Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management

Michael Bjørn Russell, Anne Ducros

Hemiplegic migraine is a rare form of migraine with aura that involves motor aura (weakness). This type of migraine can occur as a sporadic or a familial disorder. Familial forms of hemiplegic migraine are dominantly inherited. Data from genetic studies have implicated mutations in genes that encode proteins involved in ion transportation. However, at least a quarter of the large families affected and most sporadic cases do not have a mutation in the three genes known to be implicated in this disorder, suggesting that other genes are still to be identified. Results from functional studies indicate that neuronal hyperexcitability has a pivotal role in the pathogenesis of hemiplegic migraine. The clinical manifestations of hemiplegic migraine range from attacks with short-duration hemiparesis to severe forms with recurrent coma and prolonged hemiparesis, permanent cerebellar ataxia, epilepsy, transient blindness, or mental retardation. Diagnosis relies on a careful patient history and exclusion of potential causes of symptomatic attacks. The principles of management are similar to those for common varieties of migraine, except that vasoconstrictors, including triptans, are historically contraindicated but are often used off-label to stop the headache, and prophylactic treatment can include lamotrigine and acetazolamide.

Introduction

Migraine is a common disorder that causes attacks of disabling headaches that can be accompanied by an aura in a third of patients. The few patients who have a motor weakness during the aura qualify for hemiplegic migraine. Isolated cases are diagnosed as having sporadic hemiplegic migraine, whereas patients who have at least one affected first-degree or second-degree relative are diagnosed as having familial hemiplegic migraine. Recurrent motor paralysis in migraine was first described in 1910, and then again more than 40 years later. Analysis of publications on affected families suggests that familial hemiplegic migraine has an autosomal dominant mode of inheritance. This conclusion led to extensive searches in the 1990s for the gene(s) for familial hemiplegic migraine. The first major breakthrough was the identification of a linkage with chromosome 19p, followed by identification of mutations in three different genes involved in ion transportation, which can all cause familial hemiplegic migraine.

Typical hemiplegic migraine attacks start in the first or second decade of life and include gradually progressing visual, sensory, motor, aphasic, and often basilar-type symptoms, accompanied by headaches. Most patients also have attacks of migraine with typical aura—without weakness. Co-occurrence of migraine without aura is similar to the prevalence reported in the general population. The clinical presentation of sporadic and familial cases with identified mutations varies from pure hemiplegic migraine to severe early-onset forms with recurrent coma and cerebral oedema, permanent cerebellar ataxia, and, rarely, epilepsy, elicited repetitive transient blindness, or mental retardation.

In this Review, we focus on the clinical presentation of sporadic and familial hemiplegic migraine, with a detailed description of hemiplegic migraine attacks, including associated paroxysmal and permanent neurological features and phenotypic heterogeneity. We assess pathophysiological and genetic evidence to facilitate insight into the clinical picture, and we discuss the mechanisms leading from genetic mutations to various manifestations and the association between hemiplegic migraine and the most common forms of migraine. We also provide an approach to the diagnostic assessment, differential diagnosis, and management of this challenging disorder.

Classification

The International Classification of Headache Disorders II (ICHD II) distinguishes two main forms of attacks: migraine without aura and migraine with aura; the latter is further subdivided according to the various aura and headache symptoms. Typical migraine with aura includes hemispheric symptoms but no motor aura. Basilar-type migraine includes symptoms originating from the brainstem or both hemispheres, but no weakness. Patients with hemiplegic migraine have complex aura symptoms that, in addition to motor aura, can include any of the aura symptoms of migraine with aura or basilar-type migraine. Diagnostic criteria for sporadic and familial hemiplegic migraine are similar, except for familiarity—ie, no affected relatives vs affected first-degree or second-degree relative(s).

Epidemiology

Whereas migraine without aura affects 15% of the population and migraine with aura affects 8% of the population, occurrence of hemiplegic migraine is rare. About 100–200 families affected by familial hemiplegic migraine and about 200 patients affected by sporadic hemiplegic migraine have been published, although no...
worldwide studies have been done.2–142 The only population-based epidemiological survey of sporadic and familial hemiplegic migraine was done in Denmark and these data indicated that the prevalence of the sporadic form was at least 0·002%29 and that the prevalence of the familial form was at least 0·003%.28

Hemiplegic migraine can be divided into two main clinical subgroups. Most patients have pure sporadic or familial hemiplegic migraine. In the remaining cases, hemiplegic migraine attacks are associated with other neurological manifestations, the most frequent being permanent cerebellar signs.8,13,17–20,24–26,28,30–45

### Genetics

#### Familial hemiplegic migraine

Mutations in the ion transportation genes CACNA1A, ATP1A2, and SCN1A can all cause the familial hemiplegic migraine phenotype, thus indicating genetic heterogeneity in this disorder (table 1 and figure 1).20–22 The familial forms of hemiplegic migraine caused by these mutations are referred to as FHM1, FHM2, and FHM3, respectively. CACNA1A encodes the main subunit of Ca₂.1 neuronal channels.20 More than 30 FHM1 mutations have been identified in familial and sporadic cases:20,21,26,31–33,37,39–36,46,50,58–66 they are mostly of the missense type. The mutation that causes the Thr666Met substitution is present in 40% of unrelated FHM1 families. Different CACNA1A mutations cause episodic ataxia type 2 and spinocerebellar ataxia type 6.20,34 CACNA1A was first reported as the main familial hemiplegic migraine gene, and was first reported to be mutated in half the large families affected, including all those with permanent cerebellar signs.20,26

ATP1A2 encodes the α2 subunit of the A1A2 glial sodium–potassium ATPase pump.21 More than 60 FHM2 mutations have been identified in familial and sporadic cases.20,27–29,33,36 Most are missense mutations found in single families with pure familial hemiplegic migraine. Other ATP1A2 mutations were reported in a family with basilar-type migraine34 and in two families with common migraines, but without functional proof of causality.57 Screening of the 44 Danish families with familial hemiplegic migraine identified mutations in only 14%, with an equal percentage in CACNA1A and ATP1A2.44

