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REVIEW

# Diagnostic and therapeutic aspects of hemiplegic migraine

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## ABSTRACT

Hemiplegic migraine (HM) is a clinically and genetically heterogeneous condition with attacks of headache and motor weakness which may be associated with impaired consciousness, cerebellar ataxia and intellectual disability. Motor symptoms usually last <72 hours and are associated with visual or sensory manifestations, speech impairment or brainstem aura. HM can occur as a sporadic HM or familial HM with an autosomal dominant mode of inheritance. Mutations in CACNA1A, ATP1A2 and SCN1A encoding proteins involved in ion transport are implicated. The pathophysiology of HM is close to the process of typical migraine with aura, but appearing with a lower threshold and more severity. We reviewed epidemiology, clinical presentation, diagnostic assessment, differential diagnosis and treatment of HM to offer the best evidence of this rare condition. The differential diagnosis of HM is broad, including other types of migraine and any condition that can cause transitory neurological signs and symptoms. Neuroimaging, cerebrospinal fluid analysis and electroencephalography are useful, but the diagnosis is clinical with a genetic confirmation. The management relies on the control of triggering factors and even hospitalisation in case of long-lasting auras. As HM is a rare condition, there are no randomised controlled trials, but the evidence for the treatment comes from small studies.

## INTRODUCTION

Hemiplegic migraine (HM) is an uncommon subtype of migraine with aura that usually starts in the first or second decade of life.<sup>1</sup> It is a clinically and genetically heterogeneous condition that represents a challenge for the clinician because it can occur with a dramatic and crippling clinical situation, resembling other more severe neurological diseases (ie, stroke).<sup>1,2</sup>

HM can occur as a sporadic or familial condition if at least one first-degree or second-degree relative has the same form of migraine.<sup>3</sup> Familial hemiplegic migraine (FHM) is the only migraine form for which an autosomal dominant mode of inheritance has been documented. Genetic studies have demonstrated the involvement of at least three distinct genes that encode proteins involved in ion transport (CACNA1A, ATP1A2 and SCN1A).<sup>2</sup> Mutation of those genes explains for about 7%–14% of FHM in two population studies.<sup>4,5</sup> Some authors have

hypothesised a role for gene PRRT2 in migraine pathophysiology, but its specific implication in HM is still debated. Given the lack of a recognised fourth autosomal dominant gene for FHM, other genetic mechanisms might be supposed and further genetic analyses are needed.<sup>2</sup> Sporadic hemiplegic migraine (SHM) shares similar clinical characteristics with FHM but it differs for the absence of family history for HM.<sup>6</sup>

As HM is a rare condition, few studies are reported and there are no specific treatments. In this review, we will discuss in detail about epidemiology, clinical presentation, diagnostic assessment, differential diagnosis and treatment of this complex disorder.

## Epidemiology

Although migraine is a common condition with a prevalence between 15% and 20% in the general population, HM is rare. The onset is generally in adolescence between 12 and 17 years<sup>1,4,7,8</sup> and the overall estimated prevalence is 0.01%.<sup>9</sup> Females are more frequently affected, with a variable female/male ratio among 2.5:1 and 4.3:1.<sup>9,10</sup> The frequency and severity of attacks progressively decrease with increasing age.<sup>1</sup>

## Clinical manifestations

HM is characterised by recurrent attacks with headache and aura manifestations. Emotional and intense physical stress, viral infections and head trauma are the more common reported trigger factors for HM attacks.<sup>11,12</sup> Table 1 describes diagnostic criteria for HM, according to the definition of the third edition of International Classification of Headache Disorders.<sup>3</sup>

Headache is almost always present during attacks and it is often severe. The localisation of headache is variable: bilateral, unilateral, ipsilateral or contralateral to the motor symptoms.<sup>1</sup>

Associated symptoms in HM can be distinguished in aura symptoms that occur during attacks and chronic symptoms that can be present interictally.

