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HEADACHE (JR COUCH, SECTION EDITOR)

Familial and Sporadic Hemiplegic Migraine: Diagnosis and Treatment

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Opinion statement

Hemiplegic migraine (HM) is a rare subtype of migraine with aura, characterized by transient hemiparesis during attacks. Diagnosis is based on the International Classification of Headache Disorders criteria (ICHD-II). Two types of HM are recognized: familial (FHM) and sporadic hemiplegic migraine (SHM). HM is genetically heterogeneous. Three genes have been identified (*CACNA1A, ATP1A2,* and *SCN1A*) but more, so far unknown genes, are involved. Clinically, attacks of the 3 subtypes cannot be distinguished. The diagnosis can be confirmed but not ruled out by genetic testing, because in some HM patients other, not yet identified, genes are involved. The presence of additional symptoms (such as chronic ataxia or epilepsy) may increase the likelihood of identifying a mutation. Additional diagnostics like imaging, CSF analysis, or an EEG are mainly performed to exclude other causes of focal neurological symptoms associated with headache. Conventional cerebral angiography is contraindicated in HM because this may provoke an attack. Because HM is a rare condition, no clinical treatment trials are available in this specific subgroup of migraine patients. Thus, the treatment of HM is based on empirical data, personal experience of the treating neurologist, and involves a trial-and-error strategy. Acetaminophen and NSAIDs often are the first choice in acute treatment. Although controversial in HM, triptans can be prescribed when headaches are not relieved sufficiently with common analgesics. An effective treatment for the severe and often prolonged aura symptoms is more warranted, but currently no such acute treatment is available. Prophylactic treatment can

be considered when attack frequency exceeds 2 attacks per month, or when severe attacks pose a great burden that requires reduction of severity and frequency. In no strictly preferred order, flunarizine, sodium valproate, lamotrigine, verapamil, and acetazolamide can be tried. While less evidence is available for prophylactic treatment with topiramate, candesartan, and pizotifen, these drugs can also be considered. The use of propranolol in HM is more controversial, but evidence of adverse effects is insufficient to contraindicate beta-blockers.

Introduction

Hemiplegic migraine (HM) is a rare, autosomal dominantly inherited, severe subtype of migraine with aura, with an estimated prevalence of 0.01 % [1]. Beside common aura symptoms and migrainous headaches, attacks include transient hemiparesis varying from mild paresis to hemiplegia. Two types of HM are recognized. In Familial Hemiplegic Migraine (FHM) there is at least 1 first- or second-degree family member with HM attacks. In Sporadic Hemiplegic Migraine (SHM), the family history is negative for HM [2]. The core pathophysiological mechanisms of HM are considered to be similar to those in migraine, especially in migraine with aura (MA), possibly occurring with lower threshold and more intensity, which would cause the more severe phenotype.

Migraine is considered a neurovascular disorder, with primary neuronal events secondarily affecting blood vessels [3]. The aura is caused by Cortical Spreading Depression (CSD), a brief wave (lasting seconds) of intense neuronal and glial depolarization that slowly (2–5 mm/min) propagates across the cerebral cortex, followed by neuronal suppression [4]. This would account for the spreading character and propagation rate of aura symptoms. Depressed neuronal function presumably leads to oligemia, which passes across the cortex, preceded by a short phase of hyperemia, respectively representing negative and positive aura features [5]. Functional neuroimaging studies revealed similarities between blood flow changes in patients experiencing auras and CSD in experimental animals, suggesting CSD indeed occurs in humans [6]. Genetic and environmental factors may lower the CSD threshold, thereby increasing migraine susceptibility. The theory that dilatation of cranial arteries would cause migraine headaches, was reinforced by the beneficial effects of the potent vasoconstrictors ergot alkaloids and triptans [7, 8]. However, imaging studies showed conflicting results, with some demonstrating dilatation of cerebral arteries, while others did not detect any blood flow changes during migraine headache [9, 10]. Nowadays the trigeminovascular system is thought to play a central role. Activation of trigeminovascular efferents, which may be initiated by CSD, is postulated to cause release of vasoactive neuropeptides (eg, CGRP, substance P, and NO) and thus leads to neurogenic inflammation and headache [11]. In addition, peripheral or central sensitization may cause altered perception of usually non-painful stimuli [12].

