

Intellectual Decline in a Patient with Migraine and APT1A2 Mutation: A Case Report

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Case report

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Abstract

Background: Hemiplegic migraine (HM) is a rare type of migraine with aura. Some reports have described the clinical manifestations in HM patients with the ATP1A2 mutation. But the impact of the ATP1A2 mutation on intelligence in HM patients has not been evaluated in detail. Here we report a patient with intellectual decline in specific area.

Case presentation: A 15-year-old boy with an aura that included disturbances in consciousness, associated with fever, vomiting, hemiplegia, and aphasia. He was diagnosed HM with the ATP1A2 mutation before. He had trouble in mathematics and depicting three-dimensional things.

Conclusions: The HM with ATP1A2 patient could develop permanent intellectual disabilities. Therefore, the intelligence quotient should be carefully and comprehensively evaluated.

Background

Hemiplegic migraine (HM) is a rare type of migraine with aura, with an incidence of 0.1% in the European population [1, 2]. The specific clinical manifestations include completely reversible limb weakness, paresthesia, aphasia, etc [3]. HM is divided into two types: sporadic and familial based on its occurrence in first and second degree relatives [4]. This diagnosis is not definitive since it changes from sporadic hemiplegic migraine (SHM) to familial hemiplegic migraine (FHM) once its presence is confirmed in relatives. HM is a monogenic disorder with incomplete penetrance [5]. The confirmed pathogenic genes are mapped to be CACNA1A, ATP1A2, and SCN1A [5]. Some reports have described the clinical manifestations in HM patients with the ATP1A2 mutation and indicated that they are more prone to disturbances in consciousness, fever, epilepsy [6], and sometimes experience psychotic aura [7]. However, the impact of the ATP1A2 mutation on intelligence in HM patients has not been evaluated in detail. We carefully assessed the cognitive function of a 15-year-old boy who was diagnosed with HM and had an ATP1A2 mutation. We found that there was a decline in certain intellectual categories in this patient.

Case Presentation

In 2009, a 4-year-old developmentally normal boy, studying in kindergarten (born without birth asphyxia) was brought with sudden onset of vomiting, convulsions, crying, fever, and restlessness after intake of food. At admission in the emergency department, he developed altered sensorium. The boy was thus transferred to the intensive care unit (ICU) for further treatment. In the ICU, a lumbar puncture, magnetic resonance imaging (MRI) of the brain, and blood investigations were performed. All test results were normal. A diagnosis of "viral encephalitis" was considered and he was treated for the antiviral therapy. The family was unable to recall the specific antiviral medications administered to him. His fever settled after 4 days and he opened his eyes after 6 days. After 2 weeks, he could talk briefly but had not started walking yet. After 1 month, he could speak and walk normally.

By March 2018, he had experienced four similar episodes. All episodes were precipitated by increased intake food, with disturbances in consciousness, associated with fever, vomiting, hemiplegia, and aphasia. He was diagnosed as having "viral encephalitis" at least twice in two different hospitals. In 2010, he was diagnosed as having "epilepsy" following an abnormal electroencephalogram (EEG) report and was initiated on oral phenobarbital at 0.1 g that was administered once a day. After taking phenobarbital for 3 years, he was asked to discontinue its use after a repeat EEG examination because there were no further similar episodes.

In July 2018, wanted to figure out the episodes, boy was referred to another hospital, where he underwent whole-exome gene sequencing. The presence of a mutation in the ATP1A2 gene was confirmed and he was diagnosed with HM. He was treated with flunarizine and nimodipine subsequently. He stopped taking his medications after developing hypotonia, sweating, decreased night sleep, increased daytime sleep, and rash.

In May 2020, he suffered from right limb hemiplegia, aphasia, altered sensorium, fever, and vomiting after increased food intake, and was referred to our hospital. Physical examination revealed a body temperature of 39°C and a Glasgow Coma Scale of 9/15. Based on his medical history and the presentation at the time of admission, we performed a lumbar puncture, brain MRI, EEG and blood investigations including biochemistry, and coagulation tests after admission. His cerebrospinal fluid (CSF) pressure was 120 mmH₂O. And the rest of the CSF analysis was normal, too. His brainMRI showed increased cortical sulci in the left cerebral hemisphere on the flair sequences (figure 1). EEG shows abnormal slow waves were present on the left frontal area, central area, parietal area, with bilateral epileptiform discharge (Fig. 2). Blood test results revealed an increase in the percentage of white blood cells and neutrophils. He was treated with mannitol to reduce edema and cefuroxime for infection control. His fever settled 3 days later, physical activity on the right side improved and he could get out of bed, but he continued to be aphasic. After 6 days in the hospital, he developed sudden left-sided gaze palsy and convulsions after an increase in food intake. We added 250 mg of levetiracetam orally, twice daily. He was discharged from our hospital after 10 days of treatment. At discharge, he had no fever, and his right limb muscle strength was 5/5, but he could only say some simple words. One month later, he was followed up in the outpatient clinic when he was able to walk and communicate normally.

