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Genetics of familial hemiplegic migraine

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Abstract Familial hemiplegic migraine is an autosomal dominant form of migraine with aura, characterized by the occurrence of a motor deficit during the aura. In 20% of families, permanent cerebellar signs (ataxia or nystagmus) are observed. This condition is genetically heterogeneous. A first gene, CACNA1A, located on chromosome 19 and encoding the main subunit of P/Q type neuronal calcium channels, is implicated in 50% of unselected families and in all families with cerebellar symptoms. Thirteen distinct point mutations of CACNA1A have been identified so far in familial and sporadic cases. A second yet unidentified gene located on chromosome 1 is implicated in 20% of the families. One or more other genes are still to be mapped. Various approaches have been used to understand the mechanisms leading from the CACNA1A mutations to hemiplegic migraine, including in vitro electrophysiological studies as well as detailed analysis of the CACNA1A mutant mice tottering and leaner.

Key words Familial hemiplegic migraine • Autosomal dominant • Ataxia • Calcium channel CACNA1A

Introduction

Hemiplegic migraine represents one of the most recent incomers in the growing list of neurological channelopathies. In 1996, missense mutations in the neuronal P/Q type calcium channel α1A subunit gene (CACNA1A) on chromosome 19 were shown to cause familial hemiplegic migraine (HM) [1]. In addition, distinct mutations within CACNA1A were shown to cause two other human autosomal dominant disorders: episodic ataxia type 2 (EA2) and chronic spinocerebellar ataxia type 6 (SCA6) [1, 2]. This paper presents the various clinical patterns and molecular alterations observed in familial as well as in sporadic hemiplegic migraine.

Clinical features

Familial hemiplegic migraine (HM) is an hereditary form of migraine with aura characterized by the presence of a motor weakness during the aura [3]. HM is the only migraine subtype for which a monogenic, autosomal dominant mode of inheritance has been clearly established. Besides the familial forms, some sporadic cases have been reported.

Typical attacks include a unilateral motor deficit associated with paresthesias, speech disturbancies or visual signs [4, 5]. Most patients have a moderate hemiparesis. Bilateral sensorimotor symptoms occur in about 25% of patients [6–9]. These aura symptoms last 10 minutes to a few hours and are followed by a migraine headache. Aura and headache features may be highly variable within a given patient or among patients from a given family [6]. Severe episodes with prolonged aura (up to several days or weeks), consciousness impairment ranging from confusion to profound coma, agitation, fever and meningismus occur in about 40% of the patients [6, 10–13]. A few patients may have seizures during a severe episode. In addition, about 15% of the patients have migraine with non-hemiplegic aura alternating with HM attacks and 34% have migraine without aura [6, 8, 10, 12, 14–16].

Triggering factors are reported by about two-thirds of the patients, the most frequent being stress and minor head

trauma [6, 9]. In several cases, a severe HM episode was precipitated by injection of contrast enhancement products during cerebral or extracerebral angiography [4]. Age at onset is usually between 10 and 15 years, but ranges from 1 to 75 years [17]. Frequency of attacks varies from several per week to only a few in the whole life, with an average of 3–4 per year. In general, the attack frequency decreases after age 20–25 years.

In 20% of unselected families, some HM patients have permanent cerebellar symptoms such as nystagmus and/or mild to moderate ataxia. Ataxia may be diagnosed prior to the first HM attack and progresses independently of the frequency and/or severity of these attacks. In some patients, progressive ataxia is the major clinical feature of the disease. Autonomous gait generally remains possible even after years of evolution [9, 10, 15, 16, 18–22]. Other associated neurological symptoms have been reported in a few HM families or cases: essential tremor [22], Usher's syndrome and cataract [16], cognitive impairment [14] and mental retardation [10, 22].

Diagnosis

The diagnosis of HM is entirely dependent upon obtaining a precise description of the transient neurological episodes and a family history of similar attacks. The major diagnosis problem concerns first, the severe attacks with coma and prolonged aura which are often diagnosed as being meningoencephalitis and second, the sporadic cases.