As HM is rare and attack frequency is low, clinical drug trials have so far been deemed impossible and treatment largely follows guidelines for the common forms of migraine. There are no specific treatments for patients with known mutations. Most migraine-specific drugs for acute treatment only affect headache, whereas auras in HM often pose a greater burden to patients. Prophylactic treatment may not be strictly required because of low attack frequencies, but still prescribed because of the attacks' severity. Case reports and case series are currently the only guidelines for acute and prophylactic treatment of HM, and will be discussed in greater detail.

Diagnosis

Clinical symptomatology

Clinical diagnosis of HM is based on a physician's interview, led by the ICHD criteria of the International Headache Society (IHS) (see Table 1 [2]), and a physical examination, which mainly serves to exclude other disorders. To diagnose FHM, obtaining the family history is essential. HM patients have an increased risk to also suffer from attacks of the common forms of migraine with (MA) and without aura (MO) (ie, a co-prevalence risk of 55 % for MA and 25 % for MO), which often makes the interview difficult [13]. It may be challenging to distinguish complaints of sensory disturbances from those of a mild paresis. Apart

Table 1. Criteria for familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM) by the International Headache Society

Diagnostic criteria for FHM:
- A. At least 2 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 (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
  2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
  3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
  1. at least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
  2. each aura symptom lasts ≥5 min and <24 h
  3. headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows onset of aura within 60 min
- D. At least one first- or second-degree relative has had attacks fulfilling these criteria A–E
- E. Not attributed to another disorder

Diagnostic criteria for SHM:
- A. At least 2 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 (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
  2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
  3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
  1. at least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
  2. each aura symptom lasts ≥5 min and<24 h
  3. headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows onset of aura within 60 min
- D. No first- or second-degree relative has attacks fulfilling these criteria A–E
- E. Not attributed to another disorder

from motor auras, which are only experienced by HM patients, the symptoms and their order of appearance during attacks are very similar for HM and MA [14]. However, HM patients are more likely to experience 2 or more aura symptoms, symptoms of longer duration, and more often have basilar-type auras than MA patients [14, 15]. The mean age at onset of FHM is around 17 years (95 % CI: 15–18; range 1–45 years), which is lower than the average of 21 years for familial MA [14]. HM attack frequency, though variable, is much lower than that of MA with an average of 3 attacks per year [16•]. Similar to MO and MA, HM is 2–4 times more prevalent in females [1, 14]. Severe atypical HM attacks may be prolonged (up to 6 weeks) and accompanied by confusion, decreased consciousness, fever, seizures, and even coma [17–19]. These symptoms may divert physicians to other diagnoses. Triggering of attacks by a minor head trauma is commonly reported, with an average prevalence of 9 % in a large FHM cohort. Cerebral or coronary angiography can also trigger attacks [17]. Based on clinical symptoms alone, subtypes of HM cannot be distinguished, although the presence of additional symptoms (such as chronic progressive ataxia or epilepsy) may be suggestive of certain genetic subtypes.

Genetic testing

HM is genetically heterogeneous, with 3 identified genes. FHM shows autosomal dominant inheritance. FHM1 and SHM1 are caused by mutations in the *CACNA1A* gene on chromosome 19p13, encoding the ion-conducting, α_{1A} -subunit of P/Q-type voltage-gated Ca^{2+}-channels [20]. These channels are localized in presynaptic nerve terminals of central neurons and when activated increase neurotransmission [21]. Over 25 HM-associated *CACNA1A* mutations are identified, representing a broad clinical spectrum [21]. FHM1 families with chron-

ic progressive cerebellar signs, decreased level of consciousness and seizures during HM attacks have been described [17, 22]. The p.S218L *CACNA1A* mutation is associated with a particularly severe phenotype, in which minor head trauma led to seizures, cerebral edema, and even fatal coma [18]. The FHM2/SHM2 *ATP1A2* gene on chromosome 1q23 encodes the α_2-subunit of a Na^+/K^+-ATPase. This pump exchanges Na^+ ions for K^+ ions, creating a steep sodium gradient that facilitates removal of K^+ and glutamate from the synaptic cleft into glial cells [21]. Nearly 50 *ATP1A2* mutations have been identified, with increasing reports of additional clinical features, such as epilepsy, permanent mental retardation, prolonged hemiplegia, confusion, and coma [19, 21, 23–25]. In clear contrast to FHM1/SHM1, progressive cerebellar signs are rare in FHM2/SHM2 [26]. The FHM3 *SCN1A* gene on chromosome 2q24 encodes the α-subunit of voltage-gated Na^+-channels, which are expressed on inhibitory central neurons, and when dysfunctional may cause neuronal hyperexcitability [27]. So far, *SCN1A* mutations have only been found in FHM, which justifies refraining from systematic screening of the *SCN1A* gene in SHM [28, 29].