SCN1A encodes the pore-forming subunit of neuronal Na₁.1 channels.21 So far, only five FHM3 mutations have been reported in five families.22,28–30 SCN1A was already known to be involved in epilepsy.144,145 Recently, a mutation in SLC1A3, encoding the glial glutamate transporter EAAT1, was identified in a boy with pure hemiplegic migraine.81 This mutation decreased glutamate uptake in a cellular assay.82 Two other SLC1A3 mutations that affected glutamate uptake had been previously associated with episodic ataxia type 6.82,83 Finally, a homozygous deletion in SLC4A4, encoding the electrogenic sodium bicarbonate (Na⁺–HCO₃⁻) co-transporter NBCe1, was associated with familial hemiplegic migraine in two sisters also affected by renal tubular acidosis and ocular abnormalities.84 SLC1A3 and SLC4A4 might be the fourth and fifth genes to be implicated in familial hemiplegic migraine.

### Sporadic hemiplegic migraine

Sporadic cases of hemiplegic migraine can be caused by a de-novo mutation in a gene that causes the familial form or by inheritance of a gene mutation from an asymptomatic parent with familial hemiplegic migraine.27–29 The three main genes that cause familial hemiplegic migraine seem to have minor roles in pure sporadic hemiplegic migraine because no SCN1A mutation has been found yet and only a few CACNA1A and ATP1A2 mutations have been reported in patients with the sporadic form. Similar to the nomenclature used for familial hemiplegic migraine, we suggest that sporadic hemiplegic migraine caused by mutations in the CACNA1A and ATP1A2 genes should be referred to as SHM1 and SHM2. In a Dutch clinic-based sample, the rate of mutation identification was less than 20%, and was even lower (<10%) in a Danish population-based sample.26,27 Most published sporadic cases with CACNA1A and ATP1A2 mutations have severe phenotypes with associated neurological manifestations.26,27,57,59 Furthermore, de-novo CACNA1A or

### Table 1: Ion transportation genes and hemiplegic migraine

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>Type of mutation</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACNA1A</td>
<td>19p12</td>
<td>More than 30 different missense mutations, large-scale deletions, a five base-pair deletion in the 5' end promoter</td>
<td>67–89%21–44</td>
</tr>
<tr>
<td>ATP1A2</td>
<td>1q23</td>
<td>Catalytic α2 subunit of a glial and neuronal sodium-potassium pump</td>
<td>63–87%21–44</td>
</tr>
<tr>
<td>SCN1A</td>
<td>2q24</td>
<td>Five missense mutations</td>
<td>100%21–44</td>
</tr>
</tbody>
</table>

Penetrance was calculated on the basis of results from cited studies. Only genotyped families were taken into account. FHM=familial hemiplegic migraine.
ATP1A2 mutations were reported in 76% of a series of patients with early-onset sporadic hemiplegic migraine (before the age of 16 years) and frequent associated neurological signs.\(^{75}\)

Mutations in the three genes implicated in familial hemiplegic migraine seem to be present mainly in large families, and in familial or sporadic cases with early-onset hemiplegic migraine with or without associated neurological signs. In pure sporadic and familial hemiplegic migraine, predominantly in population-based samples, other dominant genes with reduced penetrance are most probably implicated. A subset of sporadic and familial cases might even have multifactorial inheritance involving a combination of genetic and environmental factors.

**Pathophysiology**

**Cortical spreading depression**

Migraine aura is indicative of a reversible cerebral cortical dysfunction that is most probably caused by cortical spreading depression.\(^{134}\) Cortical spreading depression is characterised by a brief neuronal excitation, which initiates a depolarisation wave that moves across the cortex at a rate of 3–5 mm/min and is followed by a prolonged inhibition of neuronal activity.\(^{146,150}\) Cortical spreading depression activates the trigeminovascular system in animals.\(^{156}\)

**Electrophysiological studies**

Results from extensive studies of cellular and animal models have indicated that gene mutations in familial hemiplegic migraine increase neuronal excitability and reduce the threshold for cortical spreading depression (figure 1).\(^{73,148}\) Briefly, FHM1 mutations induce gain-of-function effects with enhanced calcium ion influx through single \(\text{Ca}_2.1\) channels and increased neurotransmitter release.\(^{73,150}\) Knock-in mice that harbour human FHM1 mutations have a reduced threshold for cortical spreading depression and a disrupted balance of cortical neurotransmission with an increased probability of excitatory glutamate release but with unaltered inhibitory GABAergic circuits.\(^{151-153}\) FHM2 mutations produce varying extents of loss of function of the \(\alpha_2\) sodium–potassium ATPase.\(^{73,161,162}\) Mutated pumps probably induce impaired glial reuptake of potassium and glutamate from the synaptic cleft with subsequent slow recovery from neuronal excitation.\(^{157}\) FHM3 mutations have complex consequences and are thought to affect the inhibitory activities of interneurons and thus also result in hyperexcitability.\(^{73,157,158}\)

Electrophysiological studies have been done in a few patients with familial hemiplegic migraine. Data from one study indicated an increased habituation of visual-evoked potentials and nociception-specific blink reflexes in patients with FHM1 and FHM2, whereas patients with common migraine have deficient habituation, suggesting differences in central neuronal processing.\(^{159}\) In studies with transcranial magnetic stimulation\(^{160}\) and single-fibre electromyography,\(^{161}\) no changes or only subtle abnormalities were reported.\(^{162}\) Future electrophysiological studies on larger samples are important for research purposes, but are not part of routine investigation of hemiplegic migraine.

