■ Clinical commentary

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Epileptic Disorders

Progression of alternating hemiplegia of childhood-related focal epilepsy to electrical status epilepticus in sleep with reversible encephalopathy

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ABSTRACT

Mutations in the *ATP1A3* gene (which encodes the main α subunit in neuronal Na+/K+-ATPases) cause various neurological syndromes including alternating hemiplegia of childhood. This rare disorder is characterized by paroxysmal episodes of hemiplegia, dystonia, oculomotor abnormalities, and occasionally developmental regression. Approximately 50% of alternating hemiplegia of childhood patients also have epilepsy, which is either focal or generalized. Seizures are often drug resistant. We report a 10-year-old girl with the D801N *ATP1A3* mutation and alternating hemiplegia of childhood who manifested with drug-resistant focal seizures as an infant and throughout childhood. At the age of about10.5 years, her epilepsy evolved into electrical status epilepticus in sleep with generalized discharges. These changes coincided with developmental regression consistent with epileptic encephalopathy. Additionally, MRI and MR spectroscopy showed new cortical atrophy and markedly depressed N-acetyl aspartate peaks compared to previous normal studies. Electrical status epilepticus in sleep resolved after medication adjustments. She, now, only four months after her diagnosis of electrical status epilepticus in sleep, has regained most of the skills that were lost only a few months earlier. Our observations document that alternating hemiplegia of childhood can result in the above-described unique features; particularly, progression of focal epilepsy to electrical status epilepticus in sleep with generalized features and reversible epileptic encephalopathy.

Key words: *ATP1A3*, alternating hemiplegia of childhood, electrical status epilepticus in sleep, epileptic encephalopathy

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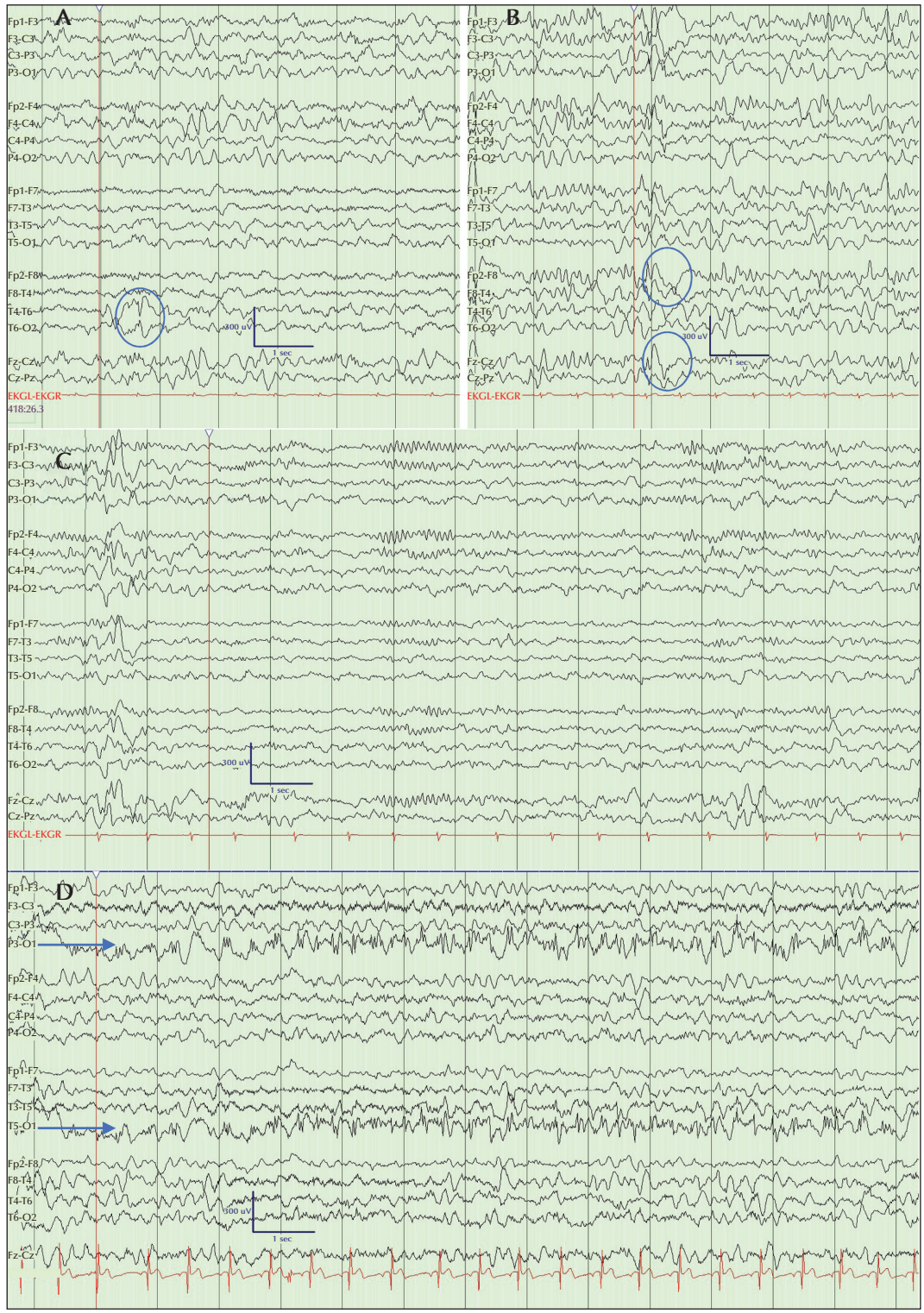
Na+/K+-ATPases are membrane-bound transporters that consist of three main subunits (α, β, and γ) which function to maintain the cellular electrochemical gradient [1-4]. The primary α subunit expressed in neurons is α3, which is encoded by the gene *ATP1A3* [1-4]. Mutations in *ATP1A3* have been identified in several rare neurological syndromes, and are responsible for the majority of alternating hemiplegia of childhood (AHC) cases [1-5]. Approximately 50% of patients with AHC have concomitant epilepsy (focal or generalized), and seizures are usually drug resistant [6].