HM mutations all convert to a mechanism of increased cerebral levels of K^+ and glutamate in the synaptic cleft, which would increase neuronal excitability, and thereby can explain the increased susceptibility to Cortical Spreading Depression (CSD) [21].

Reported mutation detection rates vary between FHM and SHM. Although mutations appear to be more often detected in FHM, large unselected cohorts of FHM patients revealed *CACNA1A* mutations in 4 %–7 % [30, 31], and *ATP1A2* mutations in 7 % [30], while reported mutation detection rates in SHM range from 1 %–36 % for *CACNA1A* [28, 29, 32, 33], and from 1 %–56 % for *ATP1A2* [28, 29, 32]. In another study, 45 % of 20 FHM families had mutations in the *CACNA1A* or *ATP1A2* gene [27]. These large differences in detection rates may be explained by confusing severe MA with HM, or by investigating families with fewer affected individuals or more phenocopies (affected family members that are expected to be mutation carriers but are in fact not). Notably, mutation detection rates in SHM appeared to be higher in early-onset SHM, especially when associated with additional neurological symptoms [28]. Some clinically unaffected relatives carry *CACNA1A* or *ATP1A2* mutations, revealing reduced penetrance [23, 29, 30]. FHM3 families have thus far shown 100 % penetrance, though only 5 *SCN1A* mutations have been described [21].

As some clinically affected individuals do not have a mutation in any of the known genes, there are likely more HM genes to be identified. It is important to realize that negative test results for mutations in *CACNA1A*, *ATP1A2*, and *SCN1A* do not exclude the clinical diagnosis of HM.

Imaging

A cerebral MRI is recommended in every new HM patient to exclude other (structural) causes, especially when aura symptoms always occur on the same side. Permanent CT or MRI abnormalities are rare in HM. Cerebellar atrophy has been described in FHM1 patients with progressive cerebellar ataxia [22, 34]. In a few cases, cortical cerebral atrophy or diffuse cortical and subcortical hyperintensities on T2-weighted MRI were found [35]. During and shortly after HM attacks, reversible CT or MRI abnormalities have been described, which can be linked to both vascular and neuronal mechanisms. Most often reported is diffuse (cortical) edema of the hemisphere contralateral to the motor deficit [36–39]. However, whether this concerns vasogenic or cytotoxic edema or both, has not been unequivocally elucidated. Some MRIs show mild gadolinium enhancement, which indicates opening of the blood-brain barrier and vasogenic edema [40–42]. Other MRIs have shown reversible decrease in water diffusion, indicative of cytotoxic edema [36, 40]. Both hyper- and hypoperfusion of a single hemisphere have been observed with different techniques [37, 42, 43]. For all these phenomena it is difficult to determine whether they are primary or secondary. Large systematic follow-up imaging series using the same techniques in each patient are still lacking.

Electroencephalography (EEG)

EEG abnormalities have been recorded many times during and after HM attacks, consisting of diffuse one-sided slow waves (theta- and/or delta-activity) in the hemisphere contralateral to the side of the motor symptoms [25]. Such EEG abnormalities can thus support the suspicion of HM. Spike-and-wave complexes have only been recorded in cases where epileptic seizures were observed simultaneously [34, 44].

Cerebral angiography

Conventional and MR angiography have shown narrowing or even obliteration of intracranial arteries in the acute phase, though never followed by signs of ischemia [45,

46]. Dilatation of the middle cerebral artery has also been demonstrated [42]. Conventional cerebral angiography has however been reported to provoke HM attacks, or worsen a patient's condition dramatically [17, 19, 35, 47]. Cerebral angiography via a catheter is therefore contraindicated in HM, and alternatives such as MR of CT angiography are recommended.

