Case report

Novel missense mutation in the ATP1A2 gene associated with atypical sporadic hemiplegic migraine

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SUMMARY

Hemiplegic migraine (HM) is a rare subtype of migraine with aura in which attacks include transient motor weakness or hemiparesis that can last several days. HM is linked to mutations in three different genes, CACNA1A, ATP1A2 and SCN1A, which encode for ion transporters. The clinical spectrum includes atypical symptoms such as impaired consciousness, epileptic seizures, permanent cerebellar ataxia or mental retardation. We describe a novel mutation found in the ATP1A2 gene in a patient with late-onset HM. His attacks were characterised by motor weakness associated with altered mental status, diplopia and ataxia. He also showed up MRI abnormalities and incomplete response to prophylactic therapy with verapamil. Late-onset HM should be considered among the possible causes of focal neurological deficits even in older patients with cerebrovascular risk factors when a stroke appears to be more likely.

BACKGROUND

Hemiplegic migraine (HM) is a rare subtype of migraine with aura (MA) in which attacks include transient motor weakness or hemiparesis that can last several days.¹ Other reversible, focal neurological signs or symptoms, such as visual disturbances, language impairment, paraesthesias and basilar-type symptoms, can be associated. HM patients also have an increased risk to suffer from migraine with typical aura, whereas co-occurrence of migraine without aura is similar to that reported in the general population.¹ The estimated prevalence of HM is about 0.01%, according to the only population-based survey performed in Denmark.^{2,3} It exists in two recognised forms: familial hemiplegic migraine (FHM) when at least one first-degree or second-degree relative is affected or sporadic hemiplegic migraine (SHM) when no relative fulfils the diagnostic criteria for HM.⁴ Typical attacks can be triggered by specific foods, emotional stress and minor head trauma.⁵ Mean age at onset ranges from 11 to 13 years old in pure FHM and from 8 to 19 years old in SHM.¹ Attacks may begin as early as age 5 years or start later in life, even at 75 years old.^{2,6} So far, FHM is linked to mutations in three genes, CACNA1A (FHM1-MIM#301011), ATP1A2 (FHM2-MIM#182340) and SCN1A (FHM3-MIM#182389), which encode for ion transporters. SHM can be caused by mutations in these genes, which can be de novo mutations

or inherited mutations from an asymptomatic parent. However, most patients with SHM do not have a detectable FHM gene mutation.¹ Recently, also proline-rich transmembrane protein 2 (PRRT2-MIM#614386) has been associated with HM.⁷ The clinical spectrum of HM varies from pure forms to those associated with other neurological disorders such as impaired consciousness, epileptic seizures, permanent cerebellar ataxia or mental retardation.⁶

We herein describe the clinical and radiologic findings in a patient with SHM.

CASE PRESENTATION

A 71-year-old man was admitted to the emergency room in March 2015 with a 2-day history of migraine associated with vomiting, left-sided weakness and paraesthesias, ataxia, diplopia and acute confusion. There was no history of head trauma, seizure or dehydration preceding the episode. His vital signs and temperature were normal. He had a history of MA since he was young and bilateral moderate internal carotid stenosis. Two similar episodes of motor weakness without loss of consciousness have occurred 25 and 10 years before that admission, with complete and spontaneous resolution after 3 days. His daughter experienced some episodes of migraine never associated with other symptoms. His family history was otherwise unremarkable.

The patient was awake, but markedly agitated and provided inappropriate responses to questions. The neurological examination showed an evident left hemiparesis. During hospitalisation, he also developed visual hallucinations.

INVESTIGATIONS

CT of the head was unremarkable. A brain MRI performed the day after admission revealed a T2 hyperintensity in the right temporoparietal region with mild cortical swelling and sulcal effacement. This area showed restricted diffusion and contrast enhancement (figure 1). Magnetic resonance angiography revealed no meaningful abnormalities except for the lower signal intensity of the left middle cerebral artery.

Meningoencephalitis was first hypothesised and then excluded through a lumbar puncture. Although cerebrospinal fluid (CSF) protein concentration (67 mg/dL; normal range 18–43 mg/dL) and CSF-serum IgG concentration quotient (4.10; normal range 1.39–3.80) were elevated, IgG index, CSF glucose levels and cell count were within normal limits. CSF

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Figure 1 MRI of the brain. Bilateral T2 hyperintensity with predominance in the right hemisphere on FLAIR sequences; mild cortical swelling and sulcal effacement in right temporoparietal region (A); lower signal intensity of the left MCA on magnetic resonance angiography (B); contrast enhancement in the right temporal region on gadolinium post-contrast graphic T1 sequences (C, D). FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery.

tests for infections were negative. His complete blood cell, coagulation profile, electrolytes, renal function and liver function were normal. Electroencephalogram (EEG) did not show the presence of epileptiform discharges or slow activity.