Neuronal hyperexcitability and abnormal glutamate metabolism might have pivotal roles not only in familial hemiplegic migraine, but also in the most common forms of migraine. A susceptibility locus for migraine with aura and migraine without aura was recently located between two genes regulating glutamate concentrations in the brain.\(^{163}\) Moreover, a mutation in the gene encoding KCNK18 (also known as TRESK), a two-pore domain potassium channel, was associated with migraine with aura in one family.\(^{164}\) KCNK18 is thought to modulate neuronal excitability. These new data strengthen the hypothesis that all migraine forms might share at least some common mechanisms.\(^{77}\)

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**Figure 1: Functional roles of proteins encoded by genes involved in FHM at a CNS glutamatergic synapse**

The presynaptic neuron receives input from an inhibitory GABAergic interneuron. An astrocyte is shown next to the synaptic cleft. \(\text{Ca}_2.1\) channels are located in the presynaptic terminal of both excitatory and inhibitory neurons. In response to an action potential, these channels allow \(\text{Ca}^{2+}\) to enter the presynaptic terminal and trigger glutamate release into the synaptic cleft. FHM1 mutations cause impairments in the \(\text{Ca}_2.1\) \(\text{Ca}^{2+}\) channels, which lead to disruption in the balance of cortical neurotransmission with increased probability of excitatory glutamate release, contrasting with unaltered inhibitory GABAergic circuits. \(\text{Na}^+\)-\(\text{K}^+\) ATPase pumps are expressed at the surface of glial cells in adults. Normal pumps remove \(\text{K}^+\) from the synaptic cleft to limit neuronal excitability and maintain a \(\text{Na}^+\) gradient across the cell membrane, which drives uptake of glutamate from the cleft by transporters such as EAAT1. FHM2 mutations result in mutated \(\text{Na}^+\)-\(\text{K}^+\) ATPase pumps that most probably impair glial reuptake of \(\text{K}^+\) and glutamate with subsequent slow recovery from neuronal excitation. Na\(_{1,1}\) voltage-gated \(\text{Na}^+\) channels are mainly expressed on inhibitory interneurons, where they initiate and propagate action potentials. FHM3 mutations lead to impairments in Na\(_{1,1}\) voltage-gated \(\text{Na}^+\) channels and are predicted to affect the inhibitory activities of GABAergic interneurons. Thus, dysfunction of the three ion transporters results in increased concentrations of glutamate and \(\text{K}^+\) in the synaptic cleft, rendering the brain more susceptible to cortical spreading depression. Data from recent studies suggest that mutations in two new genes are also associated with FHM: SLC4A4 encoding the glutamate transporter EAAT1,\(^{161}\) and SLC1A3 encoding the glutamate transporter EAAT1.\(^{164}\) Although further studies are needed, both mutated gene products could affect neuronal excitability by deregulating synaptic pH for the sodium bicarbonate cotransporter NBCe1 and by affecting glutamate reuptake for EAAT1 (also known as SLC1A3). FHM=familial hemiplegic migraine. Na\(_+=\)sodium ion. K\(_+=\)potassium ion. Ca\(_{2+}\)=calcium ion.
Clinical features

Attacks are similar in sporadic and familial hemiplegic migraine,28,29 although these episodes have a notable variability among patients, which is partly explained by the genetic heterogeneity alongside probable modifying environmental and genetic factors.26 Table 2 lists the sex distribution, mean age at onset, and attack frequency of hemiplegic migraine. Onset is usually during youth. The mean frequency of attacks is quite low (three attacks per year) but highly variable.24,26,27,40,165 Frequency and severity often decrease in adulthood.28–30 Long intervals without an attack (up to 37 years) are possible.26

Trigger factors

Minor head trauma is frequently reported as a trigger for hemiplegic migraine,8,13,17,18,24,26,27,30,37,38,43,51,63,71,88,91,92,94–96 whereas it is rarely ever reported in patients with migraine with aura.167 Catheter angiography might trigger and worsen hemiplegic migraine attacks.4,17,26,27,63 Patients with hemiplegic migraine also attribute attacks to exertion and emotional stress,26,27,168 although these factors are probably unspecific triggers because they are also frequently reported in migraine with or without aura.167,169 Patients with familial hemiplegic migraine are not hypersensitive to calcitonin gene-related peptide and nitric oxide, by contrast with patients with migraine with or without aura.170–172 These data suggest that the mechanisms leading to the initiation of cortical spreading depression might differ between familial hemiplegic migraine and the most common forms of migraine.

Aura in hemiplegic migraine

Table 3 lists aura features in patients with sporadic or familial hemiplegic migraine or migraine with aura from the Danish general population.28,29 Motor weakness is always associated with at least another aura symptom, the most frequent being sensory symptoms.20,24–29,40 The different aura symptoms slowly progress over 20–30 min and occur in succession, mainly in the order of visual, sensory, motor, aphasic, and basilar disturbances.2,28,29 Acute-onset aura evolving in less than 1 min is possible but rare.28,29

Visual symptoms in hemiplegic migraine consist of positive features (flickering spots or zigzag lines) with or without a negative feature (scotoma). Patients might describe a typical visual aura, usually a homonymous white flickering zigzag line that gradually progresses from the centre of vision to the periphery of the visual field over 20 min and then disappears.29 However, some patients have only a scotoma.

Sensory symptoms in hemiplegic migraine also combine positive (pins and needles, painful or cold sensations) and negative (numbness) features.27–29 Patients often describe a typical sensory aura that starts as tingling in one of the fingers and gradually progresses to the other fingers, up to the arm, and then affects the face, tongue, and later the body and leg.29 In other patients, positive features are followed by numbness. Sometimes negative sensory features are predominant and include alien-limb syndrome or substantial deep sensory loss.27,29

Motor weakness involves areas affected by sensory symptoms and varies from mild clumsiness to complete deficit. Sensory-motor symptoms usually start in one hand and gradually spread up to the arm and the face. These symptoms can be restricted to one limb or can spread all over one side of the body. They can be bilateral (35% in FHM1), occurring simultaneously or in succession, or remain unilateral, switching side from attack to attack, or always involving the same side.21,26,28,29 Speech disturbances mostly affect expression, with rare comprehension impairment.28,29 Basilar-type symptoms are frequent and diverse (table 3).28,29