Differential diagnosis

Sensory auras may cause the sensation of being unable to grasp or lift objects and may be interpreted as mild motor auras. Differences between loss of strength, numbness or lack of coordination must be emphasized during patient interviews. Symptomatic causes must be suspected when auras always occur on the same side, and cerebral vasculitis, arteriovenous malformations, arterial dissections, and brain tumors must be excluded by CT or MRI imaging. Though epilepsy and HM often co-occur, Todd's palsies can be confused with motor auras [17, 24, 44]. Migraine auras often start insidiously (within minutes), in contrast to vascular events or epileptic seizures that develop suddenly or within seconds. If an ischemic event cannot be excluded sufficiently, patients must be screened for thromboembolic disease.

HM may be accompanied by fever and decreased level of consciousness, making it difficult to distinguish from a meningo-encephalitis [38]. CSF lymphocytosis and elevated protein levels have often been reported during HM attacks [48].

Approximately 100 cases of transient headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) have been described, with remarkable resemblance to HM [49, 50]. CSF analysis reveals lymphocytosis and often increased protein levels, with normal neuroimaging, CSF culture, and virological tests. Transient, focal, nonepileptiform EEG changes, provocation of attacks by cerebral angiography, and even reversible radiological abnormalities are however reported [49–52]. While these characteristics are all congruent with HM, the spontaneous resolution of HaNDL within 3 months by definition is not. However, recurrence of attacks after 3 months cannot be excluded in most HaNDL patients, despite follow-up of up to 3 years. Apart from an incidental fever, the viral prodrome and fever in 50 % of HaNDL cases has not been described in HM. Visual auras were reported by 18 % of HaNDL patients, compared with 89 %–91 % of HM patients [16•, 49]. Genetic screening for HM was negative, but was only performed for the *CACNA1A* gene in 8 HaNDL patients [53]. Given all these similarities, HaNDL may not be a separate disorder, but part of the HM phenotypic spectrum, which however remains to be established.

When episodic hemiplegia occurs before the age of 18 months, alternating hemiplegia of childhood (AHC) may be considered. Recently, mutations in the *ATP1A3* gene were discovered in over 70 % of AHC patients, enabling confirmation of AHC and differentiation from HM [54].

A positive family history may point towards FHM, but it must be kept in mind that hemiplegic or prolonged aura attacks have been described in familial disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [55], and mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke (MELAS) [56].

Treatment

Diet and lifestyle

Stress, bright lights, sleep disturbances, physical exertion, drinks, and food products have all been reported as trigger factors for HM [57]. Recent evidence suggests that stress is more likely part of the premonitory phase of the migraine attack than a trigger, which may also apply to the other trigger factors [58]. A trigger factor that is convincingly described in HM is (minor) head trauma, which is often followed by severe attacks, sometimes including coma [17, 22, 25, 43, 44]. In specific cases with the p.S218L *CACNA1A* mutation, attacks were even fatal [18]. Based on these cases, patients can be advised not to practice contact sports.

Pharmacologic treatment

Prophylactic treatment with reported efficacy (see Table 2 for additional drug information)

Flunarizine

In animal studies, the long-acting Ca^{2+}-channel blocker flunarizine was suggested to block neuronal Na^{+} and Ca^{2+} currents and raise CSD thresholds, possibly decreasing cortical hyperexcitability [59]. Flunarizine 10 mg daily was effective in 3 HM case reports [39, 60, 61]. In a pediatric case series including 5 FHM and 8 SHM patients, flunarizine reduced attack frequency in 85 %, compared with 51 % in MO and MA patients. Adverse events were reported by 20 % of the 72 patients, leading to discontinuation in 18 %. These results may suggest that flunarizine is effective in HM [62].

Verapamil

Verapamil blocks L-type Ca^{2+}-channels, but at high doses may also block P/Q-type channels, which are involved in FHM1 [63]. In an HM patient, attack frequency decreased with oral verapamil 240 mg daily [64]. Five other SHM patients were either headache free or reported reduced attack severity and frequency on oral verapamil dosages of 120 to 360 mg daily [65, 66].

Sodium valproate

Sodium valproate inhibits GABA transaminase, activates glutamic acid decarboxylase, and blocks Na^{+} -channels and low-voltage-activated T-type Ca^{2+}-channels, causing enhanced neuronal inhibition [67]. Efficacy in migraine is often reported, including migraine with persistent aura, but efficacy in HM is only described in a case with co-occurring epilepsy, for both the generalized tonic-clonic seizures and the following HM 304 attacks [24, 68, 69].

