Chapter 61

# Sporadic and Familial Hemiplegic Migraines

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## FAMILIAL HEMIPLEGIC MIGRAINE

### Definition

**International Headache Society (IHS) code and diagnosis:** 1.2.4 Familial hemiplegic migraine
**World Health Organization (WHO) code and diagnosis:** G43.1×5 Familial hemiplegic migraine
**Short description (Headache Classification Committee, 2004):** Migraine with aura including motor weakness and where at least one first- or second-degree relative has migraine with aura including motor weakness
**Previously used terms:** Complicated migraine

### Epidemiology

Since the first description in 1910 (13) up to today, about 150 highly selected families affected by familial hemiplegic migraine (FHM) have been described worldwide (1–3,5–7, 9,10,12,14–16,18,21,23–27,30,31,34,35,37,38,40,46–48,50, 51,53–55,59–62,66–69,71,72,75,77,79,81,84,85,87,98,100–103,106). Due to difficulties using traditional population-based methods when studying the prevalence of a rare disorder, the true prevalence of FHM is still unknown. Only recently a systematic nationwide epidemiologic survey of the entire Danish population of 5.2 million inhabitants estimated the prevalence of FHM to be 0.005% in 1999 in Denmark (88). Despite some limitations in the applicability of the statistical method used, known as capture–recapture, the study may provide a useful approximation of the number of affected subjects.

Published descriptions of families have enabled two clinical forms of the disorder to be distinguished: "pure FHM," in which the neurologic examination of all affected patients between two attacks is strictly normal, and "FHM with permanent cerebellar signs," in which at least one member has nystagmus or ataxia during attack-free intervals. The percentage of families affected by FHM with permanent cerebellar signs is close to 20% in the literature (2,3,5,12,14,18,19,25,27,30,37,46,47,53–55,66,71,72,79,81,83,84,100,102,106). This percentage is probably overestimated due to several publication biases, including the interesting character of this association and the fact that the first FHM gene to be localized and identified was responsible for the majority of FHM cases with cerebellar signs. In a systematic nationwide epidemiologic survey of the entire Danish population, 44 FHM families were identified, including only 2 with cerebellar signs (4.5%). (87) The true prevalence of FHM families with cerebellar signs is most likely less than 20%.

Besides the familial form of HM, sporadic cases of HM exist (see next chapter).

### Genetics

FHM is the only migraine subtype for which a monogenic mode of inheritance, autosomal dominant, has been clearly established. Like other autosomal dominant conditions, FHM affects males and females equally and is transmitted by fathers as well as mothers to 50% of their offspring. Penetrance of the condition is incomplete: not all mutated gene carriers have FHM (18,20,23), as demonstrated by a pair of monozygotic twin sisters (20). The twins were discordant for FHM, and the unaffected sister had a son with hemiplegic migraine. This incomplete penetrance has several implications for clinicians as well as for geneticists. First, an affected individual may have no first- or even second-degree affected relative, making it difficult to diagnose familial hemiplegic migraine. Second, an asymptomatic family member may have affected children. Third, in the mapping of FHM genes, only affected recombinants should be considered. Finally, the incomplete penetrance suggests that modifying genetic or environmental factors play a role in the expression of the FHM phenotype.

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FHM is genetically heterogeneous and at least three different genes exist (16,23,71). The first responsible gene, CACNA1A (71), mapped on chromosome 19p13 (46), is involved in approximately 50% of unselected families (FHM1) and in the vast majority of families with permanent cerebellar signs (47,72). The second gene, ATP1A2 (16), mapped on chromosome 1q21–q23 (23,31), is involved in about 20% of FHM families (FHM2) (23). Finally, about 30% of FHM families are unlinked to the chromosome 19 FHM1 locus and to the chromosome 1 FHM2 locus, demonstrating the existence of at least a third gene (23).

### FHM1 and CACNA1A Mutations

CACNA1A, the FHM1 gene, encodes the pore-forming $\alpha$1A subunit of P/Q-type voltage-dependent neuronal calcium channels (71). These calcium channels, also called $Ca_v2.1$ channels, are expressed exclusively in neurons from the central as well as the peripheral nervous system. They play a major role in the control of neurotransmitter release (including glutamate), postsynaptic calcium fluxes, and neuronal excitability. A total of 15 different CACNA1A mutations have been identified in 38 FHM1 families (including 29 with cerebellar signs) and in 4 sporadic cases (2,5,10,18,19,30,32,53,54,71,81,82,95,100). Five of these mutations (S218L, R583Q, T666M, R1668W, and I1811L) were recurrent in the absence of any founder effect. The most frequent mutation, T666M, was found in half the families and sporadic cases. All these mutations are missense mutations altering important functional domains of the predicted protein.