Case study

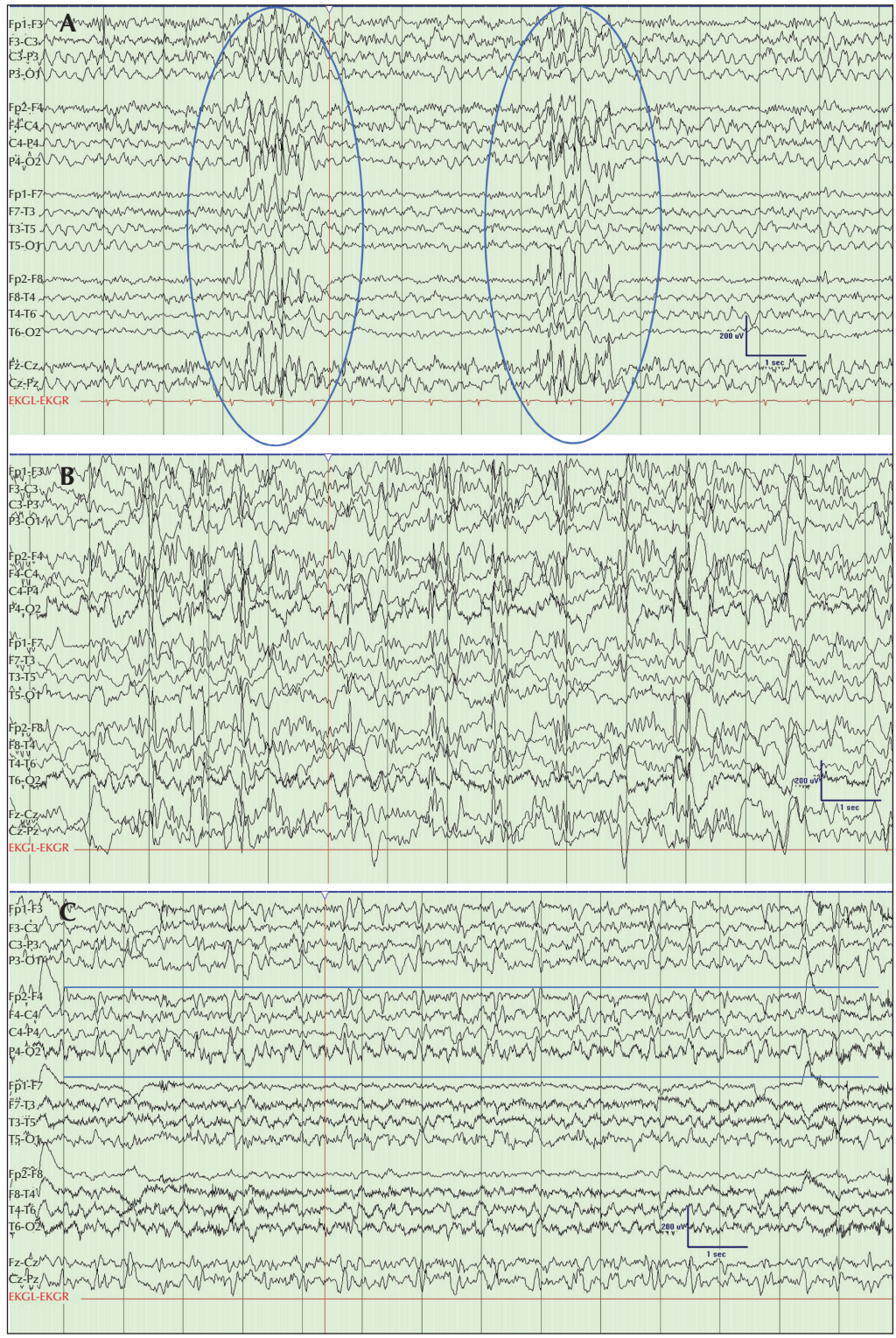
The patient is a 10-year-old, left-handed girl with focal motor seizures that started on Day 1 of life. As a neonate, her seizures consisted of right-sided tonic limb stiffening with unilateral head turn. Later in infancy and early childhood, she developed several other types of spells consistent with AHC. Specifically, she had frequent hemiplegic episodes, dystonic and hemi-dystonic events, and abnormal eye movements consistent with nystagmus, often monocular. These events occurred on a daily basis with variable duration (minutes to hours and even days). Autonomic dysfunction consisted of intermittent facial flushing and oxygen desaturations. There were also later behavioral outbursts that consisted of side-to-side head shaking and episodes where she would voluntarily ignore nearby people. She was clinically diagnosed with AHC, and this was confirmed by the presence of D801N *ATP1A3* mutation. Previous care was undertaken at an outside medical facility in a different state.

Throughout infancy and childhood, she had drug-resistant focal seizures with impaired awareness. Clinically, this manifested as being unresponsive, various automatisms, and occasionally posturing with hyperkinetic movements. Seizures usually lasted several minutes in duration and occurred daily to several times per month. When first seen by us, at age four years, EEG findings during inpatient monitoring included occasional right interictal epileptiform discharges and left focal-onset seizures with secondary generalization (*figure 1*). Sleep activity was normal without significant activation of discharges. Additionally, she had repeated episodes of status epilepticus at ages three, four, and five years with sustained seizures that ranged from 30 minutes to two hours. She did not have loss of milestones at this time, but did have slow development. Brain MRI and MR spectroscopy were normal 13 months after her last episode of status epilepticus. Over the next five years, she was treated with combination antiepileptic therapy including carbamazepine, clonazepam, lacosamide, perampanel, clobazam, phenobarbital, vagal nerve stimulator (VNS), and the ketogenic diet. Her focal seizures decreased in frequency to once every few weeks to months, but never fully resolved. Interictal EEG abnormalities remained unchanged. Additionally, she continued to have AHC-type spells despite therapy with flunarizine.