Lamotrigine

Lamotrigine inhibits glutamate release by blocking voltage-gated Na^{+}-channels and N- and P/Q-type voltage-activated Ca^{2+}-channels [70]. In a double-blind randomized trial in the common forms of migraine, lamotrigine failed to show a benefit over placebo as prophylaxis [71]. Nonetheless, in 2 MA patients, persistent visual auras resolved after 100 mg lamotrigine daily [72]. Two pilot studies, one of which included patients with motor auras, observed beneficial effects on aura frequency and duration, not specified for aura symptoms [73, 74]. A study in 59 patients showed reduced frequency and intensity of all aura symptoms in 75 % of patients, including 8 patients with motor auras [75]. Two HM patients in a cohort with severe migraine auras showed reduced attack frequency after 3 to 6 months of 100–150 mg lamotrigine daily [76]. None of the studies reported an effect on headache. The specific effect on auras in these studies suggests a role for lamotrigine in treatment of migraine with disabling auras, such as HM.

Table 2. Additional information on prophylactic and abortive drugs with reported efficacy in hemiplegic migraine

Drug	Standard dosage	Contraindications	Main drug interactions	Main side effects	Special points	Costs
Flunarizine	10 mg daily	Depression, parkinsonism, extrapyramidal syndrome.	Phenytoin and carbamazepine reduce plasma levels, antacids and proton pump inhibitors lower biological availability. Alcohol and other central depressants amplify sedative effects.	Weight gain, increased appetite, drowsiness, depression, fatigue, extrapyrimidal reactions.	Treatment should be stopped after 6 months, and only restarted when attacks return. Contraindicated during pregnancy or lactation (effects unknown).	Relatively inexpensive.
Verapamil	120 mg 2–3 times daily, with a maximum of 240 mg 3 times daily.	Heart failure, 2nd or 3rd degree atrioventricular block, Wolff-Parkinson-White syndrome, sick-sinussyndrome, paroxysmal atrial fibrillation or flutter, sinusbradycardia, hypotension or recent myocardial infarction.	Beta-blockers, flecainide and amiodarone increase cardiac depressant effects; increased risk of bradycardia, conduction disturbances and digoxin toxicity with digoxin; remifentanil and sufentanil increased risk of bradycardia and hypotension; lithium has unpredictable interactions; verapamil increases blood alcohol levels.	Dizziness, headache, chest tightness, flushing, bradycardia, atrioventricular block (1^{st} degree), worsening of heart failure, hypotension, edema, nausea, fatigue and hyperprolactinemia.	Contraindicated during the first trimester of pregnancy, and only on strict indication during second and third trimester.	Relatively inexpensive.
Sodium valproate	500–2,000 mg daily, in divided doses.	Liver or pancreas dysfunction, hemorrhagic diathesis, porphyria.	Increased effects of barbiturates, antipsychotics, MAO-inhibitors, benzodiazepines, primidone, antidepressants, acetylsalicylic acid and anticoagulants; potentiation of toxic effect of carbamazepine; decreased metabolism of lamotrigine with increased risk of skin rashes; increased levels of valproate with felbamate; increased metabolism of valproate and risk of convulsions with mefloquine; decrease of valproate levels with carbapenenems.	Gastro-intestinal complaints, weight gain, tremor, liver damage, drowsiness, apathy, ataxia, confusion, encephalopathy, increased bleeding time due to an effect on trombocyte aggregation, and rarely bone marrow suppression.	Contraindicated in pregnancy because of risk of teratogenicity. Check children for side effects during lactation.	Relatively inexpensive.

Table 2. (Continued)