The consequences of FHM1 mutations have been studied by electrophysiology and by the analysis of mutant mice. Seven FHM1 mutations (R192Q, R583Q, V714A, D715E, T666M, V1457L, and I1811L) have been investigated so far to detect their putative effects on $Ca_v2.1$ currents (39,56,57). In these studies, calcium fluxes were compared in cells expressing wild-type and mutant CACNA1A. All analyzed mutations induced a lower activation threshold and an increased opening probability of $Ca_v2.1$ channels. FHM1 mutations are thus "gain-of-function," responsible for an enhanced calcium influx through single $Ca_v2.1$ channels. No difference was observed between mutations associated with pure FHM and mutations associated with FHM and permanent cerebellar signs. However, in vitro experimental conditions probably do not reflect the complexity of the situation in vivo.

CACNA1A knockout mice are born with severe ataxia and die within a few days (29). These mice have no P/Q-type calcium currents. Mice with various recessive CACNA1A mutations display different phenotypes called tottering, leaner, or rocker, characterized by the association of various paroxysmal manifestations (absence epilepsy, motor attacks) with a permanent cerebellar ataxia of variable severity (28,107). Tottering mice have an abnormal control of acetylcholine release at the neuromuscular junction (74). Leaner mice have a decrease in depolarization-induced glutamate release with almost no changes in $\gamma$-aminobutyric acid (GABA) (4). Leaner mice also have an increased threshold for initiating cortical spreading depression (CSD) and a slower propagation of CSD (4). Knocking mice with the FHM1 mutation R192Q display an increased cerebellar $Ca_v2.1$ current, increased neuromuscular transmission, and a lowered threshold for initiating CSD with a higher velocity of CSD propagation (97). This mutant mouse represents the first animal model of FHM. Altogether, these different abnormalities suggest that the increased susceptibility to initiate CSD and aura in FHM are due to cortical hyperexcitability.

Finally, mutations in CACNA1A cause two other autosomal dominant conditions: episodic ataxia type 2 (EA2) (71) and spinocerebellar ataxia type 6 (SCA6) (105). EA2 is responsible for paroxysmal attacks of gait ataxia with limb incoordination, dysarthria, and nystagmus (17,96). Acetazolamide responsiveness is a common feature. Between attacks, nystagmus and mild ataxia are often noted. EA2 is due to missense or truncating mutations within the CACNA1A gene, which are responsible for a loss of function, the mutated channels being unable to generate any calcium current (17,36). SCA6 is a late-onset progressive neurologic condition responsible for gait and limb ataxia. 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 (105).

### FHM2 and ATP1A2 Mutations

ATP1A2, the FHM2 gene, encodes the catalytic subunit of Na+/K+ ATPase. This pump is expressed mainly in neurones in neonates and mainly in astrocytes in adults. The pump utilizes ATP hydrolysis to actively maintain the sodium gradient across the cell membrane. A total of 12 different ATP1A2 mutations have been identified in 12 families and 1 sporadic case (R763H) (16,33,48,51,98). One mutation was found in two unrelated families (33,48). In another family with the R689Q mutation, FHM was found to be associated with benign familial infantile convulsions; all family members affected by FHM, infantile convulsions or both, had the R689Q mutation (98). Electrophysiologic studies have shown that FHM2 mutations induce a loss of function with a complete inhibition of pumping activity in cells expressing the mutated gene (16).

In addition, a novel ATP1A2 mutation (T378N) has been identified in a family affected by a disease showing features of FHM associated with alternating hemiplegia of

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childhood, hemiplegic and quadriplegic spells, headache, hemidystonic spells, paroxysmal ocular abnormalities, generalized tonic-clonic seizures, cognitive impairment, autonomic involvement of the affected limb, and flunarizine responsiveness (80).

## Pathophysiology

The mechanisms leading from CACNA1A or ATP1A2 mutations to hemiplegic migraine attacks are still unknown; however, most agree that the clinical presentation (phenotype) is the result of an inherited susceptibility (genotype) that is strongly modulated by both internal and external environmental factors. According to the main hypothesis, migraine is a continuum with migraine without aura at one end and familial hemiplegic migraine at the other end. Mechanisms underlying attacks of FHM are thus thought to be closely related to those underlying attacks of migraine with typical aura: sustained CSD for the aura phase and activation of the trigeminovascular system for the headache phase. Moskowitz et al. (64) recently suggested that FHM mutations render the brain more susceptible to prolonged CSD caused by either excessive synaptic glutamate release (FHM1) or decreased removal of glutamate and $K^+$ from the synaptic cleft (FHM2). By accepting this hypothesis, it is theoretically possible to comprehend how a gain-of-function mutation (FHM1) and a loss-of-function mutation (FHM2) expressed in distinct cell types and encoding different ion channels fluxing either monovalent or divalent cations generate a remarkably overlapping migraine phenotype.

