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Case Report

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Early-onset Recurrent Encephalopathy and Hemiparesis caused by a Novel de Novo ATP1A2 Variant: Importance of Genetic Testing

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Abstract

Background: *ATP1A2 gene pathogenic variants have been implicated in a variety of paroxysmal neurological disorders with phenotypic variability ranging from hemiplegic migraine to alternating hemiplegia of childhood to epilepsy. The ATP1A2 gene is one of the several genes that encode for cell membrane proteins responsible for stabilizing the electrochemical gradients of sodium and potassium ions.*

Case report: *We report an 11-year-old boy who presented at the age of 2 years with a prolonged episode of altered level of consciousness following a trivial head trauma. That episode was followed by a significant, but transient, developmental regression. Ictal brain MRI scan showed cortical oedema and subsequent imaging demonstrated periventricular white matter T2/FLAIR hyperintensities. He continued to have similar episodes in association with high fever. From around the age of 4 years started to experience episodes of migraine headaches in association with hemiparesis. Subsequently, trio genetic testing revealed a novel de novo ATP1A2 missense heterozygous variant c.1133C>T (p.Thr378Ile). This had lead to changing drug management to acetazolamide with good clinical response.*

Conclusion: *Early-onset recurrent encephalopathy, hyperthermia and MRI white matter abnormalities could be an early presentation of ATP1A2-related sporadic hemiplegic migraine. Early genetic testing can be helpful and may guide appropriate management as well as avoidance of unnecessary treatments.*

Keywords: *ATP1A2 gene, sporadic hemiplegic migraine, white matter*

Introduction

Hemiplegic migraine (HM) is a rare subtype of `migraine with aura` in which the aura is predominantly manifested by reversible unilateral objective motor weakness. This is usually a monogenic condition and can be inherited in an autosomal dominant manner (familial HM) due to mutations in the CACNA1A, ATP1A2, SCN1A and PRRT2 genes.[1] De novo mutations in the former two genes are also associated with sporadic HM cases. However, in many cases no specific genes can be found.

Given the pathophysiological and clinical similarities between migraine and epilepsy, misdiagnosis of either condition is not uncommon. We herein present an 11-year-old who was found to have a novel de novo ATP1A2 variant to highlight the importance of proper clinical phenotyping coupled with early genetic testing.

Case Report:

This 11-year-old Egyptian boy presented to our institute with episodic unilateral arm and leg weakness in association with headache, photophobia and nausea. Typically, the episode would last for up to 6 hours and would be relieved by sleep. He had already been taking sodium valproate for the last 8 years as he was given a diagnosis of `epilepsy`.

He was born at 34 weeks` gestation of non-consanguineous healthy parents. Otherwise, the birth history was unremarkable. He was admitted to the neonatal unit for initial help with feeds only. Early development in all domains was normal.

Aged 18 months; he had a witnessed trivial head trauma which was followed by a mild right-sided weakness that resolved within a few hours. At the age of 2 years, he had another mild head trauma. This was followed by generalized floppiness and altered level of consciousness. No respiratory support was needed however he had to be fed via a nasogastric tube due to unsafe swallow. Biochemical, metabolic and cerebrospinal fluid testing as well as a head CT scan were all normal. An electroencephalogram (EEG) demonstrated a non-specific left-sided slowing in the theta/ delta waves range. Brain MRI and MRA were inconclusive. He remained stuporous for 3 weeks after which he began to slowly recover. However, there was a significant regression in his motor and language skills. Within the next 6 months he slowly regained his motor abilities.

With further follow up and on recurrence of the episodes, he was given a diagnosis of `epilepsy` and was thus commenced on sodium valproate. Aged 4 years, he started to experience episodes of bifrontal headache in association with photophobia and phonophobia. Within minutes from the onset of these attacks he would have a unilateral body weakness commonly on the right that might persist for a few hours. On occasions, the episodes would be associated with cause dysarthria or aphasia. Usual triggers

are head trauma, exposure to bright light or emotional distress. At the age of 6 years he had another episode of altered consciousness and he developed a high fever. The only positive finding in the full septic workup was a CSF lymphocytic pleocytosis with increased proteins. Neuroradiological studies including MRI, MRV and MRA were inconclusive. He received a course of antibiotics and antivirals for a total of 4 weeks.