## Aura symptoms

Unilateral weakness is always present during HM attacks and it is considered the most important sign; weakness can rarely be bilateral and sometimes it may switch side. Besides motor weakness, sensory symptoms (such as tingling, numbness and paraesthesia), visual defects (scintillating scotoma,



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**Table 1** Diagnostic criteria of hemiplegic migraine

	Diagnostic criteria ICHD-3
Hemiplegic migraine	A. At least two attacks fulfilling criteria B. One or more of the following fully reversible aurasymptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over 5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5–60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 min, by headache D. Aura consisting of both of the following: 1. fully reversible motor weakness 2. fully reversible visual, sensory and/or speech/ language symptoms.
Familial hemiplegic migraine (FHM)	A. Attacks fulfilling criteria for Hemiplegic migraine B. At least one first- or second-degree relative has had attacks fulfilling criteria for Hemiplegic migraine.
Familial hemiplegic migraine type 1 (FHM1)	A. Attacks fulfilling criteria for Familial hemiplegic migraine B. A mutation on the CACNA1A gene has been demonstrated.
Familial hemiplegic migraine type 2 (FHM2)	A. Attacks fulfilling criteria for Familial hemiplegic migraine B. A mutation on the ATP1A2 gene has been demonstrated.
Familial hemiplegic migraine type 3 (FHM3)	A. Attacks fulfilling criteria for Familial hemiplegic migraine B. A mutation on the SCN1A gene has been demonstrated.
Familial hemiplegic migraine, other loci	A. Attacks fulfilling criteria for Familial hemiplegic migraine B. Genetic testing has demonstrated no mutation on the CACNA1A, ATP1A2 or SCN1A genes.
Sporadic hemiplegic migraine (SHM)	A. Attacks fulfilling criteria for Hemiplegic migraine B. No first- or second-degree relative fulfils criteria for Hemiplegic migraine.

ICHD-3, third edition of International Classification of Headache Disorders.

hemianopia) and aphasia are the most frequent aura symptoms. Sometimes, migraine attacks may include other signs and symptoms such as fever, seizure, bilateral visual disturbances, a ‘brainstem aura’ with vertigo, dysarthria, ataxia, hyperacusia, tinnitus, impaired consciousness and even, in the worse conditions, coma.<sup>1 4 10 13</sup>

The duration of symptoms is usually 20–60 min but, in some cases, the aura and motor deficit may onset quickly and simulate an ischaemic attack.<sup>8</sup> The complete recovery from attacks is the rule, but in severe migraine attacks, hemiplegia and altered consciousness may persist for weeks until total recovery.<sup>14–17</sup> There are cases of irreversible brain injury with cerebral atrophy, infarction, cognitive deficit and death secondary to severe HM attacks in cases with CACNA1A mutations.<sup>7</sup>

**Chronic symptoms**

Chronic symptoms can develop interictally in patients with HM and they usually depend on the specific gene involved. Indeed, cerebellar involvement with a gaze-evoked nystagmus and progressive ataxia has been associated with in FHM type 1 (FHM1) in about 60% of cases, but is rare in FHM type 2 (FHM2).<sup>1 8 18 19</sup> Moreover, some mutations of CACNA1A or ATP1A2 have been associated with mental retardation and cognitive impairment after severe and recurrent episodes<sup>20–23</sup>; early onset attacks, coma and seizure are considered the main risk factors for this kind of complication.<sup>1 24</sup> More recently, 50% of children (aged 3–18 years) with a pathogenic CACNA1A mutation associated with HM and other benign paroxysmal events (torticollis, vertigo or tonic upgaze) showed an heterogeneous cognitive dysfunction without a specific cognitive profile, mainly associated with vermian cerebellar atrophy for these

early onset CACNA1A-associated phenotype was proposed a classification as ‘neurodevelopmental disorders’, suggesting thus a close follow-up of psychomotor development and academic performances.<sup>25</sup>

Seizures in HM may be partial or generalised, with or without fever.<sup>26</sup> Generally, the onset of epilepsy is in childhood and sometimes it happens before the first HM attack. Hopefully, seizures in patients with HM have a benign evolution<sup>1</sup> and higher rates have been reported in families with FHM2.<sup>22</sup> Of note, in patients with HM, epileptic fits are independent of migraine attacks.<sup>7 27 28</sup> Neurological evaluation during a migraine attack can show unilateral hyperreflexia and further sensorimotor signs affecting mostly the upper limbs.<sup>4 29</sup>

**Genetics**

FHM shows an autosomal dominant pattern of inheritance with 70%–90% penetrance.<sup>30</sup> To date, linkage studies and mutational screening in FHM families have found three main causative genes—CACNA1A, ATP1A2 and SCN1A—which encode for ion transporters. FHM can be classified as FHM1 (MIM #141500), FHM2 (MIM #602481) or FHM3 (MIM #609634) according to mutations in CACNA1A, ATP1A2 or SCN1A, respectively.<sup>1 30</sup> Individuals with mutations in the same gene, or even family members with the same mutation, can show wide variability in clinical presentation.<sup>31</sup> This suggests that unknown genetic or environmental factors can influence phenotype.<sup>30 32</sup>