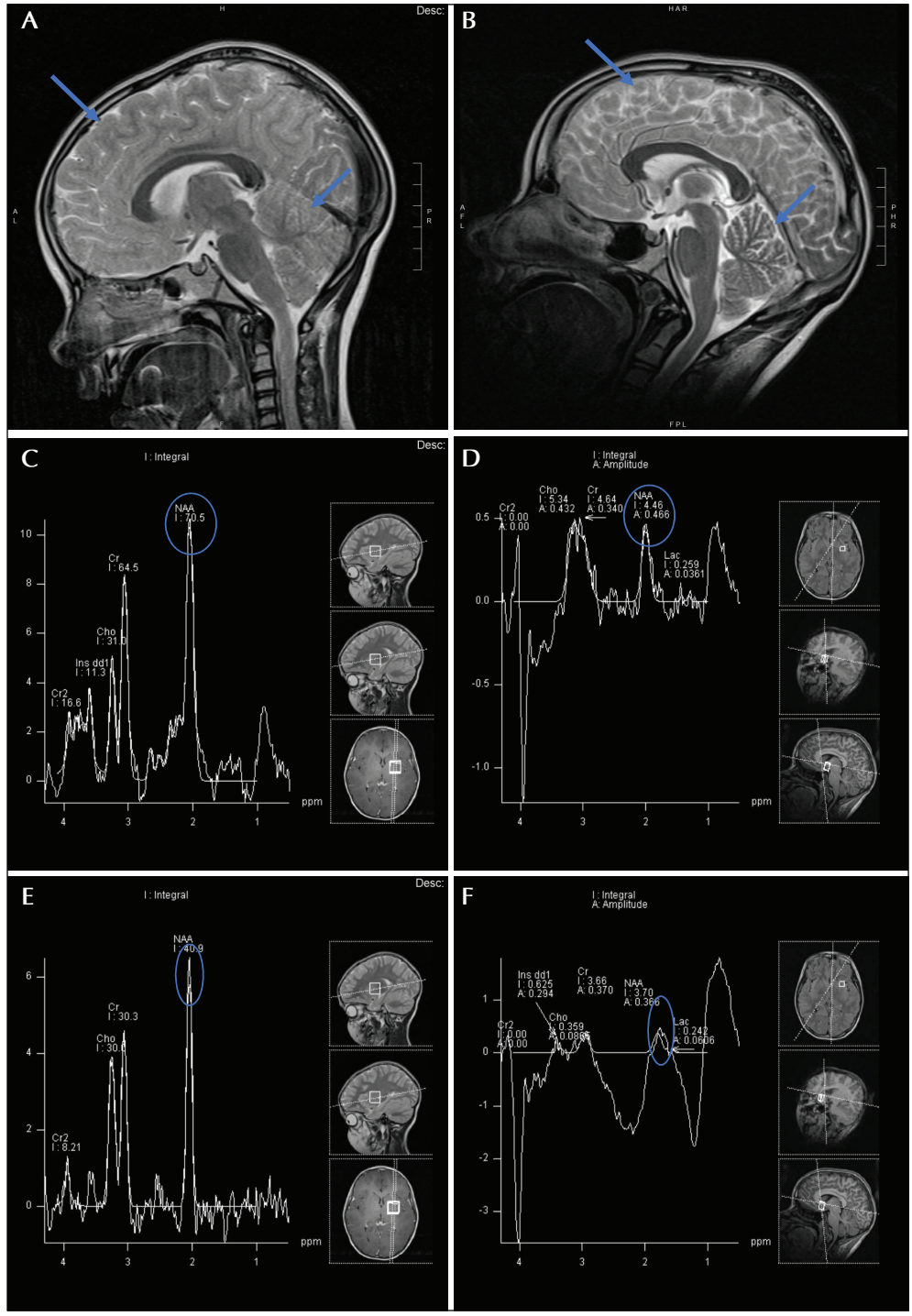
Starting at the age of 10 years and six months old, she manifested with subacute neurologic decline with several new symptoms and exacerbation of prior delays. Despite being able to previously speak in five-word sentences and carry out simple multistep commands, she regressed to minimal verbal output and showed loss of task sequencing abilities. Her cognition also slowed, she was no longer able to count and general forgetfulness worsened. There was new regression of both fine and gross motor skills. Specifically, she lost the ability to perform accurate pincer grasp, developed dysphagia, and had gait instability. She developed new staring spells with episodes of head/body atonia associated with falls that raised concerns for atypical absence seizures and atonic seizures. Her other usual seizures and AHC spells remained unchanged. Because of the concern for possible new seizure types, she was admitted for video-EEG monitoring. EEG monitoring revealed slow background with rare generalized 4-Hz spike/slow-wave interictal epileptiform discharges during wakefulness (*figure 2*), however, in sleep, the EEG showed ESES with 95-100% spike index during the first two hours of sleep (*figure 2*). This then fluctuated between 40-100% during the rest of the night. Two distinct patterns of ESES changes were noted. The first pattern consisted of continuous/near-continuous generalized spike/polyspike-wave discharges observed in the first half of the night (*figure 2*). The second pattern was identified as near-continuous bilateral parasagittal spike-and-sharp-wave discharges that occurred in the