Clinical commentary

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Alternating hemiplegia of childhood and a pathogenic variant of *ATP1A3*: a case report and pathophysiological considerations

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ABSTRACT – We describe a case of a child suffering from alternating hemiplegia with a heterozygous p. E815K pathogenic variant of *ATP1A3*. The patient started to present abnormal eye movements in the first days of life, followed by the appearance at 2 months of dystonic episodes, and later on, by recurrent episodes of alternating hemiplegia more often on the right side. A severe epilepsy started at the age of 2 years with episodes of status epilepticus since the onset which frequently recurred, requiring admission to the intensive care unit. MRI showed bilateral mesial temporal sclerosis and a left-sided ischaemic lesion. Interictal EEG showed bilateral abnormalities, whereas postictal EEG after status epilepticus showed overt slowing on the left side, suggesting a predominant involvement of ictal activity of the left hemisphere. We hypothesize that in our patient, the left hemisphere might have been more prominently affected by the pathogenetic abnormalities underlying alternating hemiplegia of childhood, rendering it more prone to early ischaemic lesions and recurrent unilateral status epilepticus. We speculate whether alternating hemiplegia of childhood shares some common pathophysiological mechanisms with familial hemiplegic migraine that may be associated with a pathogenic variant of *ATP1A2*.

Key words: alternating hemiplegia of childhood, *ATP1A3*, cerebral infarction, epilepsy, EEG

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Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder with an incidence rate of 1/100,000 (Hoei-Hansen *et al*., 2014). Clinical diagnostic criteria include (Bourgeois *et al*., 1993; Panagiotakaki *et al*., 2010):
– age at onset of <18 months;
– episodes of hemiplegia alternating in laterality;
– episodes of bilateral hemiplegia/quadriplegia;
– other paroxysmal disorders;
– disappearance of symptoms during sleep;
– permanent neurological dysfunction.
No other conditions should be present that might account for the symptoms, however, this last criterion is not always taken into account when patients present with typical clinical features (Neville and Ninan, 2007). Recently, *de novo* pathogenic variants of *ATP1A3* (which encodes a sodium-potassium-ATPase subunit) have been found in the great majority of AHC cases (Heinzen *et al*., 2012).
Here, we describe a child affected by an *ATP1A3*-mutated form of AHC with severe epilepsy. Brain MRI showed a small infarction in the left hemisphere and EEG suggested a predominant involvement of the left hemisphere according to ictal activity. We speculate on the possible pathophysiological significance of these findings.

Case study

A 5-year-old male with unremarkable family history, born with uneventful pregnancy and delivery, presented abnormal ocular movements in the first days of life. Initial brain MRI, performed at six days of life, showed normal brain structures and myelination, a small acute ischaemic injury in the posterior parasagittal left frontal lobe, and a small right-sided germinal matrix haemorrhage. Within the next two months, dystonic episodes started to occur. A presumptive diagnosis of AHC was made following video-EEG monitoring showing no epileptiform abnormalities during the episodes. EEG background activity was also normal, possibly because of the small size and deep location of the MRI lesions. The child developed normally until 6 months of age, and then started to present a progressive psychomotor delay, with inability to walk without support and no language acquisition. During the first year of life, episodes of hemiplegia, more often right-sided as well as bilateral, occurred up to 40 times per month, lasting from two to five minutes, up to 45 minutes, and typically disappearing during sleep. Treatment with flunarizine was started at the age of 5 months with reduction of the frequency of the attacks. Epilepsy onset occurred at the age of 2 years with two episodes of right-sided refractory motor status epilepticus which required admission to the intensive care unit with respiratory support, and lasted one hour and two and a half hours, respectively. The patient kept on presenting with focal seizures characterized by staring, head deviation mainly to the right, followed by a tonic posture that occurred several times per week in spite of AED polytherapy (levetiracetam, topiramate, and oxcarbazepine). Moreover, episodes of status epilepticus continued to occur. MRI of the brain at the age of 3 years and 5 months showed focal gliosis in the white matter in the left posterior frontal lobe, corresponding to the ischaemic lesion which was revealed during the previous MRI, and bilateral mesial temporal sclerosis (MTS) (*figure 1*). At the age of 5 years and 9 months, he presented a severe psychomotor disability. EEG recordings showed bilateral epileptiform abnormalities, predominant at the frontal leads, and slow activities prevailing in the left hemisphere (*figure 2A*). In particular, an EEG performed immediately after an episode of status epilepticus clearly evidenced slow activity on the left hemisphere (*figure 2B*). Genetic investigation showed a heterozygous p.E815K pathogenic variant of *ATP1A3*. DNA was isolated from an EDTA (ethylenediaminetetraacetic acid) blood sample by standard methods and the entire coding and 35-50-bp exon-flanking sequence of the *ATP1A3* gene was PCR (polymerase chain reaction)-amplified, purified, and directly Sanger sequenced using standard techniques. The pathogenic variant was identified through the Mutation Surveyor (SoftGenetics), validated via the bioinformatic tools of Alamut (Interactive Biosoftware), and verified by repeated PCR and sequencing. NM_152296.3 was used as the reference sequence. At the age of 6 years, after an attempt with a ketogenic diet without success, vagus nerve stimulation (VNS) was performed without any clear benefit after one year of treatment.