SHM is diagnosed when there is no family history of HM. SHM can be caused by de novo mutations in the FHM genes.<sup>1</sup> Early onset and presence of associated neurological symptoms increase the probability of finding an FHM mutation in sporadic cases.<sup>2 32</sup> In a Danish population-based study of SHM, the

majority of patients (92/100) did not show a mutation in the FHM genes.<sup>33</sup> In a Finnish sample of patients with HM, none of the 201 studied patients with SHM had exonic mutations in the FHM genes.<sup>5</sup> However, clinical similarities between FHM and SHM suggest that SHM is very likely to be a genetic disorder. So that, SHM could probably be caused by mutations in still unknown specific genes.<sup>1</sup> Another possible explanation is that complex polygenic interaction of multiple gene variants with small size effects may occur in SHM, like in common migraine phenotypes.<sup>2</sup> Similar pathogenic mechanisms may also play a role in patients with FHM without confirmed mutations in FHM genes.<sup>2</sup>

CACNA1A gene is localised on chromosome 19p13. It encodes the pore-forming  $\alpha 1$  subunit of the neuronal voltage-gated Cav2.1 channel, predominantly localised at the presynaptic terminals in the central nervous system.<sup>30</sup> More than 30 FHM1 mutations have been identified in familial and sporadic cases.<sup>1</sup> The majority are missense variants in functional domains of the calcium channel, but also deletions have been reported.<sup>34</sup> These mutations result in gain-of-function effects, with increased  $\text{Ca}^{2+}$  influx and enhanced glutamate release (but unaltered GABA release) at cortical synapses.<sup>35</sup> The consequence is an altered excitatory-inhibitory balance and increased susceptibility to cortical spreading depression (CSD).<sup>35–37</sup> Besides FHM1, CACNA1A mutations can also be found in episodic ataxia type 2 (EA2; MIM #108500) and spinocerebellar ataxia type 6 (SCA 6; MIM #183086). Clinical overlap among the three diseases has been reported.<sup>30</sup> However, EA2 mutations can be missense, truncating or cause aberrant splicing of CACNA1A, usually leading to loss-of-function and decreased  $\text{Ca}^{2+}$  influx. On the other side, SCA6 mutations are usually small expansions of a polyglutamine in the C-terminal of the gene, which are responsible for accumulation of mutant Cav2.1 channels and selective degeneration of Purkinje cells.<sup>30</sup>

ATP1A2 gene is localised on chromosome 1q23.2. It encodes the  $\alpha 2$  subunit of the glial sodium-potassium ATPase pump.<sup>1</sup> More than 80 causal variants have been linked to FHM2. Most are missense mutations localised in the catalytic P domain, the transmembrane domain or in the central region between them.<sup>30</sup> The spectrum of FHM2 mutations also includes some deletions and an exonic duplication found in a patient with SHM phenotype.<sup>38</sup> Functional studies have demonstrated that FHM2 mutations can either alter pump sensitivity to potassium, reduce the sodium/potassium turnover or generate non-functional proteins,<sup>22</sup> leading to impaired glial reuptake of potassium and glutamate from the synaptic cleft and consequently increased the propensity to CSD.<sup>39 40</sup>

SCN1A gene is localised on chromosome 2q24.3. It encodes the pore-forming  $\alpha 1$  subunit of the neuronal voltage-gated sodium channel Nav1.1, which regulates sodium permeability on GABAergic interneurons. Patients with SCN1A mutations can have pure HM or associated neurological disorders like generalised tonic-clonic epilepsy, elicited repetitive transient daily blindness or childhood epilepsy.<sup>30</sup> FHM3 mutations are usually missense.<sup>41</sup> In contrast with the folding-defective epileptogenic Nav1.1 mutations which showed loss of function also when rescued,<sup>42</sup> FHM3 mutations (including a folding-defective mutation) provoke gain of function of Nav1.1 channels and hyperexcitability of GABAergic neurons.<sup>43</sup> The increase of extracellular potassium concentration consequent to the increased firing of GABAergic interneurons has been proposed as a possible mechanism underlying increased propensity to CSD in FHM3.<sup>44</sup>

Searching for other potential HM genes, PRRT2 has been suggested as the fourth HM gene.<sup>45 46</sup> It encodes a presynaptic

transmembrane protein which is involved in synaptic vesicles fusion and regulation of voltage-gated calcium channel in glutamatergic neurons. Truncating mutation is the most common in PRRT2-related conditions.<sup>30</sup> This gene is associated with paroxysmal kinesigenic dyskinesia and childhood epilepsy/seizure disorders. HM has been reported in a few PRRT2 mutation carriers with a 'typical PRRT2 phenotype'.<sup>47</sup> PRRT2 variants show a low-penetrance mode of co-segregation. It is possible that PRRT2 gene acts as a disease modifier gene in HM with a complex polygenic mechanism.<sup>47</sup>