Over the years, he has been having scholastic difficulties. Interictal physical examination had been repeatedly normal. A brain MRI scan was obtainted at the age 11 years. When compared to the previous studies this had shown significant reduction in the hyperintensity in periventricular white matter around the trigones of the lateral ventricles, accompanied by irregularity of the contour of the trigones and bodies of the lateral ventricles which persisted.There was no loss of volume. Epilepsy gene panel testing employing next generation sequencing revealed a pathogenic heterozygous mutation of the ATP1A2 gene at Exon 9,c.1133(p.Thr378ile). Both parents were not carriers of the variant upon testing. With this new diagnosis of hemiplegic migraine, sodium valproate was tapered and stopped. He was commenced on acetazolamide which brought a significant reduction in the severity and intensity of the episodes.

Discussion

Hemiplegic migraine (HM) is a rare condition, with a reported prevalence of 0.01%. A study done in Denmark indicated the prevalence of sporadic hemiplegic migraine is 0.002% and familial hemiplegic migraine is 0.003%.**[**2**]**

In our patient, the pathogenic variant, c.1133C>T (p.Thr378Ile), was identified in the ATP1A2 gene. Both parents did not have history of migraine or indeed any other neurological disorders. Parental samples were tested and showed that neither parent carried this ATP1A2 variant. Although this variant has not been reported before, it was considered pathogenic. This variant is not present in population databases. This sequence change replaces threonine with isoleucine at codon 378 of the ATP1A2 protein (p.Thr378Ile). The threonine residue is highly conserved and there is a moderate physicochemical difference between threonine and isoleucine. This variant disrupts the p.Thr378 amino acid residue in ATP1A2. Other variant(s) that disrupt this residue have been determined to be pathogenic (PMID: 15174025, 15286158). This suggests that this residue is clinically significant, and that variants that disrupt this residue are likely to be disease-causing.

The ATP1A2 gene is one of the several genes that encode for cell membrane proteins responsible for stabilizing the electrochemical gradients of the sodium and potassium ions. The gene is predominantly expressed in neurons in neonates and in glial cells in adults. Heterozygous pathogenic variants of the ATP1A2 gene can lead to a variety of clinical syndromes with occasional phenotypic overlap.

These are: familial hemiplegic migraine (FHM type 2), sporadic hemiplegic migraine, familial basilar migraine, alternating hemiplegia of childhood, epilepsy, early-onset epileptic encephalopathy and hypokalaemic periodic paralysis. Additional clinical features may include intellectual disability and ataxia.

Paediatric sporadic hemiplegic migraine is a rare form of migraine with aura and its diagnosis can pose several challenges. Symptoms` similarity with those of other neurological disorders, such as epilepsy, stoke, transient ischaemic attacks and central nervous system (CNS) infections, in addition to the absence of family history add to the diagnostic difficulties. Hemiplegic migraine can be triggered by minor head trauma, intercurrent infections and emotional stress, certain foods and odors, bright light, sleep deprivation and physical exertion. Additional well recognized but less common clinical features which might further complicate the diagnostic process include altered sensorium, coma, somnolence, hyperthermia and cerebrospinal fluid (CSF) lymphocytic pleocytosis. Recovery time is usually less than 72 hours however this may take few weeks on rare occasions **[**3**]**. Recovery in our patient from the first attack took about 6 weeks.

CSF abnormalities such as elevated protein and lymphocytosis have been reported in paediatric and adult cases of HM probably due to breakdown of the blood brain barrier **[**4**]**. Our patient received a 4-week course of antibiotics and antivirals based on a presumptive diagnosis of `meningoencephalitis` as CSF studies revealed lymphocytic pleocytosis during an episode of a febrile encephalopathy at the age of 6 years. Bacterial cultures as well as viral polymerase chain reaction (PCR) tests were however negative. Whilst it is important not to miss a potentially serious diagnosis of a CNS infection, it is equally important that alternative diagnoses, such as HM, are considered when other clinical, laboratory and radiological features are not suggestive.

Conclusion:

Migraine, is a highly disabling condition that can present in multiple forms. Correct diagnosis is critical to initiate prompt treatment. Multiple episodes of migraine associated with recurrent reversible encephalopathy (triggered by minor head trauma), should raise the suspicion of HM and prompt further diagnostic workup and genetic testing. Clinicians should always keep a high clinical suspicion of HM in every unusual presentation of migraine, seizures, recurrent encephalopathy.

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