## Clinical Features

**IHS diagnosis criteria for familial hemiplegic migraine** (Headache Classification Committee, 2004) (43):

**A.** At least two attacks fulfilling criteria B and C
**B.** Aura consisting of fully reversible motor weakness and at least one of the following:
  **1.** Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision)
  **2.** Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
  **3.** Fully reversible dysphasic speech disturbance
**C.** At least two of the following:
  **1.** At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes.
  **2.** Each aura symptom lasts ≥5 minutes and <24 hours.
  **3.** Headache fulfilling criteria B through D for 1.1 Migraine without aura begins during the aura or follows onset of aura within 60 minutes.
**D.** At least one first- or second-degree relative has had attacks fulfilling these criteria A to E.
**E.** Not attributed to another disorder. History and physical and neurologic examinations do not suggest any of the disorders listed in groups 5 to 12, or history and/or physical and/or neurologic examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

FHM is a migraine with aura characterized by the presence of a motor weakness during the aura (7,101). Since the first description by Clarke in 1910 (13), more than 150 families have been reported in the literature. Their clinical description, when available, strongly suggests a high variability in the HM attacks' symptoms and the disease course among the patients.

### *Migraine Attacks*

Trigger factors are reported by about two-thirds of the patients, the most frequent being stress and minor head trauma (18,31,83). Less then 10% of patients point out triggers of other forms of migraine, such as dietary factors, visual or auditory stimulation, climatic factors, and menstruation (18). In several cases, a severe HM episode was precipitated by injection of contrast enhancement products during cerebral or extracerebral angiography (6,7,18,48). Finally, attacks occur spontaneously in one-third of patients.

During the HM aura, motor weakness is always associated with at least one other aura symptom. The most common other aura symptoms are sensory disturbances (98%), visual symptoms (89%), and speech disturbances (79%) (18,87). In addition to these four main symptoms, 55 to 69% of the patients have basilar-type symptoms fulfilling the IHS criteria (1988) for basilar migraine (38,87). The aura usually starts with progressive sensory or visual symptoms, weakness and language disturbances rarely being inaugural. The degree of motor deficit is highly variable, ranging from mild clumsiness to total hemiplegia. Most patients report a moderate hemiparesis. Sensory disturbances, such as paresthesias or numbness, are often a major aura feature. Sensory-motor symptoms may be unilateral or bilateral. When one-sided, they involve at least the upper limb and may "respect" the lower limb and the face. Attacks may alternatively be right- or left-sided or involve always the same side in 40 to 59% (18,87). Bilateral symptoms occur in about 25 to 49% of patients, one side after the other or both sides simultaneously (18,38,87). Speech disturbances are frequently part of the aura, independent of the affected side. Various combinations of dysarthria, reduced speech fluency and, less often,

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paraphasias occur. Comprehension impairment is rare (10%). Visual signs are also frequently reported and consist in various combinations of hemianopia, scintillating scotoma, flickering light, zig-zag lines (fortification), and blurred vision. Other basilar-type aura symptoms often occur, such as lack of balance, diplopia, tinnitus, partial hearing loss, drop attacks, confusion, or loss of consciousness (38,87). The mean gradual progression time of the motor, sensory, and visual aura symptoms were, respectively, 27, 32 and 16 minutes (87). Duration of aura ranges from 10 minutes to several days (average: 1 to 6 hours) (18,87).

Headache onset generally follows the aura but may be at the onset or start of the aura. The pain may be unilateral or bilateral. If one-sided, it may be ipsilateral or contralateral to the weak limbs. Not infrequently, the pain will switch sides or become bilateral during the attack. Duration of headache is highly variable, lasting from 1 hour to 6 days (average: 24 hours). All degrees may be observed from moderate discomfort to excruciating pain. During FHM attacks, 95% of the patients always experience a headache, 4% sometimes experience a headache, and 1% never experience a headache (87). Associated autonomic signs and symptoms are indistinguishable from those accompanying any form of migraine and include nausea and vomiting, photophobia and phonophobia, and pallor.

In addition to usual episodes, up to 40% of the patients will have one or more atypical attacks (18,25,27,31, 48,54,66,67). Those atypical episodes may consist of hemiplegic migraine with prolonged aura up to several days. More dramatic episodes are characterized by impaired consciousness ranging from confusion or somnolence to profound coma with respiratory failure, associated or not with the usual aura symptoms, fever up to 41°C, and meningismus. Some of these patients need artificial ventilation over several days. In addition, some patients may have partial or generalized epileptic seizures during those episodes (24,53). More than 50% of those severe attacks occur before the age of 20. They represent the first FHM-related neurologic episode in up to 20% of cases and are often triggered by minor head trauma (18). Conventional angiography triggered or worsened several of the severe attacks. Duration of symptoms ranges from several days to several weeks in some rare cases. Whatever their severity, the symptoms usually entirely resolve within a few days or weeks. In some rare cases, complete recovery is achieved only after a few months. Rare cases have been reported of persistent confusion associated with visual and auditory delusions following HM attacks (79); a few cases of death during a severe attack of FHM also have been published (27,53,54,67). Patients having a severe attack with coma should be managed in an intensive care unit; these cases should be investigated to rule out other causes (mainly infectious meningoencephalitis).