Rarely, mutations in PNKD, SLC2A1, SLC1A3 and SLC4A4 genes have been reported in patients with HM phenotype.<sup>30 48–51</sup> All these variants might in principle disrupt excitatory-inhibitory balance and induce CSD.<sup>30 37 52</sup>

## Diagnosis

The diagnosis of HM lies in obtaining a detailed clinical history and excluding other possible causes for the patient's symptoms. There are no pathognomonic clinical, laboratory or radiological findings to diagnose HM.

Use of electroencephalography can show asymmetric slow-wave activity with delta/theta waves in the hemisphere contralateral to the hemiparesis.<sup>1 2 31 53 54</sup>

The cerebrospinal fluid (CSF) analysis may reveal increased protein concentration related to blood-brain barrier (BBB) dysfunction,<sup>38</sup> but pleocytosis has also been reported.<sup>20</sup>

Little is known about imaging abnormalities in HM due to its rarity. Imaging studies between attacks are normal, except in patients with FHM1 or SHM1 with cerebellar atrophy.<sup>1</sup> Swelling and/or cortical hyperintensity of the affected hemisphere have been described on T2/FLAIR-weighted MRI images performed during attacks.<sup>54–56</sup> Some patients present mild gadolinium enhancement on brain MRIs, probably due to an alteration in the BBB.<sup>57</sup> It is also possible to find a reversible decrease in water diffusion, due to cytotoxic oedema.<sup>53</sup> Abnormalities are contralateral to the motor weakness and tend to disappear after neurological deficits resolution.<sup>53 56</sup> To note, these abnormalities may not be viewed if MRI is performed in the very beginning after onset of symptoms.<sup>54</sup>

## Differential diagnosis

The differential diagnosis of HM is broad and includes other forms of migraine, as well as any condition that can cause transitory neurological signs and symptoms, cerebrovascular diseases, epilepsy with hemiparesis, infectious or inflammatory disease and tumour.<sup>6</sup> Table 2 summarises the most frequent differential diagnoses, underlining the principal diagnostic clues and the prevalence of the considered disorders. Given the complexity of the differential diagnosis, it is imperative to approach to HM as a diagnosis of exclusion from more common conditions that may cause weakness and headache. Moreover, the difficulty in diagnosis is influenced by the frequency and duration of the attacks. In fact, many investigations are required in the event of a first episode, especially in patients with prolonged aura.<sup>58</sup>

Migraine with aura is the third most common *stroke-mimic*, following seizures and psychiatric disorders; it is responsible for about 18% of all improper thrombolytic treatments.<sup>59</sup> When a patient presents with a motor deficit, it is more likely a secondary headache (ischaemic or haemorrhagic stroke) than a primary headache disorder.<sup>60</sup> However, it is more challenging to differentiate HM from a transient ischaemic attack (TIA), as both are fully reversible and the neuroimaging is often unrevealing. Indeed, it has been reported in a minority of patients