Discussion

We describe a patient suffering from AHC with a diagnosis initially based on the fulfilment of the clinical diagnostic criteria for AHC, and later confirmed by genetic testing, demonstrating a heterozygous p.E815K pathogenic variant of *ATP1A3*. In recent years, increasing evidence has shown that *ATP1A3* pathogenic variants are present in more than 70% of sporadic cases of AHC (Heinzen *et al*., 2012). In particular, E815K and D801N pathogenic variants account for more than 60% of all *ATP1A3* pathogenic variants resulting in AHC (Viollet *et al*., 2015). A recent study has shown that the E815K pathogenic variant is associated with a more severe course of the disease, characterized by an earlier age at onset and higher incidence of

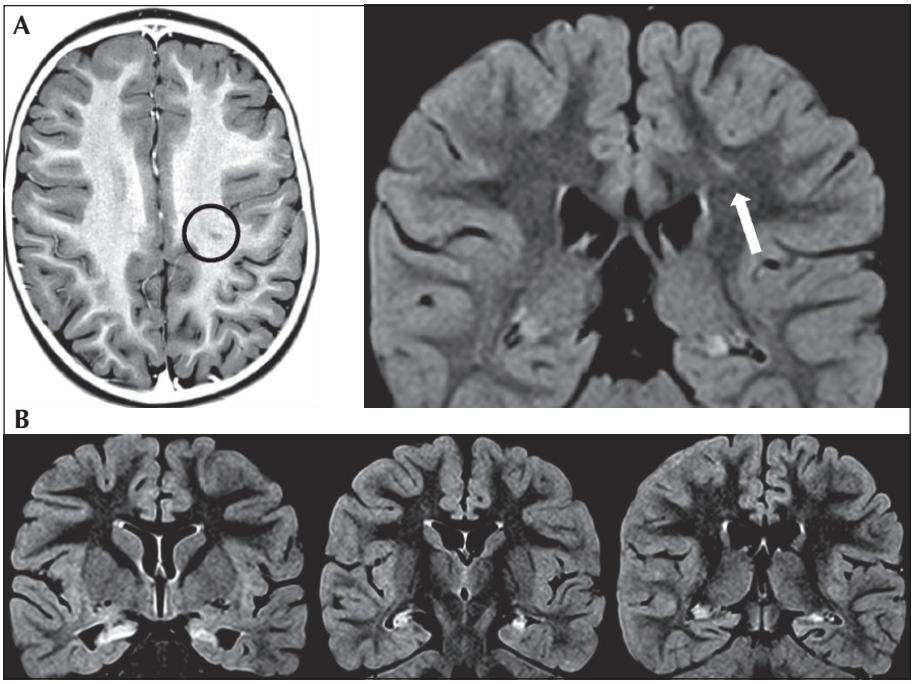

Figure 1. MRI (1.5 Tesla). (A) Axial T2W (reversed image) (left panel) and paracoronal FLAIR (right panel) showing left frontal infarction sequela. (B) Paracoronal FLAIR images through three hippocampal regions, showing bilateral hippocampal sclerosis.