Other forms of migraine may co-occur with FHM. Previous studies of selected families have shown that about 15% of the patients have migraine with nonhemiplegic aura alternating with HM attacks and 34% have migraine without aura (18,26,27,37,38,44,61,69,102). However, recently it was shown that both probands with FHM and their first-degree relatives have a highly significant increased risk of migraine with nonhemiplegic aura in comparison with the general population. Neither FHM probands nor their first-degree relatives have an increased risk of migraine without aura compared to the general population (90).

All those hemiplegic migraine features are not stereotyped. Order of onset, progression, topography, intensity, and duration of the various aura symptoms may vary from one attack to another within a given patient, as the various headache features may vary. Moreover, those features may be highly variable among patients from a given family (18) and quite similar in affected members from other families (35).

### Associated Neurologic Symptoms

Permanent cerebellar symptoms are found in about 20% of selected FHM families published in the literature and 4.5% (2/44) of nonselected FHM families (87). All FHM families with permanent ataxia analyzed so far were linked to CACNA1A mutations. Within these families, cerebellar symptoms cosegregate with FHM but have a lower penetrance; nystagmus (gaze-evoked horizontal, vertical, or multidirectional) is found in about 75% of FHM patients and slowly progressive mild to moderate statokinetic ataxia in about 40% of the patients (18). Nystagmus and other abnormal ocular motility findings are most likely the first symptoms of the progressive cerebellar syndrome (25). Some subjects will later develop ataxia. Autonomous gait remains possible even after years of evolution. Age of onset of those cerebellar symptoms is difficult to predict. Nystagmus and ataxia may begin prior to the first HM attack (18,102) but are not correlated to the frequency and the severity of HM attacks. Moreover, cerebellar signs may represent the sole manifestation of the disease in the absence of any HM attack (2,18). Computed tomography (CT) or magnetic resonance imaging (MRI) scans in some of those patients reveal cerebellar atrophy affecting mainly the anterior part of the vermis (25,27,37).

Other associated neurologic symptoms have been reported in a few FHM families: essential tremor (18,106), Usher syndrome and cataract (102), cognitive impairment (53,61), and mental retardation (12,27,48,106). Epilepsy seems to be more frequent in FHM patients than in the general population, with seizures occurring either during FHM attacks (23,24,55) or apart (12,48,85). A family in which FHM is associated with benign familial infantile convulsions has been described (85,98).

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### *Genotype–Phenotype Correlations in FHM*

FHM is characterized by an important clinical variability; age of onset, frequency and duration of attacks, aura features, and headache characteristics may vary from one patient to another even among affected members from a given family who are carrying the same mutation in the same gene (18,84). This variability suggests complex interactions between the consequences of the FHM-causing mutation and modifying environmental or genetic factors. Several studies have shown that the various genotypes play a role in producing this clinical variability.

The phenotype may vary depending on the different causative genes (FHM1, FHM2, or another gene). Two studies were conducted prior to identifying the FHM genes based on linkage analysis to the 19p13 FHM1 and 1q21-q23 FHM2 loci. In a study including five families, the clinical features of 46 patients from three chromosome 19-linked families (FHM1) were compared to those of 20 patients from two unlinked families (83). FHM1 patients had a higher frequency of attacks with loss of consciousness (39% vs. 15%) and head trauma–triggered attacks (70% vs. 40%) (83). In a study including 17 families, the clinical and genetic features of FHM were compared between three groups of families: 10 families linked to chromosome 19 including 94 patients (FHM1), 3 families linked to chromosome 1 including 24 patients (FHM2), and 4 unlinked families including 24 patients (21). No difference was observed with regard to the symptoms of attacks, the frequency of severe attacks with impairment of consciousness, the frequency of other varieties of migraine, and the evolution of the disease. Two major differences were shown; the penetration was lower in FHM2 families ($p < 0.001$) and permanent cerebellar symptoms were present in a subset of FHM1 families and were not seen in the other family groups (22). As of yet, no large study comparing FHM1 patients with CACNA1A mutations to FHM2 patients with ATP1A2 mutations has been published. However, when comparing the clinical spectrum between published cases of FHM1 and FHM2, no significant difference can be found with regard to the characteristics of HM attacks, the occurrence of severe attacks, the existence of other migraine subtypes, and the disease course. FHM1 is characterized by a high frequency of associated permanent cerebellar signs, including nystagmus and ataxia, and as has been stated previously, all FHM families with permanent cerebellar signs were linked to CACNA1A (FHM1) mutations. With regard to new data concerning patients with ATP1A2 (FHM2) mutations, this genotype–phenotype correlation seems less clear cut. Indeed, subtle cerebellar signs excluding ataxia but including nystagmus and dysarthria have also been reported in a few members of FHM2 families (12,48). Data concerning penetrance of FHM2 are controversial, with one study suggesting a lower penetrance in FHM2 than in FHM1 (22) whereas another study (48) found a high (90%) penetrance in FHM2. Finally, FHM2 seems to be associated with an increased frequency of epilepsy including seizures during severe FHM attacks or various types of seizures occurring in addition to HM attacks (12,23,24,48,85,98).