## Migraine

**Table 2** Differential diagnoses in hemiplegic migraine

Differential diagnosis	Main features	Clue for differential	Examinations required
Cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke)	Sudden onset of neurological deficits	<ul style="list-style-type: none"> <li>▶ Sudden onset (TIA and stroke) vs gradual progressive spread (HM).</li> <li>▶ Prevalence of negative symptoms in TIAs and strokes.</li> <li>▶ Timing of the headache: after motor symptoms in HM and before them in haemorrhagic strokes.</li> </ul>	CT, MRI, carotid ultrasound, transthoracic echocardiogram, special coagulation profiles, antiphospholipid antibody panel.
Cerebral amyloid angiopathy, even in absence of bleeding	Transient episodes of focal neurological deficits known as <i>amyloid spells</i>	<ul style="list-style-type: none"> <li>▶ Recurrent and stereotyped episodes of paraesthesias, focal weakness or dysphasia, usually lasting several minutes.</li> <li>▶ Cortical superficial siderosis and microbleeds on brain MRI.</li> </ul>	MRI including blood-sensitive sequences.
Epilepsy with hemiparesis	Limb jerking, head-turning and loss of consciousness at seizure onset	Prolonged migratory progression of aura over 30 min to hours vs short duration of seizures (sudden and usually <1 min).	Electroencephalogram, MRI.
Brain tumours	Progressive neurological symptoms; neuroimaging and pathological examination are required	<ul style="list-style-type: none"> <li>▶ Precipitation of headache over Valsalva manoeuvre and bending over.</li> <li>▶ Headache is typical occipital or frontal.</li> </ul>	CT, MRI, proton MR spectroscopy.
Stroke-like migraine attacks after radiation therapy	History of radiation therapy	<ul style="list-style-type: none"> <li>▶ Typical neuroimaging features (thick cortical gyral enhancement).</li> <li>▶ History of remote irradiation (even after 20–30 years).</li> </ul>	MRI with contrast.
Transient headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL)	Spinal fluid lymphocytosis	<ul style="list-style-type: none"> <li>▶ Viral-like premonitory symptoms before one-third of HaNDL attacks.</li> <li>▶ Monophasic course, with resolution in 3 months.</li> <li>▶ Rare visual symptoms in HaNDL.</li> </ul>	MRI, CSF examination.
Alternating hemiplegia of childhood	Dystonia, epilepsy and cognitive impairment	<ul style="list-style-type: none"> <li>▶ Onset before 18 months.</li> <li>▶ Paroxysmal spells of hemiplegia, quadriplegia, choreoathetotic movements and nystagmus that disappear immediately after sleep.</li> <li>▶ Attacks may resume soon after awakening.</li> </ul>	CT or MRI, electroencephalogram (preferably prolonged in order to capture an episode), ATP1A3 gene sequencing.
Central nervous system infections	Cerebrospinal fluid analysis and neuroimaging consistent with infection	<ul style="list-style-type: none"> <li>▶ Presence of systemic symptoms (in particular fever), nuchal rigidity and a variety of psychiatric and behavioural disturbances (ie, hallucinations and psychosis).</li> </ul>	Complete blood count, erythrocyte sedimentation rate, CSF examination, MRI.
Hereditary and metabolic disorders (MELAS, CADASIL, hereditary haemorrhagic telangiectasias)	Characteristic genetic mutations, lactate elevation, maternal or autosomal inheritance	<ul style="list-style-type: none"> <li>▶ Typical findings in MELAS: episodes of migrainous headache, stroke-like focal deficits, increased lactate in serum and CSF during the attack, MRI abnormalities, especially in the posterior cerebral cortex.</li> <li>▶ Cognitive impairment and sudden-onset focal neurological deficits are associated with CADASIL.</li> </ul>	Lactate, CSF examination, electroencephalogram, CT and/or MRI, muscle biopsy, genetic testing.

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HM, hemiplegic migraine; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome.

that HM attacks can have an abrupt onset and, if the duration of the attack is enough prolonged, clinicians may misdiagnose patients having a TIA, especially in the presence of risk factor for ischaemic stroke. We previously described the case of a patient with late-onset SHM (missense mutation of the ATP1A2 gene) with hypertension and severe carotid stenoses.<sup>21</sup> Conversely, recurrent TIAs can be evocative of SHM in patients with rare syndromes who fulfil criteria for HM.<sup>61</sup> Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura<sup>1</sup>; the neuroimaging can be helpful to distinguish among these conditions, but the timing of the headache also provides relevant information, because

the headache usually follows the motor weakness in HM and precedes the weakness in haemorrhagic strokes.<sup>59</sup> In addition, headache is common in haemorrhagic stroke, but it is rare in TIAs, and HM occurs more frequently in young people.<sup>59</sup>

The differential diagnosis of HM also includes hereditary cerebral angiopathies.<sup>1 62</sup> Cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL) is the most common cause of inherited stroke in adults<sup>1 63</sup> and is caused by mutations of the NOTCH3 gene on chromosome 19.<sup>64</sup> As for HM, migraine with aura can be the initial symptom in CADASIL; gradual motor symptoms can be present in CADASIL patients who have attacks of migraine with aura. Motor aura in HM usually starts in the