One week later, repeat brain MRI revealed disappearance of contrast enhancement with persistent cortical swelling. Symptoms progressively improved during hospitalisation. At discharge, there were no focal neurological deficits or headache. Therefore, we hypothesised an HM condition and performed related genetic analysis. A novel heterozygous missense mutation (NM_000702.3:c.2860G>C) was found in the ATP1A2 gene (HM type 2 mutation) causing a Gly-Arg substitution (ENSP00000354490.3:p.Gly954Arg). This nucleotide variation has not been described in the literature, and it is not reported in genetic variations database. Gly954 is highly conserved between different species. Different bioinformatics prediction programme, such as SIFT (Sorting Intolerant From Tolerant)/PROVEAN (Protein Variation Effect Analyzer) and PolyPhen-2 (Polymorphism Phenotyping), indicate a very dangerous effect for a Gly954 substitution (PROVEAN: deleterious; SIFT: damaging; PolyPhen-2: probably damaging).

The mutation was not present in his two daughters. The absence of other family members affected by HM led to a diagnosis of HM with sporadic occurrence (SHM).

TREATMENT

The patient started prophylactic long-term therapy with verapamil 40 mg two times per day, with beneficial effects on the frequency and severity of migraine attacks.

OUTCOME AND FOLLOW-UP

A follow-up visit performed 18 months later showed an alert and oriented patient without focal neurological signs. He remained

asymptomatic and experienced only moderate migraine attacks until December 2018, when he was hospitalised due to an episode of intense migraine associated with insomnia, acute confusion and visual hallucinations. On this occasion, no motor weakness was identifiable, but he presented a tendency to retro-pulsion. Given that no acute lesions were found on CT and symptoms progressively disappeared during hospitalisation, he was diagnosed with another episode of atypical migraine with concomitant altered mental status. At 4 months' follow-up, he was completely asymptomatic. To note, during the last years, he developed psychomotor slowing and mild cognitive impairment, as reported by relatives.

DISCUSSION

We present an unusual case of late-onset SHM type 2 with prolonged hemiplegia, acute confusion, visual hallucinations and brain MRI abnormalities in a 71-year-old man with a novel missense mutation found in the ATP1A2 gene. This gene encodes the $\alpha 2$ subunit of the Na^+/K^+ -ATPase, abundantly expressed in skeletal muscle and brain astrocytes, which regulates the excitable properties of muscle and nerve cells.¹ All HM mutations lead to neuronal hyperexcitability by increasing cerebral levels of K^+ and glutamate in the synaptic cleft, thus facilitating cortical spreading depression (CSD), which is likely responsible for aura symptoms.⁴

Our patient experienced his first hemiplegic attack at 46 years, that is quite late compared with the literature data.^{1,2,8} One-third of patients experienced their first attack by age 30 years, while 97% had the onset of SHM by age 45 years. Moreover, patients often stop experiencing attacks after the age of 50 years.²

According to a French study, patients who experienced their first attack before 16 years old and those showing permanent neurological symptoms associated with HM have a high of carrying an FHM gene mutation.⁹ On the contrary, our patient developed his first hemiplegic attack in the middle age and he did not show permanent neurological deficits, except for mild cognitive impairment and bradypsychism, which could be attributable to ageing.

The clinical presentation was atypical for SHM because motor weakness was associated with altered mental status, diplopia and ataxia.⁴ These unusual characteristics made the proper diagnosis quite difficult. However, self-limited acute encephalopathy accompanying familial or sporadic HM has been described as the presenting symptom even in a previously healthy 10-year-old boy with a *de novo* mutation in the CACNA1A gene.¹⁰

There are only sparse data on imaging abnormalities in HM. The rarity of the entity did not allow to establish a strong association between abnormal MRI findings and HM. The vast majority of patients with HM has normal neuroimaging. Some MRIs show mild gadolinium enhancement, which indicates the opening of the blood-brain barrier and vasogenic oedema. Other MRIs reveal a reversible decrease in water diffusion, due to cytotoxic oedema.¹¹ These alterations are located in the hemisphere contralateral to the motor weakness¹² and often disappear over some weeks or months, following neurological deficits resolution.¹³ Some patients present white matter hyperintensities (WMHs) on MRI T2 sequences, especially in the posterior regions.^{10,12,14,15} A recent study compared the occurrence of WMHs in 50 patients with SHM and migraine headache, showing that WMHs are significantly more common in the SHM group, especially in the parietal lobe.¹² WMHs could be the result of a transient hypercoagulable state during an acute HM attack, with consequent silent infarcts appearing as hyperintense lesions

on T2-weighted images.¹⁴ Their predilection for parietal lobe in SHM patients may be explained by taking into account that sensory auras are more frequent than motor ones, since obstacles like central sulcus may prevent cortical depression wave progression.¹² This suggests a possible role for hypoperfusion occurring during aura in generating WMHs, even if some studies found no significant differences in their prevalence among subjects with and without aura.^{12–14} In our patient, mild gadolinium enhancement and alterations in water diffusion were present in the first MRI. According to literature, changes in water diffusion are not usually observed even in cases with prolonged aura symptoms, but they can often be identified in severe attacks associated with altered mental status.¹⁶ As expected, T2-weighted images also revealed bilateral WMHs in subcortical and deep white matter due to our patient's long history of MA.