Clinical variability may be observed also among subjects having mutations in the same FHM gene. Striking correlations between genotype and phenotype have been shown in patients with CACNA1A mutations. The frequency of symptoms was studied in the 85 subjects with the three most frequent mutations out of a series of 117 patients (18). Those three mutations were linked to FHM with cerebellar signs: T666M (55 subjects), R583Q (16 subjects), and D715E (14 subjects). Several significant differences were observed. Subjects with T666M had the highest penetrance of hemiplegic migraine (98%), severe attacks with coma (50%), and nystagmus (86%). Subjects with R583Q had the highest penetrance of gait ataxia (81%) in the absence of any nystagmus. Subjects with D715E had the lowest penetrance of hemiplegic migraine attacks (64%). The existence of different CACNA1A mutations partly accounts for the clinical variability.

### *Neurologic Investigations*

Cerebrospinal fluid (CSF) abnormalities during FHM attacks have been described in about 20 patients; most patients had attacks with impaired consciousness. The white cell count (around 12 to 290 cells) was elevated, while glucose levels were always normal and protein levels were either elevated or normal (65,78). During attacks, the electroencephalogram was always abnormal, showing a diffuse slow wave activity predominantly over the hemisphere contralateral to the limb weakness (58,61,99). Other abnormalities were reported rarely, including periodic sharp waves (34) and dysrhythmia (35,66), persisting several days or weeks after an attack. Isolated case studies using transcranial Doppler have been reported; during one attack (right hemiplegia and aphasia) in one patient, diffuse vasoconstriction of the vessels at the base of the skull and of small arteries within the hemisphere contralateral to the limb weakness was demonstrated (73).The few CT scans performed during or just following an HM attack were all normal with the exception of hemispheric edema during a severe attack with coma and fever in one patient (27). The majority of CT scans performed in interictal periods also have been normal, but 25% showed cerebellar atrophy. Cerebellar atrophy has been found only in patients having FHM with permanent cerebellar signs.

A recent study using serial MRI found cerebral edema, dilation of intracerebral vessels, and decreased water diffusion contralateral to the hemiparesis, not respecting vascular territories, with subsequent complete resolution of both clinical and imaging abnormalities (9). Previously, only a few studies had been reported: MRI was normal in a

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patient having permanent cognitive dysfunction (61) and disclosed cerebellar atrophy in patients with nystagmus and ataxia (2,25,27,37,88,100).

Cerebral angiography performed during or after an attack was normal, except for two reports of arterial diameter changes during one HM attack (basilar artery spasm (45) and narrowing of the middle cerebral artery contralateral to the hemiplegic side (106). Angiography does not support neurologic symptoms being due to spasm or arterial occlusion. In addition, angiography may be unsafe in FHM patients, being responsible in 60% of the cases for the onset or for the aggravation of attacks associated with fever, prolonged aura, and coma (6,7,18,48).

A single patient was shown on an ictal single photon emission computerized tomography (SPECT) scan to have decreased perfusion in the parietooccipital region and the opposite cerebellar hemisphere, consistent with crossed cerebellar diaschisis (62). Finally, Uncini et al. (94) found spectroscopic magnetic resonance abnormalities of muscle and brain in several patients from the same FHM family, suggesting a mitochondrial dysfunction.

## Course and Prognosis

Age of onset is usually between 10 and 18 years old. In the Danish population-based study of FHM, mean age at onset was 17 years (95% confidence interval (CI): 15 to 18; range 1 to 45) (87). Almost 250 FHM patients with an identified CACNA1A or ATP1A2 mutation have been published with detailed clinical data: Their mean age at onset was lower than noted above, close to 12 years (range 1 to 56). Onset before 5 years old is not infrequent, and one initial attack of hemiplegic migraine in a 75-year-old patient has been reported (75).