**Table 3** Pharmacological treatments in hemiplegic migraine

Drug	Mechanism of action	Administration	Clinical outcome	Level of evidence
<b>Acute management of aura</b>				
Verapamil	<ul style="list-style-type: none"> <li>▶ Calcium antagonism on L-type calcium channel, blocking calcium influx and reducing vasoconstriction.</li> <li>▶ Less prominent effects on P/Q calcium channels.</li> </ul>	Intravenous verapamil (5 mg over 5 min), followed by an oral maintenance dose of 120 mg/day.	Significant reduction of headache, but not completely resolution of hemiplegia, especially in patients with CACNA1A mutations.	Low; case reports and small studies (Yu <i>et al</i> <sup>64</sup> ).
Ketamine	▶ NMDA glutamate receptors antagonism.	Intranasal administration.	May be beneficial in about 45% of cases.	Low; a study on 11 patients with FHM (Kaube <i>et al</i> <sup>65</sup> ).
Triptans	▶ 5-HT <sub>1B/1D</sub> agonism.	Oral or subcutaneous.	In a study on 76 patients with HM, 62% reported a good or excellent response with moderate adverse events (chest pain, nausea and fatigue).	Debated; the evidence comes from a study of 76 patients with HM (Arto <i>et al</i> <sup>61</sup> ).
Corticosteroid pulses and hypertonic solution	<p>Steroids:</p> <ul style="list-style-type: none"> <li>▶ indirect inhibition of the activity of voltage-dependent calcium channels;</li> <li>▶ reduction of CSD.</li> </ul> <p>Hypertonic solution:</p> <ul style="list-style-type: none"> <li>▶ unknown.</li> </ul>	Intravenous dexamethasone 0.5 mg/kg/day in three pulses/day for 3 days followed by gradual oral tapering and hypertonic solution at 3% 1.5 mL/kg/hour, maintaining sodium between 145 and 155 mEq/L. In another report, a scheme with a 5-day treatment of 100 mg/day methylprednisolone was used.	Rapid reduction in severity and duration of acute attacks in the presence of encephalopathy and cerebral oedema in patients with CACNA1A mutations.	Low; single reports (Sánchez-Albuisa <i>et al</i> <sup>62</sup> ; Garcia Segarra <i>et al</i> <sup>60</sup> ; Camia <i>et al</i> <sup>61</sup> ).
Prochlorperazine and magnesium sulfate	<ul style="list-style-type: none"> <li>▶ Dopamine D2 receptors antagonism.</li> <li>▶ Blockage of CSD due to magnesium.</li> </ul>	Intravenous.	Intravenous prochlorperazine and magnesium sulfate seemed to resolve prolonged migrainous aura.	Putative; little evidence based on a single report (Rozen <i>et al</i> <sup>63</sup> ).
Naloxone	▶ Opiate antagonism (possible role for endorphins).	0.4 mg of intravenous naloxone.	Aborted neurological sequelae in two patients with SHM.	Putative; little evidence based on a single report (Centonze <i>et al</i> <sup>66</sup> ).
Furosemide	▶ Possible cessation of CSD.	Intravenous.	Seemed to resolve prolonged migrainous aura in two patients.	Putative; little evidence based on a single report (Rozen <i>et al</i> <sup>61</sup> ).
<b>Prophylactic treatment</b>				
Verapamil	<ul style="list-style-type: none"> <li>▶ Calcium antagonism on L-type calcium channel, blocking calcium influx and reducing vasoconstriction.</li> <li>▶ Less prominent effects on P/Q calcium channels.</li> </ul>	Oral verapamil (120 mg twice or three times in a day).	May be effective in reducing the burden of attacks in HM.	Low; case reports and small studies (Lai <i>et al</i> <sup>63</sup> ; Razavi <i>et al</i> <sup>66</sup> ; Yu <i>et al</i> <sup>65</sup> ; Lastimoso <i>et al</i> <sup>65</sup> ; Hsu <i>et al</i> <sup>102</sup> ; Rispoli <i>et al</i> <sup>61</sup> ).
Acetazolamide	▶ Unknown; a local pH change around the P/Q Ca <sup>2+</sup> channel may result in improved channel functioning.	Oral 250–500 mg twice a day.	May be effective in reducing the burden of attacks in HM and nystagmus, especially in patients with CACNA1A mutations (EA2, SCA6) and CADASIL.	Low; little evidence based on case reports and case series (Athwal <i>et al</i> <sup>66</sup> ; Battistini <i>et al</i> <sup>63</sup> ; Striano <i>et al</i> <sup>103</sup> ; Suzuki <i>et al</i> <sup>18</sup> ).
Flunarizine	<ul style="list-style-type: none"> <li>▶ Non-selective calcium ion channel and dopamine receptor antagonism.</li> <li>▶ 5-HT and antihistamine receptors antagonism.</li> </ul>	Oral 10 mg/day.	Generally effective and well-tolerated, except for low rate of adverse effects (tiredness, mood changes and weight gain).	Low; single reports (Tobita <i>et al</i> <sup>60</sup> ; Karsan <i>et al</i> <sup>1</sup> ).
Lamotrigine	▶ Blockage of the sodium channels, decreasing the neuronal release of glutamate.	Oral.	May be beneficial.	Low; a study with eight patients with motor aura, a case report (LampI <i>et al</i> <sup>64</sup> ; Camia <i>et al</i> <sup>61</sup> ).
Propranolol	▶ Unknown.	Oral 10 mg 3–4 times a day and maintenance from 1.5 to 3.0 mg/kg/day.	Effective in three patients with longer symptom-free intervals.	Low; single report (Lai <i>et al</i> <sup>63</sup> ).
Memantine and dextromethorphan	▶ NMDA antagonism.	Oral.	Significant improvement of behavioural, cognitive and cerebellar symptoms in a patient with ATP1A2 mutation.	Putative; single report (Ueda <i>et al</i> <sup>62</sup> ).
Telcagepant	▶ CGRP receptor antagonism.	Oral.	May be beneficial.	Putative (Ho <i>et al</i> <sup>101</sup> ).
Onabotulinumtoxin A	▶ Unknown.	Subcutaneous.	Reduction of aura frequency and severity.	Putative; single report (Chen <i>et al</i> <sup>69</sup> ; Young <i>et al</i> <sup>35</sup> ).
Topiramate	▶ Unknown.	Oral.	Worsening of symptoms in a single HM case: dysphasia, disorientation, and prolonged severe right-sided weakness complicating a migraine attack lasting for about 4 days.	Putative; single report (Striano <i>et al</i> <sup>103</sup> ).