second half of the night (*figure 2*). The new staring spells with atonia did not have epileptiform correlates and were, thus, considered AHC-type events rather than seizures. Due to her clinical deterioration with accompanying electrographic worsening, she was diagnosed with ESES associated with epileptic encephalopathy (EE). MRI revealed cortical atrophy (cerebral and cerebellar) and MR spectroscopy showed depressed N-acetyl aspartate (NAA), which were both new changes (*figure 3*). This was considered as an accompanying, rather than necessarily a causative finding. Over the following three months, she was weaned off carbamazepine which was given for her focal seizures. Concurrently, her cannabidiol dose was increased from 5 mg/kg/day to 10 mg/kg/day, and she was continued on clobazam, topiramate, lacosamide, and monthly intravenous pulse steroids of 1 g/day for three consecutive days each month. She was noted to regain most of her lost skills in the first few months following her hospital discharge. This coincided with improvement of spike index down to 22-28% on EEG. Her speech became more distinct, language was more structured, and ability to follow commands returned. She continued to suffer from mild dysphagia, but other fine and gross motor skills including pincer grasp and walking improved to almost her pre-regression baseline. With respect to cognition, neuropsychometric testing was performed approximately three months after the resolution of ESES at the age of 11 years and four months old, and was compared to the testing done at the age of eight years and six months before the onset of ESES. This performance was