During the hospitalization, his mother was probed in detail about his condition before hospitalization. His mother felt that his intellect was worse than that of his peers, especially in mathematics. He could communicate with classmates normally and interact with his friends on his own. He was very good in language but not in math. He could only solve the most basic addition and subtraction problems. When he followed up in the outpatient clinic, MoCA test was performed. His MoCA is 25(3/3/1/1/1/2/1/2/5/6). His mother disclosed that he liked to draw but had trouble depicting three-dimensional things (Fig. 3). On perusal of his family history, his father was noted to have died of brainstem hemorrhage in 2014. There was no history of headaches in his father before his death. Neither his mother nor his grandparents have migraines or other systemic diseases.

Discussion

As a rare kind of migraine with aura, HM with ATP1A2 gene mutation is described in only a few case reports. Some scholars have summarized the clinical characteristics of HM with ATP1A2 mutation [1, 3, 6, 8]. In the present case, excessive food intake was the only trigger. HM can be triggered by minor head trauma [1, 6], common cold, fatigue, emotional stress, etc [9]. The patient became comatose immediately after the onset of fever. This finding was described in other cases as well [9–14].

Approximately 15% of FHM patients suffer from coma [1]. In addition, 47% of HM patients have altered sensorium associated with fever [1]. Although experts think epilepsy occurs independently from migraine attacks [1, 15], it is one of the most severe symptoms in patients with HM [16]. There are some sporadic reports that some HM patients with the APT1A2 mutations, as in our patient, have a younger age of onset with less than one attack per year and an aura lasting more than 72 hours [9, 14]. This provides new clues for the future diagnosis of the disease.

Since the patient became unconscious soon after the onset of fever, we performed a lumbar puncture. Similar to previous reports, in the present case, the patient's CSF pressure, hematological and biochemical analysis were all normal. Although there have been previous case reports about the use of acyclovir [6, 8, 10, 13, 14], we believed that the patient's fever and coma were clinical manifestations of this type of HM, rather than viral encephalitis, and did not use any antiviral treatment. Thus, antiviral treatment is not recommended in the absence of definitive markers of intracranial infection. Symptomatic treatment is essential. The patient's MRI showed brain edema, which was treated using mannitol. When he developed epilepsy, levetiracetam was used [17]. There is insufficient evidence for long-term anti-epileptic treatment, and we believed that specific treatment plans should be made based on the patient's symptoms and EEG findings.

The most interesting thing about our patient was that his intellectual disabilities were different from others. Although he went to school and had normal social skills, his computational ability and three-dimensional spatial awareness were significantly lower than those of children in the same age group. It was previously speculated that HM could cause irreversible brain damage [1]. The patient's MRI brain and EEG were completely normal during the interictal period. It is speculated that the boy's intellectual disability could have had another pathogenesis. It has been reported that writing function improves after using memantine and dextromethorphan in patients with the ATP1A2 mutation and that they benefit from N-methyl-D-aspartate receptor antagonists [18]. However, this is only speculation because the patient did not provide consent for further investigations to determine the variant protein related to the ATP1A2 mutation. In addition, magnetic resonance spectroscopy (MRS) had not been performed during hospitalization. The reason for the intellectual disability in this patient needs to be investigated further.

In summary, some HM patients with ATP1A2 mutations may present with fever and coma at the onset of disease. If the cerebrospinal fluid test results are normal, antiviral therapy is not recommended. The patient could develop intellectual disabilities, which might manifest as a decline in computational and a

poor sense of three-dimensional spatial abilities. Therefore, the intelligence quotient of HM patients should be carefully and comprehensively evaluated.

List Of Abbreviations

EEG - electroencephalogram

FHM - familial hemiplegic migraine

HM – Hemiplegic migraine

ICU – Intensive care unit

MRI – Magnetic resonance imaging

SHM - sporadic hemiplegic migraine

TCD – transcranial doppler

Declarations

Consent for publication:

The patient's mother signed the informed consent form for publication of this case report and accompanying images.

Ethics approval and consent to participate

Because the patient is under 18 years old, the patient's mother signed the informed consent form.

Competing interests:

non-financial competing interests.