Drug	Standard dosage	Contraindications	Main drug interactions	Main side effects	Special points	Costs
Lamotrigine	Start-up dosage of 25 mg daily, slowly increasing to 100–200 mg daily, with a maximum of 500 mg daily.	None reported.	Effects on lamotrigine's glucoronidation may require dosage adjustments: decreased levels with concurrent use of phenytoin, carbamazepine, phenobarbital, primidon; increased plasma levels of oxcarbazepine and topiramate; increased levels and a higher chance of skin rash with valproate; decreased levels with oral contraceptives (which should be taken continuously).	Skin rash, dizziness, sleep disturbances, nausea, ataxia.	May increase reaction time. Abrupt withdrawal must be avoided. During pregnancy use only low doses and check blood levels. Check children for side effects during lactation.	Relatively expensive.
Acetazolamide	250 to 1,000 mg per day in divided doses.	Chronic noncongestive angle-closure glaucoma, sodium or potassium depletion, hyperchloremic acidosis, liver- and kidney insufficiency, M. Addison, pulmonary heart disease, hypersensitivity to sulphonamides.	Increased risk of metabolic acidosis and central toxicity with salicylates; increased risk of hypopotassemia with potassium wasting diuretics and corticosteroids; increased risk of osteomalacia with anticonvulsants; increased serum levels of phenytoin; increased renal excretion of lithium and primidone; reduced renal excretion of quinidine and methadon; potentiation of folic acid antagonists, oral hypoglycaemic agents and oral anticoagulants.	Paresthesiae, drowsiness, fatigue, dizziness, depression, weight loss and gastrointestinal disturbances.	With prolonged use and/or high dosages a metabolic acidosis can develop. Contra-indicated in pregnancy or during lactation.	Relatively expensive.

References: Information on contraindications, main drug interactions, main side effects, and special points: from MIMS online, Pharmacotherapeutic Compass (Dutch) Costs: based on calculations by the collective of health insurances in the Netherlands: The consumer reimbursement price is based on the Pharmacy Purchase Price and includes 6 % VAT as well as a 6.82 % clawback (with a maximum of € 6.80 per prescription), but without the dispensing fee for the pharmacist

Acetazolamide

Acetazolamide is clinically effective in episodic ataxia type 2 (EA-2), which is also caused by *CACNA1A* mutations [20]. Acetazolamide inhibits carbonic anhydrase and lowers serum bicarbonate levels. Modulation of pH may aid in stabilizing abnormal ion channels [77]. Acetazolamide 250 mg b.i.d. has been reported to either cease attacks or decrease attack frequency in 7 HM patients [22, 78–80]. Attacks relapsed in 2 patients after dosage reduction or discontinuation [79, 80]. An open trial including 5 patients with motor auras reported a stronger effect on attack frequency for MA than MO, but effects were not specified for aura symptoms [81]. A randomized, placebo-controlled trial with acetazolamide 250 mg b.i.d. for common migraine was stopped prematurely due to a high side effect rate of 80 % (especially paresthesiae) and 34 % drop out of patients [82]. Such results were unexpected, as EA-2 patients report good tolerance [77]. When other prophylactic drugs do not show efficacy, acetazolamide could be used in HM, with strict monitoring of side effects.

Other prophylactic drugs

Topiramate is a drug of first choice in prophylaxis of MO and MA and influences activity of Na^+ - and Ca^{2+}-channels, GABA-A receptors and the AMPA/kainate subtype of glutamate receptors. It may also weakly inhibit subtypes of carbonic anhydrases [68, 83]. Efficacy of topiramate in HM specifically has not been described. The only report mentions worsening of HM symptoms after 2 trials of 25 mg topiramate during 5 and 7 days, with prompt recovery after discontinuation [84].

Candesartan and pizotifen are drugs of second choice in migraine. Though clinical experience with these 3 drugs may be good, there is no literature to support prescription in HM yet.

Controversial prophylactic drugs

Beta-blockers

Propranolol and metoprolol are non-selective beta-blockers, with membrane-stabilizing properties and no intrinsic sympathicomimetic activity. Though commonly prescribed in migraine, beta-blockers have been postulated to induce cerebral infarcts or prolonged aura in migraineurs, partly by reducing cerebral blood flow [83, 85]. Other reports however, suggest that cerebral blood flow is not altered [86], and beneficial effects of propranolol in HM have been reported [22]. Cessation of attacks or decreased attack frequency was described in 2 FHM patients with propranolol and pizotifen [87]. Three other HM patients showed complete cessation of attacks for 13 months to 3 years with propanolol in daily doses of 30 to 80 mg [88]. Propranolol 160 mg daily resulted in marked reduction of aura and headache duration in another HM patient, but without improved attack frequency [43]. HM patients treated with metoprolol have not been described. Prescribing propran-

olol in HM remains controversial, and careful monitoring after the first use must be considered.

Abortive treatment with reported efficacy (see Table 2 for additional drug information)

Abortive treatment with 5 mg IV verapamil ceased headache and auras in 3 patients, during multiple HM attacks [64, 65, 89]. Acute treatment with acetazolamide in an FHM patient resolved aura symptoms within 1–3 h on 5 occasions, whereas normally hospitalization used to be required [90].