■ **Figure 1.** EEG at age four years old. (A) Awake EEG with right temporal sharp waves, best observed at T6. (B) Awake baseline with predominantly right fronto-central spike-and-slow-wave discharge. (C) Normal sleep with occasional right frontal, F8, sharp wave activity. (D) Left-posterior-onset focal seizure.



■ **Figure 2.** EEG at age 10.5 years. (A) Awake baseline shows diffusely slow ~5-Hz background with generalized 4-Hz spike-and-slow-wave discharges occurring in brief bursts somewhat better formed on the right. (B) ESES Pattern 1: near-continuous generalized spike-and-slow-wave discharges in sleep. (C) ESES Pattern 2: near-continuous bilateral parasagittal spikes and sharp-wave discharges (blue lines).



■ **Figure 3.** Brain MRI and MRI spectroscopy at age five years (left panels) and age 10 years (right panels). (A, B) Brain MRI T2 sequence axial view at midline: normal at age five years (A) and interval cerebral and cerebellar atrophy at age 10 years (B). (C-F) MRI spectroscopy: normal at age five years (C, E) and interval depressed NAA peaks at age 10 years (D, F).

notable for moderate intellectual disability and global neurocognitive impairment that remained in the <1 percentile across battery of tests, but overall was slightly worse when compared to previous testing performed three years prior. Specific tests included the Adaptive Behavior Assessment System Third Edition (ABAS-3), Comprehensive Test of Nonverbal Intelligence, Second Edition (CTONI-2), Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV), Expressive One Word Picture Vocabulary Test, Fourth Edition (EOWPVT-IV), and Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI).

Discussion

Mutations in *ATP1A3* have been identified in several neurological syndromes including AHC, cerebellar ataxia-areflexia-pes cavus-optic atrophy-sensorineural hearing loss (CAPOS) syndrome, epileptic encephalopathy (EE), rapid-onset dystonia parkinsonism (RDP), and other neurodevelopmental disorders [1-5]. Due to the various phenotypic presentations and rarity of these diseases, accurate diagnosis is often challenging.