<table>
<thead>
<tr>
<th>Sex distribution (men:women)</th>
<th>FHM1</th>
<th>FHM2</th>
<th>FHM3</th>
<th>FHM unknown genotype</th>
<th>SHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>In large families</td>
<td>1:125</td>
<td>1:125</td>
<td>1:125</td>
<td>1:1</td>
<td>–</td>
</tr>
<tr>
<td>In the general population</td>
<td>1:2:3</td>
<td>1:16</td>
<td>1:16</td>
<td>1:2.3</td>
<td>1:4.3</td>
</tr>
<tr>
<td>Mean age at onset (years; range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With pure hemiplegic migraine</td>
<td>12 (6–28)</td>
<td>11 (1–20)</td>
<td>13 (6–24)</td>
<td>16 and 21 years in men and women</td>
<td></td>
</tr>
<tr>
<td>With additional cerebellar signs</td>
<td>12 (1–51)</td>
<td>26 (6–52)</td>
<td>17 (1–45)</td>
<td>8 (1–25); 9 (4–42)</td>
<td></td>
</tr>
<tr>
<td>In the general population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In clinic samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attack frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In large families</td>
<td>One per day to five in a lifetime</td>
<td>Ten per month to four in a lifetime</td>
<td>Twice per week to five in lifetime</td>
<td>From two to &gt;100 in a lifetime</td>
<td>From two to &gt;100 in a lifetime</td>
</tr>
<tr>
<td>In the general population</td>
<td></td>
<td></td>
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</tbody>
</table>

FHM=familial hemiplegic migraine. SHM=sporadic hemiplegic migraine.
The ICHD II states that the duration of the motor aura should be less than 24 h. However, weakness frequently lasts 2–3 days in up to 20% of patients with FHM1 and FHM2, and there are several published examples of reversible hemiplegia that lasted up to 4 weeks.24,26–29,96,97 We suggest that the revised version of the ICHD II reintroduces “migraine with prolonged aura”, because the current classification does not incorporate these prolonged attacks.1

Hemiplegic versus non-hemiplegic aura
Compared with typical migraine with aura, characteristics of hemiplegic migraine auras are: presence of a motor aura and complexity with more than two aura symptoms in most patients; higher frequency of sensory, aphasic, and basilar symptoms; higher frequency of all negative aura features; lower frequency of visual symptoms; and longer duration (table 3).166,173 Positive aura features might be indicative of the neuronal excitation during cortical spreading depression, whereas negative features might be caused by the prolonged neuronal depolarisation after cortical spreading depression. Intriguingly, aphasic and motor auras result in only negative symptoms. The long duration of hemiplegic migraine aura is mainly associated with persistent negative features, suggesting a more pronounced neuronal depolarisation in hemiplegic migraine.28,29 Sensory aura and aphasic aura are infrequent in typical migraine with aura, possibly because the cortical spreading depression wave can cease anywhere after its occipital onset and thus does not reach the sensory cortex and the cortical language areas.166 Because the sulcus centralis separates the primary sensory and motor cortices, the cortical spreading depression in hemiplegic migraine needs to travel a longer distance over the surface of the brain or through deeper brain structures to spread from the sensory to the motor cortices. Therefore, the sulcus centralis possibly prevents the motor cortex being affected, meaning that motor aura is rare. The absence of visual aura symptoms in 10% of patients with hemiplegic migraine in population-based studies,28,29 and in more than 20% of patients with FHM1 and FHM2 from clinical studies,26,27 suggests that cortical spreading depression could start in the occipital cortex and become symptomatic only when reaching the sensory cortex or that it might directly start elsewhere or in the sensory cortex.

Headache
Headache is present in all attacks in most patients (95%).28,29 Pain mostly starts during the aura after onset of visual symptoms (75%), but might also start before the aura.28,29 Headache can be bilateral or unilateral, ipsilateral, or contralateral to the motor weakness.32,33 Unilateral headache that is contralateral to the aura symptoms is reported to be equally as frequent as headache ipsilateral to the aura symptoms, but the pathophysiological basis for ipsilateral headache and aura symptoms is difficult to understand and this form is