No specific abnormality on neurological investigations has been described. Cerebrospinal fluid during severe attacks often shows an elevated white cell count (12–290 cells/mm^3) [10]. During attacks, electroencephalography (EEG) shows a diffuse slow wave activity predominating on the hemisphere contralateral to the deficit, which may persist several days or weeks after the attack [23]. Periodic sharp waves [16], or dysrhythmia [12] have been rarely reported. Cranial computed tomography (CT) or magnetic resonance imaging (MRI) performed during a severe attack may show aspects of hemispheric edema. Interictal imaging is normal, except in some HM patients having permanent nystagmus or ataxia, in whom a cerebellar atrophy predominating on the anterior vermis may be observed [10, 18, 20].

Therapy

Due to the relative rarity of this condition, management of HM is mostly based on what is known about treatment of other forms of migraine with aura. Since the demonstration that HM and EA2 were allelic conditions, acetazolamide has been used to prevent HM attacks, with some good results [24]. Symptomatic treatment of HM attacks aims to relieve pain, nausea and vomiting. Vasoconstrictor agents should be avoided, such as ergotamine, dihydroergotamine and triptans. Recently, the use of intranasal ketamine was reported to shorten HM attacks in some patients [25].

Genetic heterogeneity of HM

HM is genetically heterogeneous [19, 21, 26, 27]. The first responsible gene, located on chromosome 19p13.1 [20], was identified in 1996 as CACNA1A and encodes the α1A subunit of P/Q-type voltage-gated calcium channels [1]. CACNA1A is involved, on the basis of linkage or mutation screening data, in all 18 families with HM and progressive cerebellar ataxia (HM/PCA) reported so far [19, 21, 28]. On the contrary, pure HM has been linked to at least three different genes: CACNA1A [1, 19, 20], a second yet unidentified gene mapped on chromosome 1q [11, 27], and a third gene still to be localized [27]. Moreover, an American group found linkage to 1q31 in a large family, whereas linkage to 1q21-23 has been demonstrated in three French families. Further analysis is needed to disclose whether chromosome 1q is the site of one or two HM genes.

Except for cerebellar ataxia which appears to be present only in chromosome 19-linked families, few differences have been found between families linked to different loci. In a study comparing clinical features between 3 chromosome 19-linked families and 2 unlinked families, patients belonging to the former group were more likely to have attacks triggered by minor head trauma and to have severe attacks with unconsciousness [9]. In another study comparing clinical and genetic data between three HM family groups (10 chromosome 19-linked families, 3 chromosome 1-linked families and 4 families unlinked to both loci), two major genotype-phenotype correlations were observed [28]. First, penetrance was much lower in chromosome 1-linked families. Second, associated permanent cerebellar symptoms were observed in 50% of chromosome 19-linked families and in those families only. No significant difference was observed between the three family groups with regard to the characteristics of HM attacks, the occurrence of severe attacks, the existence of other migraine subtypes and the disease course. The incomplete penetrance of HM may account for some of the apparent sporadic cases of HM. Finally, the clinical variability within a given family and the incomplete penetrance suggest that genetic and environmental factors play a role in the expression of the HM phenotype.

CACNA1A and the α1A subunit of P/Q type voltage-gated calcium channels

Mutations in the CACNA1A gene account for about 50% of hemiplegic migraine cases, including all those with cerebellar symptoms. Mutations in this same gene have been shown to cause two other autosomal dominant conditions: episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). EA2 is responsible for paroxysmal attacks of gait ataxia with limb incoordination, dysarthria and nystagmus [29–31]. Acetazolamide responsiveness is a common feature. Between attacks, nystagmus and mild ataxia are often noticed. SCA6 is a late-onset progressive neurological condition responsible for gait and limb ataxia [2, 32–34].