Clinical diagnosis of AHC is accepted using six main features known as Aicardi's criteria [7]. This includes symptom onset before age 18 months, repeated spells of hemiplegia or dystonia, episodes of oculomotor abnormalities, events of bilateral hemiplegia, improvement of symptoms during sleep, and permanent neurological / neuropsychological impairments [7]. It has further been shown that mutations in *ATP1A3* are responsible for about 75% of AHC cases, with the D801N mutation being the most common [2, 4]. One possible therapy for AHC is the calcium channel blocker, flunarizine, which may assist with reduction of attack severity and duration but is not believed to affect long-term or developmental outcomes [4, 8]. Overall, treatment options for AHC spells and particularly developmental impairments are limited and are largely restricted to supportive measures. Our patient was diagnosed with AHC after the development of several AHC-type events starting during the first year of life which was confirmed with genetic testing. In addition, she had epilepsy and long-term developmental impairments.

Epilepsy has been identified as a major condition associated with AHC and *ATP1A3* mutations [1-6, 9]. It is estimated that approximately 50% of patients with AHC have epilepsy, and this can be either focal or generalized, but, so far, not both in the same patient [2, 6]. Seizure semiology in this patient population varies greatly and includes focal with impaired awareness, focal with preserved awareness, absence, atonic, gelastic, generalized tonic-clonic, and myoclonic seizures [6, 9]. Additionally, high rates of drug resistance and recurrent episodes of status epilepticus occur [6]. Of note, episodes of status epilepticus and severe AHC spells are often associated with developmental regression that may or may not be reversible [6]. Our patient's focal epilepsy remained refractory despite improvement in seizure frequency later during childhood. Her EEG did not show ESES until the age of 10 years and six months, which coincided with the onset of her neurologic regression.

The International League Against Epilepsy (ILAE) recognizes EE according to when "the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone" [10]. The term ESES is classically used to describe the activation of epileptiform discharges during slow-wave sleep. A specific percentage is not defined by the ILAE, but some investigators accept >85% spike index in sleep while others accept lower percentages [10-12]. In the literature, there is one case of AHC and EE in an infant patient with recurrent episodes of convulsive status epilepticus and associated regression, but without ESES [5]. In our patient, the observation of the progression of focal epilepsy by ESES with generalized discharges coincided with her new subacute neurologic regression. Interestingly, we identified two distinct patterns of spike activation which consisted of either continuous generalized spike/wave, or continuous bilateral parasagittal spikes/sharps. This new epileptic burden was believed to have contributed significantly to her clinical decline, thus fulfilling the criteria for EE. Neuronal damage was indicated by new changes on MRI and MR spectroscopy. It is not possible to determine whether the MRI findings and the ESES are due to the same underlying AHC or epilepsy-related mechanisms, or whether either of these two findings are related causally to the other. However, it is important to note that both findings can occur concurrently in AHC. It is also important for physicians taking care of AHC patients to be aware that regression, which can occur in AHC [5, 13-15], is not necessarily irreversible even in the presence of the above MRI findings. One possible algorithm for patients with AHC and epilepsy who experience developmental regression is to first evaluate for any change in clinical seizure semiology, check AED levels or other laboratory work for reversible causes, and then perform 24-hour video EEG. This is particularly important since developmental regression is increasingly recognized in more AHC patients than previously suspected [15]. If there are new focal neurologic deficits, one should also consider CNS imaging. We favor the tapering of

carbamazepine as the primary factor that improved her ESES. While cannabidiol was increased initially, it was later decreased without recurrence of ESES. Her other anti-epileptic therapies, including monthly pulse-dose steroids, did not change significantly. Our case illustrates that regression in AHC patients may be due to ESES and can be, at least in part, reversible. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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Mohamad A Mikati has a pending patent for gene therapy for *ATP1A3*-related disease. The other authors have no conflicts of interest to disclose.

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TEST YOURSELF

(1) Mutations in the *ATP1A3* gene have been identified in which of the following neurological disorders?
A. alternating hemiplegia of childhood (AHC)
B. cerebellar ataxia, areflexia, pex cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome
C. epileptic encephalopathy (EE)
D. rapid-onset dystonia parkinsonism (RDP)
E. all of the above
F. A, B and D only

(2) Approximately what percent of patients with alternating hemiplegia of childhood (AHC) have epilepsy?

A. 0%
B. 10-20%
C. 50%
D. 80-90%
E. 100%

(3) Alternating hemiplegia of childhood is associated with what kind of epilepsy?

A. Focal
B. Generalized
C. Usually drug-responsive epilepsy of either type
D. Usually drug-resistant epilepsy of either type
E. Not associated with epilepsy

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