<table>
<thead>
<tr>
<th>Motor aura</th>
<th>FHM² (n=147)</th>
<th>SHM⁵ (n=105)</th>
<th>Migraine with aura¹¹ (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>100%</td>
<td>100%</td>
<td>Absent</td>
</tr>
<tr>
<td>Unilateral</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Face/tongue</td>
<td>51%/57%</td>
<td>45%/48%</td>
<td></td>
</tr>
<tr>
<td>Hand/arm</td>
<td>98%/93%</td>
<td>99%/92%</td>
<td></td>
</tr>
<tr>
<td>Foot/leg</td>
<td>59%/59%</td>
<td>50%/50%</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>30%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Acute motor aura &lt;5 min</td>
<td>10%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Mean gradual progression time</td>
<td>27 min</td>
<td>28 min</td>
<td></td>
</tr>
<tr>
<td>Mean duration</td>
<td>5 h 36 min</td>
<td>7 h 5 min</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Visual aura</th>
<th>FHM² (n=147)</th>
<th>SHM⁵ (n=105)</th>
<th>Migraine with aura¹¹ (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>89%</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>Unilateral</td>
<td>61%</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>Flickering light/zigzag lines</td>
<td>89%/50%</td>
<td>81%/50%</td>
<td>87%/81%</td>
</tr>
<tr>
<td>Scotoma</td>
<td>79%</td>
<td>81%</td>
<td>50%</td>
</tr>
<tr>
<td>Acute visual aura &lt;5 min</td>
<td>16%</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>Mean duration</td>
<td>16 min</td>
<td>22 min</td>
<td>25 min</td>
</tr>
<tr>
<td>Mean duration</td>
<td>1 h 40 min</td>
<td>2 h 04 min</td>
<td>33 min</td>
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<table>
<thead>
<tr>
<th>Sensory aura</th>
<th>FHM² (n=147)</th>
<th>SHM⁵ (n=105)</th>
<th>Migraine with aura¹¹ (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>98%</td>
<td>98%</td>
<td>31%</td>
</tr>
<tr>
<td>Unilateral</td>
<td>100%</td>
<td>99%</td>
<td>84%</td>
</tr>
<tr>
<td>Face/tongue</td>
<td>85%/81%</td>
<td>93%/82%</td>
<td>67%/62%</td>
</tr>
<tr>
<td>Hand/arm</td>
<td>99%/95%</td>
<td>100%/95%</td>
<td>96%/78%</td>
</tr>
<tr>
<td>Foot/leg</td>
<td>68%/67%</td>
<td>59%/60%</td>
<td>23%/23%</td>
</tr>
<tr>
<td>Body</td>
<td>35%</td>
<td>28%</td>
<td>18%</td>
</tr>
<tr>
<td>Acute sensory aura &lt;5 min</td>
<td>9%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Mean duration</td>
<td>32 min</td>
<td>30 min</td>
<td>32 min</td>
</tr>
<tr>
<td>Mean duration</td>
<td>3 h 43 min</td>
<td>4 h 54 min</td>
<td>1 h 12 min</td>
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<thead>
<tr>
<th>Aphasic aura</th>
<th>FHM² (n=147)</th>
<th>SHM⁵ (n=105)</th>
<th>Migraine with aura¹¹ (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>72%</td>
<td>81%</td>
<td>18%</td>
</tr>
<tr>
<td>Paraphasia or difficulty finding words</td>
<td>66%</td>
<td>52%</td>
<td>75%</td>
</tr>
<tr>
<td>Impaired language production</td>
<td>96%</td>
<td>94%</td>
<td>72%</td>
</tr>
<tr>
<td>Impaired comprehension</td>
<td>10%</td>
<td>5%</td>
<td>38%</td>
</tr>
<tr>
<td>Mean duration</td>
<td>3 h 7 min</td>
<td>3 h 19 min</td>
<td>43 min</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Basilar-type aura</th>
<th>FHM² (n=147)</th>
<th>SHM⁵ (n=105)</th>
<th>Migraine with aura¹¹ (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>69%</td>
<td>72%</td>
<td>10%²⁰¹*</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>73%</td>
<td>69%</td>
<td>53%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>72%</td>
<td>54%</td>
<td>61%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>29%</td>
<td>17%</td>
<td>45%</td>
</tr>
<tr>
<td>Hypacusia</td>
<td>48%</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>51%</td>
<td>28%</td>
<td>45%</td>
</tr>
<tr>
<td>Bilateral visual symptoms</td>
<td>53%</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>Ataxia or loss of balance</td>
<td>72%</td>
<td>54%</td>
<td>9%</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>31%</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>Simultaneous bilateral paresthesias</td>
<td>11%</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>Mean duration</td>
<td></td>
<td></td>
<td>1 h</td>
</tr>
</tbody>
</table>

The percentage within each category is the percentage of the total (overall figure) of those with the specific aura symptom. FHM=familial hemiplegic migraine. SHM=sporadic hemiplegic migraine. *From 105 families with 362 individuals affected by migraine with aura.

Table 3: Comparison of aura symptoms in patients with FHM, SHM, and typical migraine with aura from the Danish general population
probably caused by recall bias. Ipsilateral aura and headache symptoms were reported in only 10% and 6% of attacks in two prospective studies.\textsuperscript{40, 57} Characteristics are usually those of a typical attack of migraine without aura (ie, a severe pulsating unilateral headache with nausea, vomiting, phonophobia, and photophobia).\textsuperscript{36, 58} However, headache can last for more than 3 days in 2% of patients with hemiplegic migraine and can sometimes reach an excruciating intensity.\textsuperscript{26, 29, 30} By contrast, some patients with hemiplegic migraine have mild headaches (non-migraine without aura) or, rarely, no headache at all.\textsuperscript{20, 39}

**Other paroxysmal features**

**Severe attacks with impaired consciousness**

Patients with hemiplegic migraine are at risk of major episodes of coma and encephalopathy.\textsuperscript{36, 41, 42, 43, 51, 56, 57, 62, 63, 66, 67, 68, 95–101} Attacks with coma are rare in the Danish population-based sample (<2%), which mainly includes families without CACNA1A and ATP1A2 mutations.\textsuperscript{28} By contrast, severe attacks with coma affect up to a third of patients with FHM1 and 15% of patients with FHM2.\textsuperscript{26, 27} Decreased consciousness ranging from confusion and somnolence to profound coma with respiratory failure is frequently but not always associated with motor deficit (80%), fever (47%),\textsuperscript{12, 16} and meningismus (16%).\textsuperscript{26, 36} Severe attacks can also include seizures, agitation, and complex delusions.\textsuperscript{26, 36, 37} Seizures (8% in FHM1) can be tonic or clonic and partial or generalised, sometimes evolving to status epilepticus.\textsuperscript{26, 37, 41, 51, 66, 72, 86–89} Seizures occurring independently from hemiplegic migraine attacks have been reported in more than 10% of the Danish patients with familial hemiplegic migraine and migraine without aura.\textsuperscript{26, 37} Impaired consciousness and all aura symptoms of severe hemiplegic migraine attacks last several days to several months until full recovery is achieved.\textsuperscript{26, 40, 52, 96, 102, 103} Clinical investigations frequently indicate CSF pleocytosis and cortical oedema in these patients.\textsuperscript{37, 51, 52, 94, 101, 102, 106–108} Severe attacks mostly occur during youth but can affect patients from the age of 1 year to older than 80 years.\textsuperscript{26, 27} The first attack\textsuperscript{36, 37} can occur during pregnancy\textsuperscript{25, 93, 103} or be triggered by trauma (25%)\textsuperscript{26, 29, 30, 41, 70, 89} or by angiography.\textsuperscript{37} Recurrence is possible.\textsuperscript{36} Rarely, major attacks can cause irreversible brain damage and atrophy,\textsuperscript{99} stepwise cognitive deterioration,\textsuperscript{51} or even death.\textsuperscript{36, 37, 41, 46, 103} The FHM1 Ser218Leu mutation seems to confer the highest risk of severe trauma-triggered attacks with brain oedema.\textsuperscript{51, 93, 102, 111} Results from cellular and murine models of the Ser218Leu mutation have indicated more pronounced consequences than for the Arg192Gln mutation, which is associated with a mild form of pure FHM1.\textsuperscript{101, 103}

