Diagnostic and therapeutic aspects of hemiplegic migraine

Vincenzo Di Stefano, 1 Marianna Gabriella Rispoli, 2 Noemi Pellegrino, 3 Alessandro Graziosi, 3 Eleonora Rotondo, 3 Christian Napoli, 4 Daniela Pietrobon, 5, 6 Filippo Brighina, 1 Pasquale Parisi 7

1 Department of Biomedical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy; 2 Department of Neuroscience and Advanced Diagnostic Imaging, University of Palermo, Palermo, Sicilia, Italy; 3 Department of Biomedical Imaging and Clinical Sciences, ‘G. d’Annunzio’ University, Chieti, Abruzzo, Italy; 4 Department of Medical Sciences and Translational Medicine, ‘G. d’Annunzio’ University of Chieti Pescara, Chieti Scalo, Chieti, Italy; 5 Department of Biomedical Sciences & Padova Neuroscience Center, University of Padova, Padova, Italy; 6 CNR Neuroscience Institute, Padova, Italy; 7 Dipartimento di Neuroscienze Salute Mentale e Organi di Senso (NESMOS), University of Rome La Sapienza Faculty of Medicine and Psychology, Rome, Lazio, Italy

Correspondence to Professor Pasquale Parisi, Dipartimento di Neuroscienze Salute Mentale e Organi di Senso (NESMOS), University of Rome La Sapienza Faculty of Medicine and Psychology, Roma 00189, Lazio, Italy; pasquale.parisi@uniroma1.it

Received 21 January 2020 Revised 22 April 2020 Accepted 24 April 2020 Published Online First 19 May 2020

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.


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 familiar 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 aura. 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.1 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).1 2 3 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.3 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).2 Mutation of those genes explains for about 7%–14% of FHM in two population studies.3 4 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.2 Sporadic hemiplegic migraine (SHM) shares similar clinical characteristics with FHM but it differs for the absence of family history for HM.6 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 years1 4 7 8  and the overall estimated prevalence is 0.01%.9 Females are more frequently affected, with a variable female/male ratio among 2.5:1 and 4.3:1.5 9 10 The frequency and severity of attacks progressively decrease with increasing age.1

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.11 12 Table 1 describes diagnostic criteria for HM, according to the definition of the third edition of International Classification of Headache Disorders.3

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.1

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,
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.14 10 11

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.8 The complete recovery from attacks is the rule, but in severe migraine attacks, hemiplegia and altered consciousness may persist for weeks until total recovery.14–17 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.7

**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).1 8 18 19 Moreover, some mutations of CACNA1A or ATP1A2 have been associated with mental retardation and cognitive impairment after severe and recurrent episodes20–23; early onset attacks, coma and seizure are considered the main risk factors for this kind of complication.14 24 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 vermican 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.25

Seizures in HM may be partial or generalised, with or without fever.26 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 evolution2 and higher rates have been reported in families with FHM2.22 Of note, in patients with HM, epileptic fits are independent of migraine attacks.7 27 28 Neurological evaluation during a migraine attack can show unilateral hyperreflexia and further sensorimotor signs affecting mostly the upper limbs.4 29

**Genetics**

FHM shows an autosomal dominant pattern of inheritance with 70%–90% penetrance.30 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.1 30 Individuals with mutations in the same gene, or even family members with the same mutation, can show wide variability in clinical presentation.31 This suggests that unknown genetic or environmental factors can influence phenotype.30 32

SHM is diagnosed when there is no family history of HM. SHM can be caused by de novo mutations in the FHM genes.3 Early onset and presence of associated neurological symptoms increase the probability of finding an FHM mutation in sporadic cases.7 32 In a Danish population-based study of SHM, the

---

**Table 1** Diagnostic criteria of hemiplegic migraine

| Hemiplegic migraine | A. At least two attacks fulfilling criteria
|                     | B. One or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, 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 onthe CACNA1A, ATP1A2 or SCN1A genes.
| Sporadic hemiplegic migraine (SHM) | A. Attacks fulfilling criteria for Hemiplegic migraine
|                                | B. No first- or second-degree relative fulfills criteria for Hemiplegic migraine.

