine (20), even though this has been challenged (21). A significant association with migraine has also been reported in some of the acute disorders that are due to functional changes of neuronal ion channels (channellopathies) (22). These clinical forms are characterised by episodically occurring excess depolarisation of cell membranes producing variable ion channel conductance alterations and hence a modification of the balance between excitatory and inhibitory phenomena (Table 1). For the time being, however, it is unclear whether all migraine forms can be included in the nosographic group of channellopathies (23).

Table 1. Examples of channellopathies with known genetic alterations (* forms associated with migraine)

	Gene / Locus	Product	Molecular alteration
Familial hemiplegic migraine (FHM)*	CACNA1A / 19p	A subunit of P/Q calcium channel	Point mutations
Episodic ataxia type-2 (EA-2)*	CACNA1A / 19p	A subunit of P/Q calcium channel	Prematurely truncated protein
Spino-cerebellar ataxia type-6 (SCA-6)*	CACNA1A / 19p	A subunit of P/Q calcium channel	Pathological expansion of terminal sequence
Benign neonatal epilepsy type-1 (BNE-1)	KCNQ2 / 20q	Voltage dependent KQT-like potassium channel	Point mutations
Benign neonatal epilepsy type-2 (BNE-2)	KCNQ3 / 8q	Voltage dependent KQT-like potassium channel	Point mutations
Congenital Myotonia (Thomsen)	CLC-1 / 7q	CLC-1 chloride channel (muscle)	Point mutations or microdeletions
Hypokaliemic periodic paralysis type II	CACNL1A3 / 1q	Alfa-1 subunit of DHP-sensitive calcium channel (muscle)	Point mutations
Long Q-T syndrome	KCNQ1 / 11p	Voltage dependent KQT-like potassium channel	Point mutations

Heterogeneity of migraine evolution

A further aspect of migraine heterogeneity which appears to be extremely relevant to clinical research is that the phenotypical expression of comorbidity may vary over time. The importance of this *phenotypical heterochronia* emerges upon simple observation of the natural history of migraine in the lifetime of different individuals. The phenotypical manifestations remain unchanged over the years in some patients, while in others the clinical picture becomes more complicated, and may include arterial hypertension (*per se* 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 headache ("transformed migraine") (24).

The reciprocal links between migraine and the associated diseases remain obscure (14). Similarly, the factors affecting the variable evolution of the clinical picture deserve further investigation, although it is likely that age and gender are among the most critical ones. This is suggested by the reported observations that the risk of stroke is increased in young migrainous women under 35 years of age (25) and that the association between migraine and mood disorders becomes closer with increasing age (17).

Concluding remarks

In the light of the above considerations, it would appear that the clinical-descriptive approach to the patient, demanded by the current diagnostic criteria, allows only a partial understanding of migraine, the nature of which certainly appears to be more complex and heterogeneous than previously thought. It is possible to visualise the extremely large population of migraine patients as distributed, according to the clinical appearance of their "migraine", across a broad continuum: cases with familial predisposition or otherwise carrying a genetically determined "vulnerability", but still totally asymptomatic, would lie at one end of this continuum, while at the other we would find those who fully express the phenotype and also present clinical manifestations of comorbid diseases.

Be it an iceberg or a broad continuum, migraine still remains an enigma. However, there is little doubt that the attempts to revise migraine nosography and to identify more appropriate symptomatic and prophylactic treatments will be greatly facilitated by any novel approach wherein the study of genotype-environment interactions is considered of critical importance.

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Nota degli autori

Sono trascorsi molti anni dalla pubblicazione di questo contributo scientifico: in quest'arco temporale sono state numerose le acquisizioni ottenute in tema di fisiopatologia dell'emicrania, grazie soprattutto allo sviluppo delle tecniche di analisi genetica e alla disponibilità di più sofisticate metodiche di neuroimaging. Rispetto allo stato dell'arte descritto nell'articolo, oggi conosciamo infatti almeno altre tre alterazioni genetiche in grado di causare l'emicrania emiplegica familiare (FHM) (1-3), così come ci appaiono meglio definiti i meccanismi sottesi alla cronicizzazione dell'emicrania e sono identificabili alcune variabili individuali strettamente connesse al rischio di questo tipo di outcome (4). Lo stesso modello "poligenico", applicato all'emicrania, sembra oggi cedere il passo ad uno "omnigenico": uno scenario in cui essendo i network di regolazione genica altamente interconnessi, tutti i geni espressi in circuiti cellulari legati alla malattia sono in grado di modulare la funzione dei geni *"core"* per quella malattia, influenzandone così significativamente l'ereditarietà

(5). Rimane tuttavia valida la visione di insieme delineata nel nostro lavoro originale, che vuole l'emicrania come disordine complesso in quanto risultato di quella peculiare integrazione di fattori genetici ed epigenetici che si realizza nel singolo individuo, ma anche come disordine eterogeneo alla luce della sua potenzialità di fenoconversione nel tempo.

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