**Migraine without aura and typical migraine with aura**

In previous studies of selected large families, about 15% of patients with familial hemiplegic migraine also had migraine with aura and 34% had migraine without aura.\textsuperscript{26, 37, 41, 51, 62, 63} In a Danish population-based study, the occurrence of migraine without aura and typical migraine with aura in probands with familial hemiplegic migraine and their first-degree relatives was investigated.\textsuperscript{103} Compared with the general population, probands and first-degree relatives had no increased risk of migraine without aura, indicating that familial hemiplegic migraine and migraine without aura are unrelated. By contrast, probands and first-degree relatives with familial hemiplegic migraine had a significantly increased risk of typical migraine with aura, suggesting that typical migraine with aura in these cases might be attributable to abortive attacks of hemiplegic migraine. Moreover, in the few Danish families with identified FHM1 and FHM2 mutations, the penetrance of hemiplegic migraine was incomplete (about 65%) and five of the 13 mutation carriers without hemiplegic migraine had attacks of typical migraine with aura.\textsuperscript{104} Incomplete penetrance of familial hemiplegic migraine could thus explain the small size of most affected families identified in the Danish population-based studies, and the fact that some family members might have attacks of typical migraine with aura only as a milder phenotype.

In another Danish study, the occurrence of migraine with and without aura in probands with sporadic hemiplegic migraine and their first-degree relatives was investigated.\textsuperscript{105} Compared with the general population, sporadic hemiplegic migraine probands had no increased risk of migraine without aura but had an increased risk of typical migraine with aura. First-degree relatives of all sporadic hemiplegic migraine probands, including those with other types of migraine attacks, had an increased risk of migraine with and without aura. First-degree relatives of probands who exclusively had sporadic hemiplegic migraine attacks had no increased risk of migraine without aura but had an increased risk of typical migraine with aura. These data indicate that some patients with sporadic hemiplegic migraine truly have a non-inherited form of this migraine with possible de novo mutations, whereas other patients with sporadic hemiplegic migraine might be part of families affected by typical migraine with aura in which only one member has exaggerated attacks of migraine with aura that present as hemiplegic migraine.

**Epilepsy**

Seizures occurring independently from hemiplegic migraine attacks have been reported in more than 60 familial and sporadic cases with mutations in CACNA1A,\textsuperscript{27, 51, 52, 75, 89, 94, 101, 103} ATP1A2,\textsuperscript{27, 52, 93, 94, 103} and SCN1A.\textsuperscript{27, 50, 108} Seizures were partial or generalised and febrile or afebrile. Most seizures started during childhood, sometimes preceding the first hemiplegic migraine attack, and had a benign evolution. Penetration of epilepsy in familial hemiplegic migraine ranges from two or fewer cases in most families to 30–60% in a small subset of FHFM2 families.\textsuperscript{51, 107} Epilepsy was reported in 7% (n=10) of the Danish patients with familial hemiplegic migraine, whereas less than 1% (n=5) of non-affected relatives had epilepsy.\textsuperscript{36} Mutations
in all three genes associated with familial hemiplegic migraine might induce not only cortical spreading depression but also abnormal neuronal discharges leading to epilepsy in some patients.

**Elicited repetitive daily blindness**
Elicited repetitive daily blindness was reported to cosegregate with hemiplegic migraine in two unrelated families affected by FHM3 and consists of transient blindness lasting up to 10 s followed by a refractory period of about 30 s.80,118 Blindness can be triggered by sudden change of light, direct illumination, standing, and eye rubbing and develops from peripheral vision to central vision. The fast development of blindness makes it consistent with a retinal spreading depression wave-like propagation rather than with a brain cortical spreading depression that propagates slowly (3–5 mm/min).

**Permanent neurological features**
Although most patients with sporadic and familial hemiplegic migraine are affected by pure hemiplegic migraine, a few patients have permanent neurological manifestations associated with hemiplegic migraine attacks.28,29

**Cerebellar signs**
Cerebellar signs are the most frequent manifestation associated with hemiplegic migraine and are encountered in up to 20% of published families.8,13,17–20,30–35,38,119 but in only 4.5% of the Danish families.88 These signs affect two-thirds of FHM1 and SHM1 cases. In affected families, cerebellar signs cosegregate with hemiplegic migraine but are not found in all those with hemiplegic migraine.24–26,17,45,19 Cerebellar signs include a gaze-evoked horizontal, vertical, or multidirectional nystagmus with or without a slowly progressive moderate statokinetic ataxia.25 Dysarthria is less frequent 26 and gait usually remains autonomous. Cerebellar signs might be present before the first hemiplegic migraine attack,30–32 and are rarely the only phenotypic expression of FHM1.28,30–32 Up to 25% of patients have cerebellar atrophy (figure 2).7,18,21,23,30,41,113 FHM1 with ataxia is attributable to specific mutations that differ from those that cause pure FHM134 and can have peculiar consequences on cerebellar Ca2.1 currents, leading to profound Purkinje cell dysfunction and ultimately to neuronal loss with atrophy.111 Although initially thought to be restricted to FHM1, cerebellar signs have now been reported in a few patients with FHM2.27,60,70,100

**Mental retardation**
Various degrees of mental retardation have been reported in at least 36 patients with hemiplegic migraine with a mutation in CACNA1A or ATP1A2, including 15 de-novo sporadic cases.25,46,47,71,40,40,102–105,106 Most patients had severe phenotypes with early-onset hemiplegic migraine attacks, recurrent coma, and epilepsy in addition to cognitive impairment. In familial forms, only one or two family members with hemiplegic migraine had cognitive impairment. Mental retardation might be diagnosed either before the onset of hemiplegic migraine attacks35 or, more often, after the onset of severe attacks.38,43,68,89,111 In the few children with normal early development and a notable stepwise developmental regression after the onset of severe hemiplegic migraine attacks, these severe attacks are suggested to result in permanent impairment.40,43,60,89 Although rare, these cases should lead clinicians to be cautious when providing genetic counselling. Finally, late-onset cognitive decline with rapidly progressive ataxia has been reported in one patient with a CACNA1A mutation who had infrequent hemiplegic migraine attacks.56 However, data from this study did not provide any evidence of causality linking the CACNA1A mutation to the observed cognitive dysfunction.