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

---


---

J Neurol Neurosurg Psychiatry, first published as 10.1136/jnnp-2020-322850 on 19 May 2020. Downloaded from http://jnnp.bmj.com/ on March 20, 2022 by guest. Protected by copyright.
malignant kinesigenic dyskinesia and childhood epilepsy/seizure disorders. HM has been reported in a few PRRT2 mutation carriers with a ‘typical PRRT2 phenotype’.47 PRRT2 variants show a low-penetration mode of co-segregation. It is possible that PRRT2 gene acts as a disease modifier gene in HM with a complex polygenic mechanism.47

Rarely, mutations in PNKD, SLC2A1, SLC1A3 and SLC4A4 genes have been reported in patients with HM phenotype.46 48–51 All these variants might in principle disrupt excitatory-inhibitory balance and induce CSD.46 57 52

**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.1 2 31 53 54

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

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.1 Swelling and/or cortical hyperintensity of the affected hemisphere have been described on T2/FLAIR-weighted MRI images performed during attacks.54–56 Some patients present mild gadolinium enhancement on brain MRIs, probably due to an alteration in the BBB.57 It is also possible to find a reversible decrease in water diffusion, due to cytotoxic oedema.13 Abnormalities are contralateral to the motor weakness and tend to disappear after neurological deficits resolution.12 54 To note, these abnormalities may not be visible if MRI is performed in the very beginning after onset of symptoms.54

**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.6  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.1 58

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.59

When a patient presents with a motor deficit, it is more likely a secondary headache (ischaemic or haemorrhagic stroke) than a primary headache disorder.60 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
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. Conversely, recurrent TIAs can be evocative of SHM in patients with rare syndromes who fulfil criteria for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for 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. Conversely, recurrent TIAs can be evocative of SHM in patients with rare syndromes who fulfil criteria for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.

The differential diagnosis of HM also includes hereditary cerebrovascular disease (ie, transient ischaemic attack (TIA) and ischaemic or haemorrhagic stroke) with hypertension and severe carotid stenoses. Conversely, ischaemic stroke. We previously described the case of a patient having a TIA, especially in the presence of risk factor for HM. Nevertheless, TIAs and strokes have a sudden onset, while HM typically shows gradual progressive spread with aura; 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. In addition, headache is common in haemorrhagic stroke, but it is rare in TIs, and HM occurs more frequently in young people.
In HM the progression of the crisis is over 30 minutes to hours, while seizures are brief and usually last minutes; also, epilepsy with secondary motor involvement usually lasts 30 minutes or more. The motor aura usually consists of right-sided weakness complicating a migraine attack lasting for about 4 days.