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CGRP, calcitonin gene-related peptide; CSD, cortical spreading depression; HM, hemiplegic migraine; 5-HT, 5-hydroxy tryptamine; NMDA, N-methyl-D-aspartate.

hand gradually spreading to the arm and face, while ‘stroke-like episodes’ resembling the classic lacunar syndromes occur in CADASIL. Gradual motor symptoms resembling HM and acute stroke-like episodes may both fit the diagnosis of CADASIL; hence, the NOTCH3 genetic testing is warranted. Cognitive deficits, mood disorders and MRI alterations are more common in CADASIL.<sup>63</sup> *Amyloid spells* have been recently described as transient episodes of neurological deficits occurring in patients with amyloid angiopathy even in absence of bleeding, arising a further differential for HM.<sup>65–67</sup> In these cases, the diagnosis may escape on standard neuroimaging, but MRI is diagnostic revealing superficial siderosis and microbleeds.<sup>67</sup>

Epilepsy is often diagnosed incorrectly in children with HM. Seizures with postictal paralysis, specifically Todd’s palsies can be confused with motor auras.<sup>1 24 62</sup> Unfortunately, up to 7% of patients with FHM develop epilepsy complicating the differential.<sup>26 68</sup> In HM the progression of the crisis is over 30 min to hours, while seizures are brief and usually last minutes; also, epilepsy with

hemiparesis is usually characterised by limb jerking, head-turning and loss of consciousness at seizure onset. Brain tumours presenting with secondary epilepsy usually cause progressive neurological symptoms and they should be excluded by CT or MRI.<sup>6</sup>

The presence of the headache is a mainstay, but many conditions can present with headache and transient neurological deficits. As a consequence, migraine mimics are primary or secondary headache disorders with features in common with migraine<sup>69</sup>; any condition that shows neurological deficits in the absence of radiological alterations should be considered. A careful history, followed by an accurate general and neurological examination looking for red flags that suggest the possibility of a secondary headache disorder or an underlying cause of hemiparesis are necessary.<sup>70</sup>

Central nervous system infections may also cause a clinical picture similar to HM with fever and impaired consciousness. CSF analysis and neuroimaging usually allow a clear distinction between the two conditions.<sup>71</sup>

The syndrome 'stroke-like migraine attacks after radiation therapy' may also mimic HM. The history of previous cerebral irradiation and the typical neuroimaging features (thick cortical gyral enhancement) usually allow an easy recognition.<sup>72</sup> However, this condition often occurs even 20–30 years after cerebral irradiation making sometimes difficult to recall a history of irradiation.<sup>73 74</sup> Moreover, cortical gadolinium enhancement has been reported in HM.<sup>57</sup> For these reasons, any history of previous cerebral irradiation should be searched.