CACNA1A encodes the main subunit of P/Q type neuronal voltage-dependant calcium channel. These channels are responsible for the specific influx of calcium into the neuron in response to membrane depolarization [35, 36]. Six functional subclasses of voltage-dependent calcium channels are defined based on electrophysiological and pharmacological criteria [37]. Two major classes are distinguished: low-voltage activated (T type) and high-voltage activated (L, N, P, Q and R) channels. Calcium channels are multimeric complexes containing a major transmembrane pore-forming α1 subunit associated with smaller auxillary subunits (β, α2/δ and γ) [37, 38]. The α1 subunit, large hydrophobic protein which forms the ionic pore, is responsible for calcium and voltage sensitivity and the channel-gating properties. At least 9 different genes encoding α1 subunits have been identified. These different subunits are responsible for the electrophysiological and pharmacological diversity of calcium currents.

All α1 subunits contain four homologous domains (I to IV), each containing six putative α-helix membrane-spanning segments (S1 to S6). The four domains are linked by intracytoplasmic loops and fold within the cellular membrane to build the ionic pore. Small hydrophobic loops between each S5 and S6 segments are called P-loops (P standing for pore) because they line the inner part of the pore. The P-loops form a specific and dynamic filter for calcium ions. The four S4 segments are responsible for voltage sensitivity.

The CACNA1A gene in humans is localized on chromosome 19p13. The 47 known exons span about 350 kb. The 9.8 kb RNA (including 7800 bp of coding sequence) is almost exclusively expressed in central neurons: heavily in the cerebellum [39–41] but also in the hippocampus, cortex, olfactory bulb, thalamus, hypothalamus and brainstem. It is also expressed in peripheral motoneurons. At the subcellular level, α1A subunits are particularly dense at presynaptic terminals [42].

The α1A subunit, in association with auxilliary subunits, is able to generate, mainly through alternative splicing, the two different P- and Q-type calcium currents. P/Q type channels are expressed in a variety of neurons where they play an important role in the control of membrane excitability, neurotransmitter release and gene expression [36]. At the neuromuscular junction, they control acetylcholine release. P-type currents form 90% of all calcium currents observed in Purkinje cells, whereas Q-type currents are important in cerebellar granular cells (35% of all calcium currents), but also in hippocampal neurons where their preeminant role in glutamatergic neuronal transmission has been established.

CACNA1A mutations and genetic screening

Thirteen CACNA1A mutations have been identified so far in 25 families and two sporadic cases affected by HM [1, 24, 43–48]. All these mutations are missense mutations, changing a single amino-acid in the whole protein. All are located within exons coding for S4 to S6 segments. T666M, a predominant substitution, was detected in 10 of 25 families and in one sporadic case. This genetic defect was demonstrated to arise through recurrent mutation events and to be specifically associated with the presence of a permanent cerebellar ataxia [44]. Three other recurrent mutations (R583Q, R1667W and I1811L) have been also identified in HM with ataxia. A *de novo* mutation was shown to cause a severe form of HM with ataxia in one sporadic case [47]. Six of these identified mutations are associated with pure HM [1, 49].

In EA2, 11 different CACNA1A mutations have been identified in seven families and four sporadic cases [1, 50–52]. Ten of these mutations are predicted to lead to truncated or aberrant α1A subunits. In addition, a missense mutation was detected in a single family in which patients suffered from both paroxysmal episodes indistinguishable from those observed in EA2 and a rapidly progressive and severe permanent ataxia [53].

SCA6 is caused by small expansions of a CAG repeat, located within the 3' end of CACNA1A and predicted to code for a polyglutamine tract in three of the six known human splice variants [2]. Surprisingly, CAG expansions were identified in three families with paroxysmal and permanent progressive ataxia [32, 54].

Diagnostic genetic testing is now theoretically possible in HM. However, mutations are located all over the coding sequence of the gene. Screening for the T666M substitution, which is present in about 50% of families affected by HM and cerebellar ataxia, is one possibility. New methods providing time- and cost-effective mutation detection are needed for the routine screening for CACNA1A mutations in HM.