The frequency of attacks varies from several per week to only a few throughout life, with an average of three or four per year. In some patients, this frequency may range from daily attacks, usually in the first years of evolution, to years-long free intervals (18). Despite the recurrent episodes of hemiparetic aura, full recovery between attacks is the rule. In a few patients, speech disturbances, moderate concentration, and memory impairment may persist several weeks after one HM attack before complete recovery. In many individuals approaching adolescence or early adult life, attacks become less frequent and weakness less severe; in some, however, hemiplegic episodes are lifelong.

## Diagnosis of FHM and SHM

The diagnosis of FHM is entirely dependent upon obtaining a family history of similar attacks. Due to the incomplete penetrance of FHM, the familial investigation has to concern not only first-degree but also second-degree relatives. In the absence of such a history, the diagnosis of hemiplegic migraine cannot be eliminated; the patient may be affected by sporadic hemiplegic migraine (SHM). Moreover, a single attack of migraine with motor aura may occur once in a patient usually suffering from other forms of migraine attacks (migraine with typical nonhemiplegic aura or migraine with aura). The relationship between these latter cases and FHM or SHM is unknown.

### *Differential Diagnosis*

Attacks of hemiplegic migraine may be part of the clinical spectrum of several hereditary neurologic conditions whose prognosis is radically different from that of FHM, for example, various cerebral arteriopathies such as CADASIL (42) and amyloid angiopathy (93) or some mitochondrial encephalopathies such as MELAS (63). A personal or a family history of permanent neurologic deficit, stroke, seizures, or dementia should prompt the search for conditions other than FHM. Moreover, permanent interictal abnormalities other than ataxia or nystagmus should warrant further diagnosis. Patients with severe attacks of HM with confusion, coma, or fever may not be easily distinguished from patients with meningoencephalitis.

### *Indications and Limits of the Molecular Diagnosis*

The main indications for a genetic diagnosis of HM should be atypical forms:

**1.** Nonfamilial cases with a clinical picture consistent with SHM but having very severe attacks (recurrent coma, seizures) or with permanent neurologic signs other than nystagmus or ataxia (epilepsy, mental retardation, cognitive impairment) (95).

**2.** Atypical familial cases (compared to the other affected family members) because of severity or unusual neurologic features. In such cases, identifying a mutation in CACNA1A or ATP1A2 will establish the diagnosis. By contrast, identifying a mutation will neither modify the treatment options nor change the management of recurrent severe attacks for which a minimal workup (cerebral imaging and CSF examination) is necessary to rule out other causes.

Presymptomatic and prenatal genetic testing should be avoided in FHM for several reasons: First, this condition has a general very good prognosis; second, no prognosis concerning severity of FHM can be made for a single patient because of high clinical variability among subjects with the same mutation; third, there is no effective treatment that prevents development of HM or associated neurologic symptoms.

Mutation screening of both known causative genes (CACNA1A and ATP1A2) may thus be useful in atypical cases of FHM or SHM, although screening is of incomplete

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sensitivity and specificity. Sensitivity is low (about 60%) because the two known genes (CACNA1A and ATPIA2) are implicated in only 60 to 70% of all FHM cases and the techniques cannot detect all mutations. Specificity is also incomplete because a mutation in CACNA1A or ATP1A2 may be a rare nonpathogenic polymorphism. In familial as well as in sporadic HM, the diagnosis will be definite if the detected mutation has been identified already in other cases of FHM or SHM. It is thus important that genetic labs publish the new variants they identify. Several conditions have to be fulfilled before accepting a newly detected variant as the responsible mutation for the disease: its absence in a large control population and alteration of an important functional domain of the predicted protein. In addition, a definite diagnosis in familial forms requires that the mutation is cotransmitted with the disorder within the family. In sporadic HM, a de novo mutation must be absent in both parents (with verification of paternity). Thus, it is important to analyze the index case and parents in SHM as well as in FHM. Finally, a negative screen does not have predictive value or rule out the diagnosis.

## Management of FHM and SHM

Treatment can be preventive or symptomatic. In most patients, the HM attacks are so infrequent that prophylactic therapy is not considered, but is used only when other types of migraine attacks are so frequent or so severe in the same patients as to cause significant disruption of activities. In younger subjects, the HM episodes may be sufficiently frequent to warrant prevention; the relative rarity of FHM has precluded detailed reporting of a large series of patients, however. Thus, the therapeutic options for either form of HM arise from anecdotal accounts or from larger series of migraine subjects with various nonhemiplegic manifestations. Thus, management of FHM is mostly based on what is known about treatment of other forms of migraine with aura.