**Diagnosis and investigations**

**Diagnosis**
Diagnosis of hemiplegic migraine relies on a meticulous description of the aura and on the exclusion of symptomatic causes.1 Distinguishing between motor and sensory aura can be extremely difficult when relying on

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**Figure 2:** MRI and magnetic resonance angiogram of the brain of a 47-year-old patient who has had FHM since childhood
(A,B) Cerebral MRI done on day 2 of a severe attack with right hemiplegia, aphasia, fever, and substantial somnolence. Fluid-attenuated inversion-recovery sequences show a mild thickening of the cortical ribbon over the left hemisphere (arrows). (C,D) 2D time-of-flight magnetic resonance angiogram shows vasoconstriction of the left middle cerebral artery (arrows). The motor deficit resolved after 18 days and language normalised after 1 month.
Diagnosis of familial hemiplegic migraine is dependent on obtaining a family history of similar attacks, which can be hampered by recall bias. Surprisingly, elderly patients who have received a definite diagnosis of hemiplegic migraine can forget at long-term follow-up that their migraine attacks once included a motor deficit. Moreover, the diagnosis of sporadic hemiplegic migraine can change to familial hemiplegic migraine during clinical follow-up in probands with or without mutations in the known genes when another family member develops hemiplegic migraine attacks. Severe attacks with coma remain a diagnostic challenge even in patients with a firm diagnosis of hemiplegic migraine. These attacks require systematic investigations to rule out other causes and need close monitoring until improvement.

Differential diagnosis
A first episode of motor deficit with or without headaches requires urgent and exhaustive investigations to search for all possible causes, which mainly include stroke, mass lesions, and infectious or inflammatory diseases. In hemiplegic migraine, clinical signs and eventual CSF and imaging abnormalities are reversible (table 4), but no firm diagnosis can be made after a single attack.

A diagnosis of epilepsy is often made incorrectly in hemiplegic migraine, mostly in children or in the few patients who have attacks without headaches, although a detailed description usually helps to differentiate seizures (sudden and usually <1 min) from hemiplegic migraine auras (progressive and >20 min). A few patients with hemiplegic migraine have seizures and assessment follows routine epilepsy management. Similarly, recurrent transient ischaemic attacks (abrupt negative symptoms, rare headaches, vascular risk factors) are usually distinguished from hemiplegic migraine attacks (progressive and successive positive and negative symptoms, headaches, no vascular risk factors). Doubtful cases should be investigated as transient ischaemic attacks.

The most severe early-onset forms of SHM1 and SHM2 can be difficult to distinguish from alternating hemiplegia of childhood. This sporadic disorder has an onset before 18 months and causes paroxysmal spells of hemiplegia, quadriplegia, choreoathetotic movements, and nystagmus that disappear immediately after sleep, along with progressive mental retardation, dystonia, and ataxia.

Isolated cases have been reported in which recurrent hemiplegic migraine attacks were considered as symptomatic of meningioma, meningitis and encephalitis, Sturge-Weber syndrome, and various inflammatory or metabolic disorders. Finally, hemiplegic migraine attacks have been reported in patients with hereditary cerebral angiopathies, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and amyloid angiopathy and with mitochondrial encephalopathies such as mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke (MELAS). Therefore, personal or familial history of permanent neurological deficits, strokes, seizures, dementia, and MRI abnormalities should prompt the search for disorders other than familial hemiplegic migraine.

Genetic testing
Screening of the three genes for familial hemiplegic migraine is most useful in early-onset sporadic cases with associated neurological signs and in familial cases when the severity of attacks or permanent neurological features are different from those of affected relatives. The identification of a disease-causing mutation will establish a definite diagnosis and might avoid the need for repeated unnecessary investigations. However, in

<table>
<thead>
<tr>
<th>Possible abnormal findings during a severe attack</th>
<th>Between attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT or MRI of the brain</td>
<td>Cerebral oedema with swelling of cortical ribbon Cerebellar atrophy (FHM1)</td>
</tr>
<tr>
<td>Cerebral angiography</td>
<td>Vasocostriction or vasodilatation</td>
</tr>
<tr>
<td>Transcranial doppler of the cerebral arteries</td>
<td>Diffuse or localised increase in intracranial velocities</td>
</tr>
<tr>
<td>EEG</td>
<td>Diffuse slow waves contralateral to the motor deficit can persist for several weeks Sometimes sharp waves or dysrhythmia Seizures or status epilepticus are rare</td>
</tr>
<tr>
<td>CSF</td>
<td>White blood cells are elevated (aseptic meningitis); usual findings are 12–290 white blood cells per mm³, mainly lymphocytes but sometimes neutrophil granulocytes Protein elevated up to 3 g/l, Normal glucose concentrations</td>
</tr>
</tbody>
</table>

FHM=familial hemiplegic migraine. SHM=sporadic hemiplegic migraine. *Catheter angiography should be avoided as it might trigger a severe attack.

Table 4: Paraclinical findings in patients with FHM and SHM during a severe hemiplegic migraine attack and between attacks
the absence of functional studies that are not routinely feasible, the identification of a novel point mutation often raises the question of whether the mutation will cause disease or whether it is a non-pathogenic polymorphism.