Controversial abortive drugs

Ergot alkaloids and triptans

Ergot alkaloids and triptans are migraine-specific drugs for acute headache treatment. Ergot alkaloids interact with adrenergic, dopaminergic, and serotoninergic receptors, including agonist effects on several 5-HT_1 receptor subtypes, and block release of substance P, and CGRP [7]. Triptans are 5-$HT_{1B/1D}$ receptor agonists, which constrict distended cerebral blood vessels and inhibit release of vasoactive neuropeptides and neurotransmitters from trigeminal nerves [8]. Triptans seem more effective than ergot alkaloids in clinical studies, and are preferred because of fewer side effects [91]. A study in isolated human coronary arteries deemed it unlikely that therapeutic levels of ergot alkaloids and triptans would cause cardiac ischemia in healthy individuals, though they remain contraindicated in coronary disease. Vasoconstriction lasted approximately 3 times longer with ergots than with triptans, making triptans the safer choice [92]. As auras were ascribed mainly to vasoconstriction, a fear of migrainous strokes or aggravation of auras led to the contraindication of triptans in HM. As CSD is now thought to underlie auras, physicians are questioning this contraindication [93]. Thirteen migraineurs with prominent auras, including motor auras in 4 patients, were treated with several triptans without adverse events [93]. A Finnish cohort of 40 FHM and 36 SHM patients showed good to excellent response to triptans in 47 patients and poor response in only 11 patients. Side effects were minor, like chest pain, nausea and fatigue, although a triptan may have induced or enhanced 1 HM attack [94]. Serious adverse events with triptans in HM appear to be rare, and beneficial effects on the disabling attacks may overrule the risks.

Ketamine

Ketamine is a non-competitive N-methyl-d-aspartate-receptor Ca^{2+}-channel antagonist that blocks glutamate, and may also interact with opioid receptors. In clinical studies, ketamine produced general and local anesthesia [95]. As NMDA-receptor antagonists blocked CSD in animal studies, trial doses of 25 mg ketamine were administered via a nasal spray to 11 FHM patients, with some improvement of auras and headache severity, while 6 patients reported no benefits, and

feelings of alienation and mild ataxia were reported as side effects [96]. Because ketamine may cause dependence and tolerance with prolonged use, and has dangerous effects in larger dosages, its use is currently not considered appropriate for HM patients.

Nimodipine

Apart from possible efficacy of flunarizine and verapamil, not all calcium antagonists appear to be safe in HM. A trial treatment with IV nimodipine 5–10 ml per h in HM with prolonged aura led to worsening of aura symptoms within hours and a generalized tonic-clonic seizure the next day. Though nimodipine may prevent vasospasms by lowering the calcium influx, in this case it may have increased arterial hypotension, resulting in cerebral hypoperfusion and hypoxia. Because of the severe adverse events in this case, nimodipine is not advised in prolonged HM attacks [43].

Future pharmacologic treatment

CGRP receptor antagonists

CGRP is involved in sensory neurotransmission, and is present in meningeal trigeminovascular afferents that may be involved in migraine [11]. CGRP antagonists, such as telcagepant, have been effective in acute migraine treatment in several clinical trials and appear not to cause vasoconstriction, which would be a major benefit compared with triptans [97, 98]. Evidence of liver toxicity with prophylactic use has however halted further trials with telcagepant, and efficacy in HM has not yet been investigated [99•].

Interventional procedures – surgery-assistive devices

Neuromodulation is rapidly emerging in the treatment of various headache disorders [100]. No studies have yet been performed in HM, and although some devices seem promising in headache treatment, specific trials will have to be awaited. The same is true for injections with botulinum toxin.

Pediatric considerations

Because HM attacks often start at a young age, many case reports concern children. Children under 5 years old are rarely diagnosed with HM, because they are unable to express their complaints. The prophylactic drugs acetazolamide, lamotrigine, sodium valproate, flunarizine, propranolol, topiramate, and pizotifen can be used in dosages adjusted to the child's body weight. The efficacy and safety of candesartan has not been investigated in children. Ergot alkaloids are insufficiently investigated in children and should not be prescribed. Triptans should not be prescribed to children under 12 years old and only considered if children just under 18 years old have an adult body weight.

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