### *Abortive Agents*

Intranasal ketamine was used to reduce severity and duration of neurologic symptoms during attacks of familial hemiplegic migraine in 5 of 11 patients (50). Two with SHM were administered 0.4 mg naloxone intravenously, which aborted the neurologic symptoms within 2 minutes but not the pain (11). One patient with FHM received intravenous verapamil, with resolution of all symptoms in minutes (103). The role of ergotamine and dihydroergotamine in migraine with hemiparetic aura is controversial. While Heyck (41) reported that the intravenous administration of dihydroergotamine on multiple occasions shortened the episodes of hemiparesis in one patient and did not result in any permanent deficit, Tfelt-Hansen et al. (86) showed that ergotamine caused a minor degree of constriction of cerebral arteries in young healthy male volunteers; most clinicians feel it prudent to avoid ergotamine and dihydroergotamine in migraine with a prolonged or a motor aura. Triptans have been used without side effects in a few cases of FHM, basilar migraine, and migraine with prolonged aura (52); this approach cannot be recommended without larger trials confirming its safety (89). For instance, Kors et al. (53) have reported a patient (with a FHM1 mutation in CACNA1A) who had a severe attack with hemiplegia and coma at 16 years old. Subcutaneous sumatriptan was given and the patient continued to deteriorate. Four days later a cerebral MRI disclosed a right middle cerebral artery infarction and 3 days later the patient died during seizures.

Usual attacks should be treated by oral analgesics, aspirin, or nonsteroidal antiinflammatory drugs (NSAIDs) soon after onset of the aura to prevent or alleviate headache. No treatment has proven efficient in reducing the aura phase. In severe attacks with confusion, coma, and sometimes seizures, intravenous analgesics, aspirin, or NSAIDs may be used together with antipyretics and antiepileptics.

### *Preventive Agents*

Rare reports suggest that beta-blocking agents, specifically propanolol, may be harmful in FHM patients (68), while others have shown benefit (31,49,53,58,62). Therefore, the use of propanolol in FHM must be carefully monitored. Reassuringly, Olesen et al. (70) reported that propanolol failed to alter regional blood flow in the awake human with no adverse effects on cerebral metabolism. The most promising data exist for verapamil as a preventative for hemiplegic migraine. Four patients with SHM were administered 120 mg verapamil orally from once to three times daily and experienced a significant reduction of attack frequency (58,104). Furthermore, a female with exertion-induced SHM enjoyed remission taking verapamil (76). Several case reports indicate that acetazolamide may be effective in preventing FHM with progressive cerebellar ataxia, usually around 250 mg twice daily (3,5,53).

# SPORADIC HEMIPLEGIC MIGRAINE

## Definition

**IHS code and diagnosis:** 1.2.5 Sporadic Hemiplegic Migraine
**WHO code and diagnosis:**
**Short description (Headache Classification Committee, 1988):** Migraine with aura including motor weakness but no first- or second-degree relative has aura including motor weakness
**Other terms:** Complicated migraine

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## Epidemiology

Previously, persons suffering from sporadic hemiplegic migraine (SHM) attacks were classified as migraine with typical aura (typical MA) or migraine with prolonged aura. However, for the first time, the revised edition of the International Headache Classification recognizes SHM as a distinct subtype of migraine with aura (43). About 215 SHM patients are described worldwide. Recently the prevalence of hemiplegic migraine was estimated to be about 0.01% in Denmark, where sporadic cases occurred with approximately the same prevalence as familial cases (88). Despite some limitations in the applicability of the statistical method used, the study provides a useful approximation of the total number of affected subjects. However, SHM is probably a heterogeneous disorder. Nonfamilial cases of HM may be divided in two groups:

**1.** Some cases are due to a mutation in one of the genes causing FHM. A few cases may have a de novo mutation (mutation identified in the patient and absent in both parents) that will be transmitted to 50% of offspring (95). Moreover, the mutation may have been transmitted by one parent clinically unaffected because of the incomplete penetrance of FHM. Finally, a sporadic case may be the result of false paternity. The true percentage of SHM cases due to FHM gene mutations is unknown but is probably low.

**2.** Other SHM cases are most likely related to typical migraine with aura and probably have a multifactorial origin with conjunction of environmental factors and complex genetic factors.

Female:male gender ratios for SHM range from 3:1 to 4.3:1 (8,92).

## Genetics

A few genetic studies have been performed in SHM. A total of 39 SHM patients, including 4 with permanent cerebellar signs, have been screened for a CACNA1A mutation (10,18,30,82). A mutation was identified in 4 patients (10%), including 3 out of the 4 cases with SHM and cerebellar signs, and in only 1 out of the 35 cases with pure SHM (2.8%). In one case with cerebellar signs, a de novo CACNA1A mutation was identified (95). A total of 24 cases with SHM have been screened for an ATP1A2 mutation, leading to the identification of only one mutation in a single patient (4%) (48).