Alternating hemiplegia of childhood is a very rare genetic condition, caused by mutations in the ATP1A3 gene and characterised by periodic episodes of hemiplegia or quadriplegia. Associated features including dystonia, epilepsy and cognitive impairment help the clinician to make the correct diagnosis.<sup>75</sup>

Headache with neurological deficits and CFS lymphocytosis (HaNDL) is a rare sporadic condition that can present with episodic headache, hemiparesis and aphasia, and may have regional blood flow abnormalities during the ictal phase. The diagnosis requires spinal fluid lymphocytosis.<sup>76 77</sup> Of interest, there are described cases of patients with FHM1 presenting CSF pleocytosis.<sup>20</sup> However, HaNDL is monophasic with resolution in 3 months, while HM recur for decades<sup>62</sup>; also, only a minority of attacks of HaNDL include visual symptoms, while visual aura is very common in HM.<sup>11 76</sup>

Various inflammatory or metabolic disorders should be considered in the differential diagnosis of HM as well as some mitochondrial diseases.<sup>78</sup> These conditions, including recurrent migraine-like headaches and neurological deficits, are distinguished based on their clinical, neuroimaging and genetic features.<sup>79</sup> Finally, Sturge-Weber disease (which can be easily differentiated for the peculiar cutaneous features) has recently been considered as possible cause of apparently isolated HM.<sup>80</sup>

## Treatment

As there are no randomised controlled trials in patients with HM, the treatment remains empirical, similarly to the more common types of migraine, based on small studies and single reports.<sup>20 21 80–103</sup>

The management of HM relies on the control of triggering factors and sometimes severe attacks can require hospitalisation to ensure fluid balance and food intake. Fever and seizures can be treated symptomatically.<sup>1 58</sup> There are reports of exacerbations due to vasoconstrictive drugs (ergotamine and dihydroergotamine) in patients with HM, raising the concern that vasoconstriction might aggravate the aura.<sup>58</sup> As a consequence, the use of triptans is debated and they are historically contraindicated; hence patients with HM have been excluded from clinical trials.<sup>1</sup> In a retrospective study, triptans appeared to be effective in the treatment of headache; of interest, about half of patients preferred to use triptans during aura as opposed to patients with migraine with aura.<sup>91</sup> Finally, in a single case, a woman affected by HM worsened after starting prophylactic treatment with topiramate.<sup>103</sup> Hence, a medication that can abolish the long-lasting and bothersome aura symptoms is in demand. Many authors support the idea that the propagation of CSD, mediated by the release of glutamate and activation of NMDA receptors, may be the correct target for the acute management of the aura. According to this theory, any medications that inhibit CSD might be useful in the treatment of aura. Nasal administration of ketamine reduced the duration of the aura in patients with FHM.<sup>82</sup> Furosemide and magnesium exploit a similar mechanism acting in CSD.<sup>87 88</sup> Moreover, intravenous verapamil has shown to be effective for the recovery of both headache and aura

in three out of four patients with HM in a single report.<sup>95</sup> Moreover, a prompt recovery has been described in three patients with CACNA1A mutations through the combined use of steroids and hypertonic solutions in course of encephalopathy and cerebral oedema.<sup>89 97 100</sup> However, the current evidence is still based on single reports or studies on a small cohort of patients, often lacking a confirmed genetic diagnosis of HM.

Current therapeutic recommendations are based on isolated reports and suggest a possible prophylactic treatment with verapamil and acetazolamide to reduce frequency and severity of migraine attacks, but many new agents have been proposed<sup>7 20 21 63 80–103</sup> (table 3).

## CONCLUSIONS

HM is a complex monogenic disorder related to a mutation in genes encoding for ion transporters. However, our knowledge on the pathophysiology of HM is evolving with new insights coming from the last 2 years.<sup>2 5 11 21 25 26 30 31 34 44 52 54 68 92 93 99</sup>

The diagnosis of HM is moreover clinical, but genetic testing is necessary to find out the genetic subtype; neuroimaging with MRI and neurophysiology techniques have an important role in the differential diagnosis from conditions that might cause transient neurological deficits, mimicking an attack of HM.

There is a little evidence for agents for the acute setting during attacks and prophylactic treatment with verapamil and acetazolamide to reduce frequency and severity of migraine attacks. Abortive treatments are quite effective when started early from disease onset; however, the current therapeutic recommendations are based on isolated reports but there is no adequate evidence due to the lack of controlled trials. Hence, a medication that can abolish the long-lasting and bothersome aura symptoms is in demand.

Furthermore, our understanding of pathophysiology in HM has improved in the last years. Recent advances have improved our understandings on the pathogenesis of HM. Several drugs might be candidates for possible use in clinical practice, but their efficacy and safety profiles have to be demonstrated.

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