The management of HM is empirical and similar to that of common types of migraine.¹ Current therapeutic recommendations based on isolated case reports suggest prophylactic treatment with flunarizine, verapamil, valproate, lamotrigine and acetazolamide to reduce frequency and severity of migraine attacks.² Verapamil appears to be effective in treating headache and hemiplegia, especially when intravenously administered and in patients with CACNA1A mutations. It is a calcium antagonist that acts on the L-type calcium channel, blocking calcium influx and reducing vasoconstriction.¹⁷ We chose verapamil among the other drugs to achieve a combined therapeutic effect on blood pressure, which was mildly elevated during hospitalisation. Prophylactic treatment was successful in reducing the frequency and severity of common migraine attacks. However, verapamil did not prevent the second episode of severe headache associated with psychotic symptoms, which required hospitalisation. Of note, our patient takes verapamil 40 mg two times per day, due to concomitant mild bradycardia, while the recommended dose is 120 mg two or three times in a day.⁴

Patients affected by HM may be misdiagnosed for years, receiving inappropriate testing and therapies. A strong suspicion is necessary to achieve the correct diagnosis since there are no specific signs and symptoms. For example, they can arrive at the emergency room mimicking an acute ischaemic stroke. Nevertheless, while vascular events develop suddenly or within seconds, migraine auras often start insidiously requiring at least some minutes.² Our patient had different risk factors for cerebrovascular disease, like high cholesterol levels and atherosclerosis. However, the absence of acute ischaemic lesions on brain MRI excluded the ischaemic aetiology. Meningoencephalitis was also ruled out through CSF analysis. We only found abnormal protein levels in CSF, probably due to the alteration of the blood-brain barrier secondary to CSD associated with migraine aura.¹⁸

Through CSF analysis, we also excluded the syndrome of transient headache and neurological deficits with CSF lymphocytosis

(HaNDL) that can present with migraine, hemiparesis and aphasia without a family history.¹⁹

Subarachnoid haemorrhage was another possible explanation due to ongoing severe headache and disorientation, but CT of the head excluded bleeding in the subarachnoid space. EEG did not show epileptiform abnormalities, thus excluding a seizure with subsequent Todd's paralysis. CADASIL (MIM#125310) was also taken into consideration due to migraine, psychosis and focal neurological deficits, but no mutation was discovered in the NOTCH3 gene (MIM#600276) by sequencing. Other possible differential diagnoses were metabolic abnormalities associated with focal deficits, but carbon dioxide, glucose blood level, electrolytes, liver function and renal function were within normal limits.

Since there are no pathognomonic clinical, laboratoristic or radiologic findings to diagnose HM, a thorough diagnostic workup is needed to exclude other possible explanations for the patient's symptoms. Our patient suffered from MA since he was young but presented his first episode of motor weakness at 46 years old. Prolonged SHM attacks lasting up to 3 weeks have been reported in children with de novo mutations in the ATP1A2 gene.^{20–22} Only one of them developed acute confusion,²¹ while MRI abnormalities were described in two cases.^{21–22} None of them experienced visual hallucinations. Even if reported mutations are scattered throughout the gene, the majority of them are concentrated in the intracellular linker between the fourth and fifth transmembrane segments, which may affect the correct folding of the protein.^{21–22} On the contrary, we found a novel mutation in the ninth transmembrane domain, which could be responsible for the atypical phenotype, since different mutations in FHM genes partly account for clinical variability.⁶ However, more extensive clinical studies are needed to establish a genotype-phenotype correlation.

Correction notice This article has been corrected since it was first published online. The spelling of "sporapedic" has been corrected to "sporadic" in the article title.

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Learning points

- Hemiplegic migraine is a genetic disorder linked to mutations in CACNA1A, ATP1A2 and SCN1A genes, encoding for ion transporters;
- Late-onset hemiplegic migraine can present with atypical symptoms, like acute confusion, visual hallucinations and brain MRI abnormalities;
- Hemiplegic migraine should be taken into consideration among the possible differential diagnoses even in older patients with cerebrovascular risk factors.

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