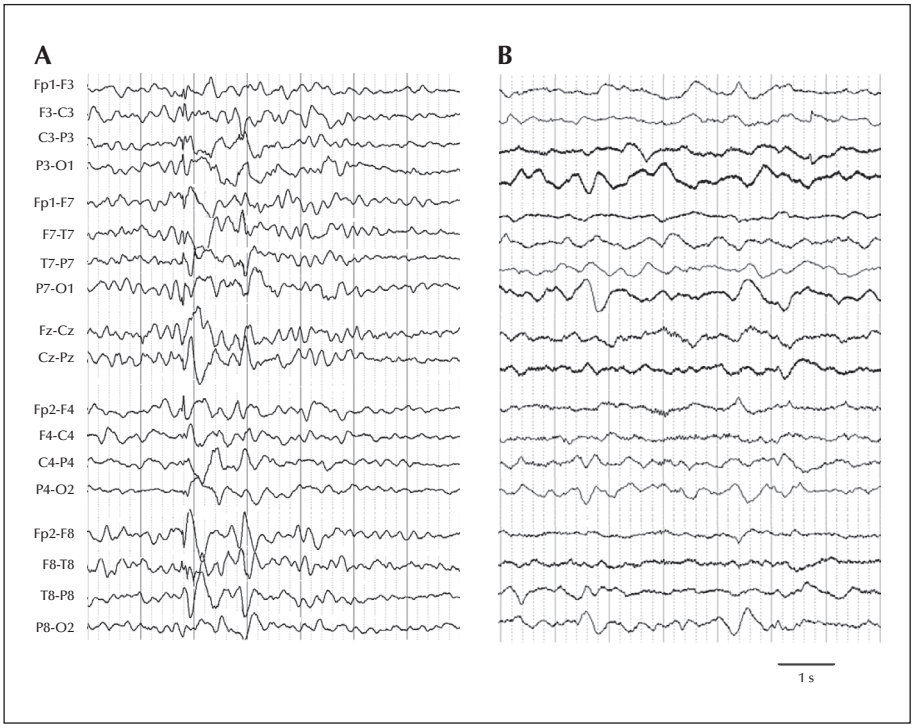

Figure 2. Interictal EEG shows irregular spike and waves complexes, with maximum amplitude in the prefrontal derivations bilaterally (A). Postictal EEG slowing following status epilepticus, with a clear prevalence in the left hemisphere in the mid-temporo and parieto-occipital regions (B).

both status epilepticus and acute clinical decompensations (Viollet *et al*., 2015). The clinical features of our patient harbouring the E815K pathogenic variant are in agreement with these findings, since he showed a severe disease evolution, in particular, regarding the epileptic disorder, characterized by refractoriness to several antiepileptic treatments, including VNS, and recurrent episodes of status epilepticus requiring intensive care support.

The role of the *ATP1A3* pathogenic variant in the pathogenesis of epilepsy has not been clarified yet, although it is known that an impaired ATPase activity can significantly modulate neuronal excitability by altering intracellular proton concentration. In addition, a higher proportion of AHC patients affected by epilepsy have been shown to harbour specific pathogenic variants of *ATP1A3,* relative to AHC patients without epilepsy (Panagiotakaki *et al*., 2015), and recent data suggests an association between *ATP1A3* pathogenic variants and susceptibility to genetic generalized epilepsies (Qu *et al*., 2015). However, in our patient, the occurrence of right-sided hemiclonic status epilepticus associated with the detection of left-sided post-status epilepticus EEG slowing suggests that the ictal focus might be located in the left hemisphere.

A peculiar finding in our patient was the early detection on MRI of a left-sided ischaemic brain lesion (at six days after birth), that was confirmed later at 3 years of age by repeated MRI, associated with bilateral MTS. In our patient, the bilateral MTS might have been the consequence of the recurrent severe episodes of status epilepticus, whereas the left-sided ischaemic lesion was detected very early, before the onset of epilepsy, suggesting that cerebro-vascular insults can occur in AHC at a very early age. Therefore, we may speculate that in our patient, the left hemisphere might have been more prominently affected by the pathogenetic abnormalities underlying AHC, rendering it more prone to early ischaemic lesions and to recurrent unilateral status epilepticus. The observation that also the episodes of hemiplegia were prevalent on the right side may further support this hypothesis.

SPECT studies have suggested that vascular mechanisms can contribute to the hemiplegic manifestations, showing that irreversible changes due to prolonged hypoperfusion occurred in some patients with repeated attacks (Zupanc *et al*., 1991; Siemes and Cordes, 1993). The finding of small vessel abnormalities in skin and muscles biopsies of patients with AHC might lend further support to a possible neurovascular pathogenetic mechanism (Auvin *et al*., 2006).

Furthermore, in the literature, the occurrence of prolonged hemiplegic episodes has been reported in three children with *ATP1A2* pathogenic variants and familiar hemiplegic migraine (FHM), one of whom had a stroke in the right parietal region with left hemiplegia (Jen *et al*., 2007). Moreover, a recent study identified an association between *ATP1A2* pathogenic variants and ischaemic stroke risk (Harriott *et al*., 2013). Even though AHC and FHM are distinct disorders, the two conditions have similarities and result from similar pathogenic variants. Indeed, both *ATP1A2* and *ATP1A3* genes encode catalytic subunits of Na/K-ATPases, which play an important role in the basal electrophysiological states of nerve cells (Qu *et al*., 2015), suggesting the possibility of shared underlying pathogenetic mechanisms between AHC and FHM. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What are the 5 main clinical diagnostic criteria of AHC?

(2) Which gene is involved in more than 70% of sporadic cases of AHC?

(3) The E815K pathogenic variant is associated with which aspects of AHC?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".