Genotype-phenotype correlation in HM due to CACNA1A mutations

Both the pure form of HM and that associated with cerebellar ataxia are caused by missense mutations in important functional domains of the channel (segments S4 to S6 and P-loops). However, the mechanisms by which a given mutation causes cerebellar symptoms in addition to HM are unknown.

One important issue is the high clinical variability observed within given HM families having the same mutation. This variability concerns both episodic symptoms (hemiplegic migraine attacks) and permanent symptoms. This profound variability suggests that factors other than the sole CACNA1A mutation are important to produce the clinical phenotype. Genetic or environmental factors may play a role. With regards to allelic modifying factors, two studies found no role of the length of the intragenic CAG repeat on the severity of episodic as well as permanent symptoms in HM with ataxia [44] and in EA2 [50].

Molecular aspects of functional disturbances

In order to understand the mechanisms leading from CACNA1A mutations to the various observed phenotypes, various approaches are currently used including electrophysiological studies and analysis of mutant animals.

Altered calcium current kinetics

Seven of the CACNA1A mutations causing HM (R192Q, R583Q, V714A, D715E, T666M, V1457L and I1811L) have been investigated for their putative effects on α1A calcium currents [55–57]. In these studies, calcium currents were compared in cells expressing wild type and mutant CACNA1A. All analyzed mutations altered the calcium current kinetics. The changes mainly concerned the gating properties including the time course of inactivation.

Animal models for CACNA1A disorders: the tottering and leaner mutant mice

Two recessive mutations in the murine homolog of CACNA1A have been identified to be responsible for the tottering and leaner phenotypes [58].

Tottering mutant mice have paroxysmal and permanent neurological symptoms. They have absence epilepsy, rare motor seizures, and moderate cerebellar ataxia without cerebellar atrophy. Electron microscopy disclosed some shrunken Purkinje cells. In addition, tottering mice have an abnormal synaptogenesis of noradrenergic fibers in the locus coeruleus and an abnormal persistent expression of tyrosine hydroxylase (TH) in Purkinje cells (TH is normally expressed from the third to the fifth weeks) [59]. The tottering mutation (C1802T; Pro601Leu) [58] is located a few bases from the T666M mutation causing HM with ataxia. Tottering mice display abnormal acetylcholine release at neuromuscular junctions, a function which is regulated by P/Q-type calcium channels [60].

The leaner phenotype is also transmitted as an autosomal recessive trait. Like tottering mice, leaner mice have absence epileptic seizures and persistant TH expression in Purkinje cells. They develop severe cerebellar ataxia and their life span is reduced. Histological examination showed a dramatic loss of Purkinje cells and granular and Golgi neurons. The leaner mutation alters a CACNA1A splice site and induces the production of two aberrant transcripts [58]. It was recently shown by whole-cell recording of Purkinje neurons from leaner mice, that P-type currents, normally representing 85% of all calcium currents, were reduced by 65% [61].

CACNA1A and hemiplegic migraine: from genotype to phenotype

To date, our knowledge is not sufficient to propose detailed hypotheses. Channels formed by α1A subunits have specific functions in specific neurons, of which only some could be modified by a given mutation. These functions could be the development of specific neuronal populations, the control of specific gene expression or the neurotransmission in some peculiar neuronal pathways. This hypothesis is underlined by the remarkable neuronal phenotypic restriction in the tottering and leaner mice. This restriction, which may appear to contradict the large expression of α1A subunits throughout central and peripheral neurons, favors the hypothesis of a specialization of the various α1A channels. HM-causing CACNA1A mutations alter the gating properties of calcium channels involved in neurotransmitter release. Tottering mice exhibit abnormal neurotransmitter release at the neuromuscular junction. These observations suggest that hemiplegic migraine may be caused, at least in part, by abnormal neurotransmitter release.

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