## Pathophysiology

Sporadic hemiplegic migraine is a heterogeneous disorder, where some patients may have a pathophysiology identical to familial HM with a mutation in one of the FHM genes (at least 2 to 4%) and others, possibly the great majority of SHM patients, may have a different pathophysiologic background probably related to the mechanisms of typical MA.

## Clinical Features

### IHS diagnosis criteria for sporadic hemiplegic migraine (Headache Classification Committee, 2004):

**A.** At least two attacks fulfilling criteria B and C

**B.** Aura consisting of fully reversible motor weakness and at least one of the following:
- **1.** Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision).
- **2.** Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness).
- **3.** Fully reversible dysphasic speech disturbance.

**C.** At least two of the following:
- **1.** At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes.
- **2.** Each aura symptom lasts ≥5 minutes and <24 hours.
- **3.** Headache fulfilling criteria B through D for 1.1 Migraine without aura begins during the aura or follows onset of aura within 60 minutes.

**D.** No first- or second-degree relative has had attacks fulfilling these criteria A through E.

**E.** Not attributed to another disorder: History and physical and neurologic examinations do not suggest any of the disorders listed in groups 5 to 12, or history and/or physical and/or neurologic examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

SHM is a rare subtype of migraine with aura in which patients develop migraine symptoms that include focal weakness as a component of their aura and where there are no similar affected first- or second-degree relatives.

### *Clinical Features of Attacks*

In SHM, the presence of motor aura symptoms is essential for the diagnosis. The most common other aura symptoms are sensory (98%), visual (91%), and aphasic (81%) (91). One study found basilar-type migraine symptoms in only two of 27 (7.4%) SHM cases (82), and another study found that 72% of 105 SHM patients met the 1988 IHS criteria for basilar-type migraine during their SHM attacks, equal to the frequency seen in FHM patients (92). The distribution of the various combinations of aura symptoms

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during SHM attacks is similar to those experienced by persons with FHM. The motor aura usually lasts for 1 hour or less, although approximately 41% may have a prolonged aura for more than 1 hour and approximately 8% may have a prolonged aura that lasts for more than a day, the most common succession being from visual to sensory to motor to aphasic and basilar-type symptoms (92). Motor and sensory auras are usually unilateral, involving the upper extremities more commonly than the lower extremities (8,92). However, the unilateral symptoms may switch sides during an attack (16%) and between attacks (36%), and occasionally (13%) patients report having simultaneous bilateral progression (92). The lifetime occurrence of aura symptoms during SHM attacks is similar to those experienced by persons with FHM (92).

Headache is always present during SHM attacks (92). Headache followed the visual aura symptoms in 78% and began prior to the visual aura symptoms in 15%, while both occurred simultaneously in 8%. When comparing the aura and headache characteristics of SHM to those of FHM, Thomsen et al. (92) found similar clinical characteristics regarding frequency of aura, symptoms, combinations of symptoms, sequence, progression time, total duration of aura, headache characteristics, and accompanying symptoms. Additionally, aura was virtually always followed by headache in both conditions. When studying the relation between SHM and basilar migraine, Thomsen et al. (92) found that 72% of the SHM patients fulfilled the IHS criteria for basilar migraine during SHM attacks. FHM has the same high frequency of basilar-type symptoms (38,87), while such symptoms are rare in MA (38). Severe attacks with confusion, coma, fever, and prolonged deficits may occur in SHM as well as in FHM (95).

### *Associated Neurologic Symptoms*

Only 3 of 63 SHM patients reported in genetic studies (10,18,30,48,82) and 2 of 105 SHM patients in the study of Thomsen et al. (92) had interictal cerebellar signs or atrophy, indicating that persistent cerebellar signs are less common in SHM than in FHM.

### *Neurologic Investigations*

In the study by Thomsen et al. (92), no compelling findings were discerned in 23 of 105 SHM patients who had neuroimaging.

## Prognosis

Attacks may begin between the ages of 5 and 7 years, with a mean age of onset of 21 years for women and 16 years for men (92). One-third of patients will have their first attack of hemiplegic migraine by the age of 30 years, and 97% will experience onset of SHM by the age of 45 years (8,92). SHM is an often benign entity, with complete recovery between attacks. Patients usually stop experiencing attacks after the age of 50, but some still occur and often transition to ordinary migraine or typical migraine aura without headache (8,92). But, similar to FHM, permanent sequelae including dementia, hemiplegia, and even death occur (101).

## Diagnosis

The diagnosis is based solely on the clinical description of typical attacks and of the absence of an underlying neurologic disorder susceptible to cause migraine attacks with a motor aura. Indication of a molecular diagnosis is discussed in the chapter about FHM.

## Management

There is no evidence to support the notion that SHM should be treated differently than FHM. Unfortunately, all the therapeutic options for either form of hemiplegic migraine stem from strictly anecdotal accounts.

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