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Authors' contributions:

Name	Role	Contribution
Pian Wang	Author	Executing&writing the manuscript
Yan-Rong Yang	Author	Executing&writing the manuscript
Hong-bo Zhang	Author	Figure description
Jiang-Hong Wang	Author	Figure description
Yan Wang	Author	Review and figure description

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Figures

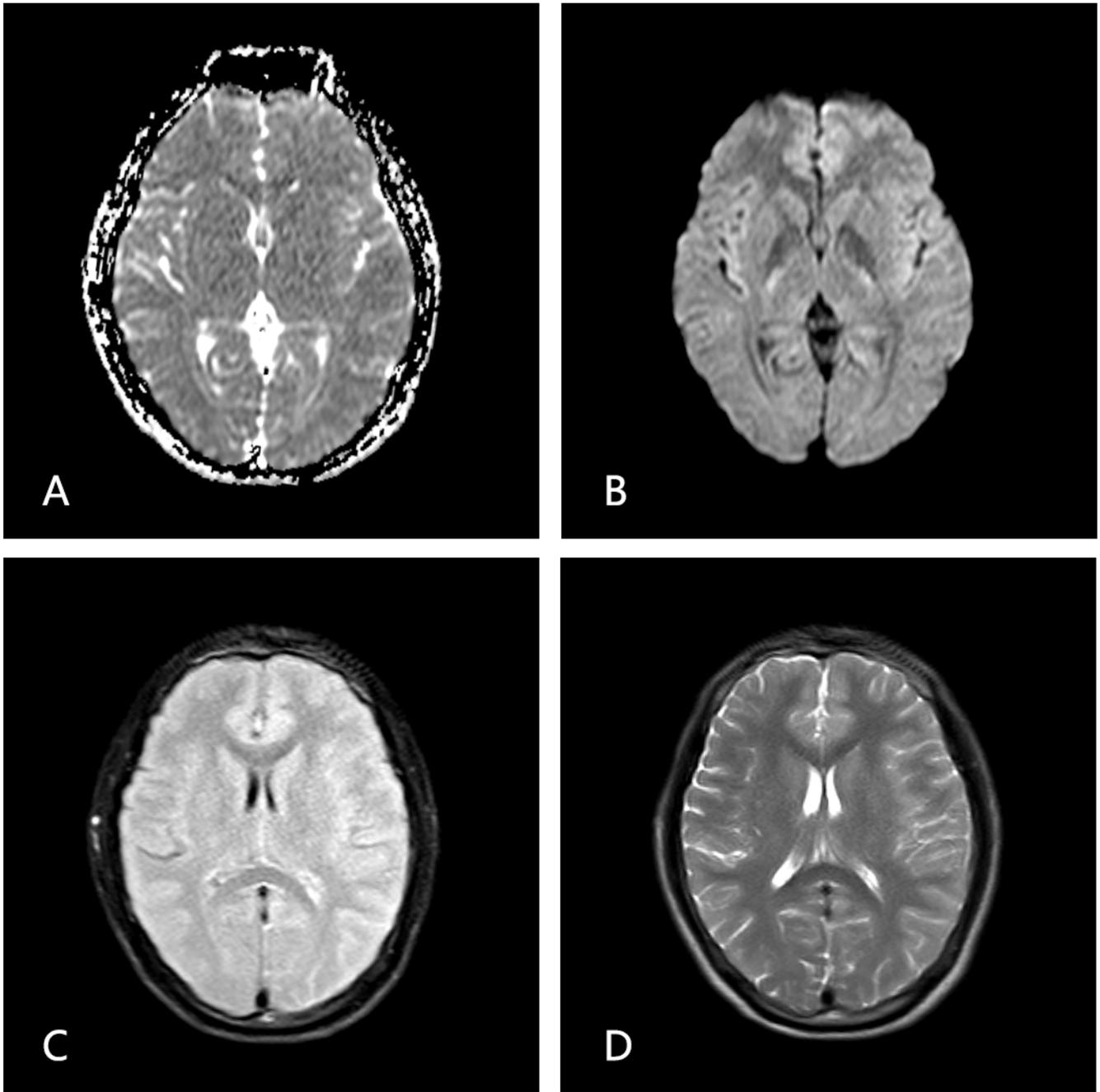


Figure 1

The ADC (A), DWI (B) and T2 (D) are negative, but FLAIR (C) shows increased cortical sulci in the left cerebral hemisphere



Figure 2

Abnormal slow waves were present on the left frontal area, central area, parietal area, with bilateral epileptiform discharge.



Figure 3

The patient's painting