Mutations that affect an important functional domain of the protein and that co-segregate with hemiplegic migraine in the affected family, or that are de-novo mutations in sporadic hemiplegic migraine, are probably pathogenic.

Clinical investigations
So far, no prospective studies of clinical investigations in large series of patients with familial or sporadic hemiplegic migraine have been done. Imaging and CSF studies done during or after a usual attack have normal results (or might show incidental abnormalities), except in FHM1 or SHM1 with cerebellar atrophy (figure 2 and table 4). By contrast, investigations during severe attacks with confusion, coma, and prolonged deficit can indicate substantial abnormalities (table 4). Use of CT and MRI can reveal a cortical oedema contralateral to the hemiparesis, sometimes involving the whole hemisphere.17,37,61,71,88,91,92,95,96,99,107,108,128–130 MRI scans can show hyperintensities on fluid-attenuated inversion-recovery (FLAIR) and T2-weighted images (figure 2), normal or hyperintensities in fluid-attenuated inversion-recovery both the headache and hemiplegia in one patient with CACNA1A mutations. SHM=sporadic hemiplegic migraine.

Because aura symptoms are sometimes more bothersome than headaches, a treatment that abolishes the aura is in demand. Ketamine blocks NMDA glutamate receptors, and nasal administration of ketamine reduced the duration of aura in five of 11 patients with familial hemiplegic migraine.138 Intravenous verapamil abolished both the headache and hemiplegia in one patient with familial hemiplegic migraine,133 but only stopped the headache and did not affect the hemiplegia in another patient.139 Nimodipine given during a prolonged attack of FHM2 provoked a seizure and should therefore be avoided.66

The use of triptans in hemiplegic migraine is still being debated. These drugs are historically contraindicated by manufacturers for this type of migraine, and patients with hemiplegic migraine have been excluded from clinical trials. Some physicians and health professionals still fear that the vasoconstrictor properties of triptans can worsen the aura. However, triptans have been shown to be safe and effective in typical migraine with aura. In a retrospective study of 76 patients with hemiplegic migraine, triptans were indicated to be safe and effective for the treatment of the headache in attacks, although one patient had a prolonged attack that lasted several months after triptan treatment.66 One of the authors (AD) uses triptans for the treatment of headaches in hemiplegic migraine attacks, except in patients with severe attacks. Dihydroergotamine and Midrin (isometheptene mucate, dichloralphenazone, and paracetamol) are also contraindicated in sporadic and familial hemiplegic migraine, on the basis of the same concern that vasoconstriction might aggravate the aura.

Prophylactic management is applied to patients with frequent, long-lasting, or severe attacks. All drugs that are effective in the prevention of common migraines can be used in hemiplegic migraine. Oral verapamil 120 mg 1–3 times daily was an effective prophylactic treatment in five patients with sporadic hemiplegic migraine.164,165,166 However, one of the authors (AD) used verapamil in
several patients with sporadic or familial hemiplegic migraine without notable efficacy. Additionally, drugs that are ineffective in the prevention of migraine without aura could be used in hemiplegic migraine. Acetazolamide was tried on the basis of its remarkable efficacy in episodic ataxia type 2 and had a beneficial effect in some patients with familial hemiplegic migraine. Lamotrigine, a sodium channel blocker that decreases neuronal release of glutamate, was effective in a study that included 59 patients with migraine with aura of whom eight had motor aura, but the effect was not specified for those with hemiplegic migraine. Therefore, lamotrigine can be tried in patients with sporadic or familial hemiplegic migraine.

Finally, the effects of the most recent acute and prophylactic migraine treatments, such as calcitonin gene-related peptide antagonists or onabotulinum toxin A, are unknown in patients with hemiplegic migraine.

Conclusions

Sporadic and familial hemiplegic migraine are rare forms of migraine with aura that also involve motor aura in addition to other aura symptoms. Genetic studies have implicated three genes in familial hemiplegic migraine, which are all involved in ion transportation. Data from studies of cellular and murine models have indicated that neuronal hyperexcitability and glutamate have a pivotal role in the mechanisms of familial hemiplegic migraine and most probably in the most common forms of migraine. However, only a subset of sporadic and familial hemiplegic migraine cases has a mutation in one of the known familial hemiplegic migraine genes. These patients have a wide range of clinical symptoms, from pure hemiplegic migraine to severe early-onset hemiplegic migraine with permanent ataxia, comatose attacks with brain oedema, epilepsy, elicited repetitive daily blindness, or mental retardation. By contrast, most cases of sporadic and familial hemiplegic migraine in population-based studies have no mutations in the known genes, have pure hemiplegic migraine with benign course, and have an increased risk of migraine with aura, possibly owing to abortive attacks of hemiplegic migraine; however, these patients do not have an increased risk of migraine without aura. These data suggest that these cases are associated with autosomal dominant mutations in other as-yet unidentified genes with reduced penetrance or multifactorial inheritance.

As familial hemiplegic migraine will continue to be one of the main models to study molecular genetics of migraine, future studies should focus on the identification of the genes implicated in pure familial hemiplegic migraine. This approach should be followed by studies of the functional consequence(s) of the identified genes. Because of the intrafamilial phenotypic variations, other genes most probably have a modifying effect on the major autosomal dominant genes for familial hemiplegic migraine identified so far. Identification and investigation of these genes will be important for elucidating the full story of hemiplegic migraine. Subsequently, the main challenge is to establish whether the research findings for hemiplegic migraine are also valid for the common types of migraine.

Contributors
Both authors contributed equally to the conception, design, literature search, and writing of this Review.

Conflicts of interest
MBR has received payment for board membership and lectures from Allergan. AD has received payment for board membership from Novartis, payment for lectures from Almirall, AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer, and has received travel or accommodation and meeting expenses from Almirall and Pfizer. MBR has received grants paid to his institution (from the University of Oslo, Helse SørØst, Akershus University Hospital). AD has received grants paid to her institution (from the Fondation Thérèse et René Paniol pour l’étude du Cerveau).

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