Table 3 Pharmacological treatments in hemiplegic migraine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Administration</th>
<th>Clinical outcome</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute management of aura</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calcium antagonism on L-type calcium channel, blocking calcium influx and reducing vasocostriction.</td>
<td>Intravenous verapamil (5 mg over 5 min), followed by an oral maintenance dose of 120 mg/day.</td>
<td>Significant reduction of headache, but not completely resolution of hemiplegia, especially in patients with CACNA1A mutations.</td>
<td>Low; case reports and small studies (Yu et al.89).</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA-gluamate receptors antagonism.</td>
<td>Intranasal administration.</td>
<td>May be beneficial in about 45% of cases.</td>
<td>Low; a study on 11 patients with FHM (Kaufe et al.90).</td>
</tr>
<tr>
<td>Triptans</td>
<td>5-HT1b,1d agonism.</td>
<td>Oral or subcutaneous.</td>
<td>In a study on 76 patients with HM, 62% reported a good or excellent response with moderate adverse events (chest pain, nausea and fatigue).</td>
<td>Debated; the evidence comes from a study of 76 patients with HM (Arts et al.91).</td>
</tr>
<tr>
<td>Corticosteroid pulses and hypertonic solution</td>
<td>Steroids: indirect inhibition of the activity of voltage-dependent calcium channels; reduction of CSD.</td>
<td>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 mmol/L. In another report, a scheme with a 5-day treatment of 108 mg/day methylprednisolone was used.</td>
<td>Rapid reduction in severity and duration of acute attacks in the presence of encephalopathy and cerebral oedema in patients with CACNA1A mutations.</td>
<td>Low; single reports (Sánchez-Abisua et al.92; García Segarra et al.93; Camia et al.94).</td>
</tr>
<tr>
<td>Prochloproprazine and magnesium sulfate</td>
<td>Dopamine D2 receptors antagonism.</td>
<td>Intravenous.</td>
<td>Intravenous prochloproprazine and magnesium sulfate seemed to resolve prolonged migrainous aura.</td>
<td>Putative; little evidence based on a single report (Rozen et al.95).</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Opiate-antagonist (possible role for endorphins).</td>
<td>0.4 mg of intravenous naloxone.</td>
<td>Aborted neurological sequelae in two patients with SIHM.</td>
<td>Putative; little evidence based on a single report (Centenzo et al.96).</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Possible cessation of CSD.</td>
<td>Intravenous.</td>
<td>Seemed to resolve prolonged migrainous aura in two patients.</td>
<td>Putative; little evidence based on a single report (Rozen et al.97).</td>
</tr>
<tr>
<td><strong>Prophylactic treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calcium antagonism on L-type calcium channel, blocking calcium influx and reducing vasocostriction.</td>
<td>Oral verapamil (120 mg twice or three times in a day).</td>
<td>May be effective in reducing the burden of attacks in HM.</td>
<td>Low; case reports and small studies (Lai et al.98; Razazi et al.99; Yu et al.89; Lattimore et al.100; Kuo et al.101; Ricardi et al.102).</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Unknown; a local pH change around the P/Q Ca2+ channel may result in improved channel function.</td>
<td>Oral 250–500 mg twice a day.</td>
<td>May be effective in reducing the burden of attacks in HM and nystagmus, especially in patients with CACNA1A mutations (EA2, SCA6) and CADASIL.</td>
<td>Low; little evidence based on case reports and case series (Athey et al.103; Battistini et al.104; Striano et al.105; Suzuki et al.106).</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>Non-selective calcium ion channel and dopamine receptor antagonism.</td>
<td>Oral 10 mg/day.</td>
<td>Generally effective and well-tolerated, except for low rate of adverse effects (tiredness, mood changes and weight gain).</td>
<td>Low; single reports (Tobita et al.107; Karsan et al.108).</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Blockage of the sodium channels, decreasing the neuronal release of glutamate.</td>
<td>Oral.</td>
<td>May be beneficial.</td>
<td>Low; a study with eight patients with motor aura, a case report (Lamp et al.109; Camia et al.110).</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Unknown.</td>
<td>Oral 10 mg 3–4 times a day and maintenance from 1.5 to 3.0 mg/kg/day.</td>
<td>Effective in three patients with longer symptom-free intervals.</td>
<td>Low; single report (Lai et al.111).</td>
</tr>
<tr>
<td>Memantine and dextromethorphan</td>
<td>NMDA antagonism.</td>
<td>Oral.</td>
<td>Significant improvement of behavioural, cognitive and cerebellar symptoms in a patient with ATP1A2 mutation.</td>
<td>Putative; single report (Ueda et al.112).</td>
</tr>
<tr>
<td>Telcagepant</td>
<td>CGRP receptor antagonism.</td>
<td>Oral.</td>
<td>May be beneficial.</td>
<td>Putative (Ho et al.113).</td>
</tr>
<tr>
<td>Onabotulinumtoxin A</td>
<td>Unknown.</td>
<td>Subcutaneous.</td>
<td>Reduction of aura frequency and severity.</td>
<td>Putative; single report (Chen et al.114; Young et al.115).</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Unknown.</td>
<td>Oral.</td>
<td>Worsening of symptoms in a single HM case: dypheasia, disorientation, and prolonged severe right-sided weakness complicating a migraine attack lasting for about 4 days.</td>
<td>Putative; single report (Striano et al.116).</td>
</tr>
</tbody>
</table>

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. 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. In these cases, the diagnosis may escape on standard neuroimaging, but MRI is diagnostic revealing superficial siderosis and microbleeds. Epilepsy is often diagnosed incorrectly in children with HM. Seizures with postictal paralyses, specifically Todd’s palsy can be confused with motor auras. Unfortunately, up to 7% of patients with FHM develop epilepsy complicating the differential. In HM the progression of the crisis is over 30 minutes 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.

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; 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. 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.
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. However, this condition often occurs even 20–30 years after cerebral irradiation making sometimes difficult to recall a history of irradiation. Moreover, cortical gadolinium enhancement has been reported in HM. 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.

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. Of interest, there are described cases of patients with FHMI presenting CSF pleocytosis. However, HaNDL is monophasic with resolution in 3 months, while HM recur for decades; also, only a minority of attacks of HaNDL include visual symptoms, while visual aura is very common in HM.

Various inflammatory or metabolic disorders should be considered in the differential diagnosis of HM as well as some mitochondrial diseases. These conditions, including recurrent migraine-like headaches and neurological deficits, are distinguished based on their clinical, neuroimaging and genetic features. 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.

**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.

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. 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. As a consequence, the use of triptans is debated and they are historically contraindicated; hence patients with HM have been excluded from clinical trials. In a retrospective study, triptans appeared to be effective in the treatment of headaches; of interest, about half of patients preferred to use triptans during aura as opposed to patients with migraine with aura. Finally, in a single case, a woman affected by HM worsened after starting 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 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.

**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. 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 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.

**REFERENCES**


63 Rosi G, Shambali S. Hemiplegic migraine as the initial presentation of biopsy positive cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Cephalalgia* 2018;10:e2631.


Migraine


