■ Clinical commentary

Epileptic Disord 2022; 24 (1): 183-190

Epileptic Disorders

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

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Introduction and Background:

- Mutations in *ATP1A3* have been identified in several rare neurological syndromes including the following: alternating hemiplegia of childhood (AHC), cerebellar ataxia, areflexia, pex cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome, epileptic encephalopathy (EE), rapid-onset dystonia parkinsonism (RDP), and other neurodevelopmental disorders
- Mutations in *ATP1A3* are responsible for about 75% of AHC cases. *ATP1A3* encodes the α3 subunit, the main α subunit in neuronal Na+/K+-ATPases . Specifically, D801N is the most common pathologic variant
- AHC is clinically diagnosed using six main features known as the Aicardi criteria:
  - 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
  - permanent neurological / neuropsychological impairments
- Flunarizine (a calcium channel blocker) may assist with reduction of attack severity and duration

Introduction and Background:

- Epilepsy occurs in approximately 50% of patients with AHC. This can be either focal or generalized
- Observed seizure semiology varies greatly and includes the following: absence, atonic, focal with impaired awareness, focal with preserved awareness, gelastic, generalized tonic-clonic, myoclonic seizures
- High rates of drug-resistant epilepsy and status epilepticus have been reported
- Epileptic encephalopathy (EE)- ILAE definition: “Epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from underlying pathology alone”
- Electrical status epilepticus in sleep (ESES)- definition: activation of epileptiform discharges; some investigators accept activation of >85% spike index in sleep, others did not specify or accept 41.4%.

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Case History:

- 10-year-old left-handed girl with right focal motor seizures that started on Day 1 of life
- Later in infancy, developed daily hemiplegic episodes, dystonic spells, and abnormal eye movements of variable duration
- Clinically diagnosed with AHC, which was confirmed by D801N *ATP1A3* mutation
- Throughout early to mid childhood, had daily drug-resistant focal seizures with impaired awareness lasting several minutes
- EEG showed bilateral independent focal discharges (Figure 1)

- She had repeat episodes of status epilepticus (at age 3, 4, and 5 years) with sustained seizure duration of 30 min– 2 hours, however, no loss of milestones at that time
- AHC-type spells continued despite therapy with flunazarine
- MRI remained normal more than one year after last episode of status epilepticus
- Seizures improved in late childhood down to one seizure every few weeks or months during late childhood. Therapies received: carbamazepine, clonazepam, lacosamide, perampanel, phenobarbital, vagal nerve stimulator (VNS), ketogenic diet
- Starting at age 10 years and 6 months, she manifested with subacute neurologic decline (decreased language, loss of fine motor skills, gait instability, dysphagia with choking, overall cognitive decline) and new staring spells with head/body atonia. Other AHC spells remained unchanged

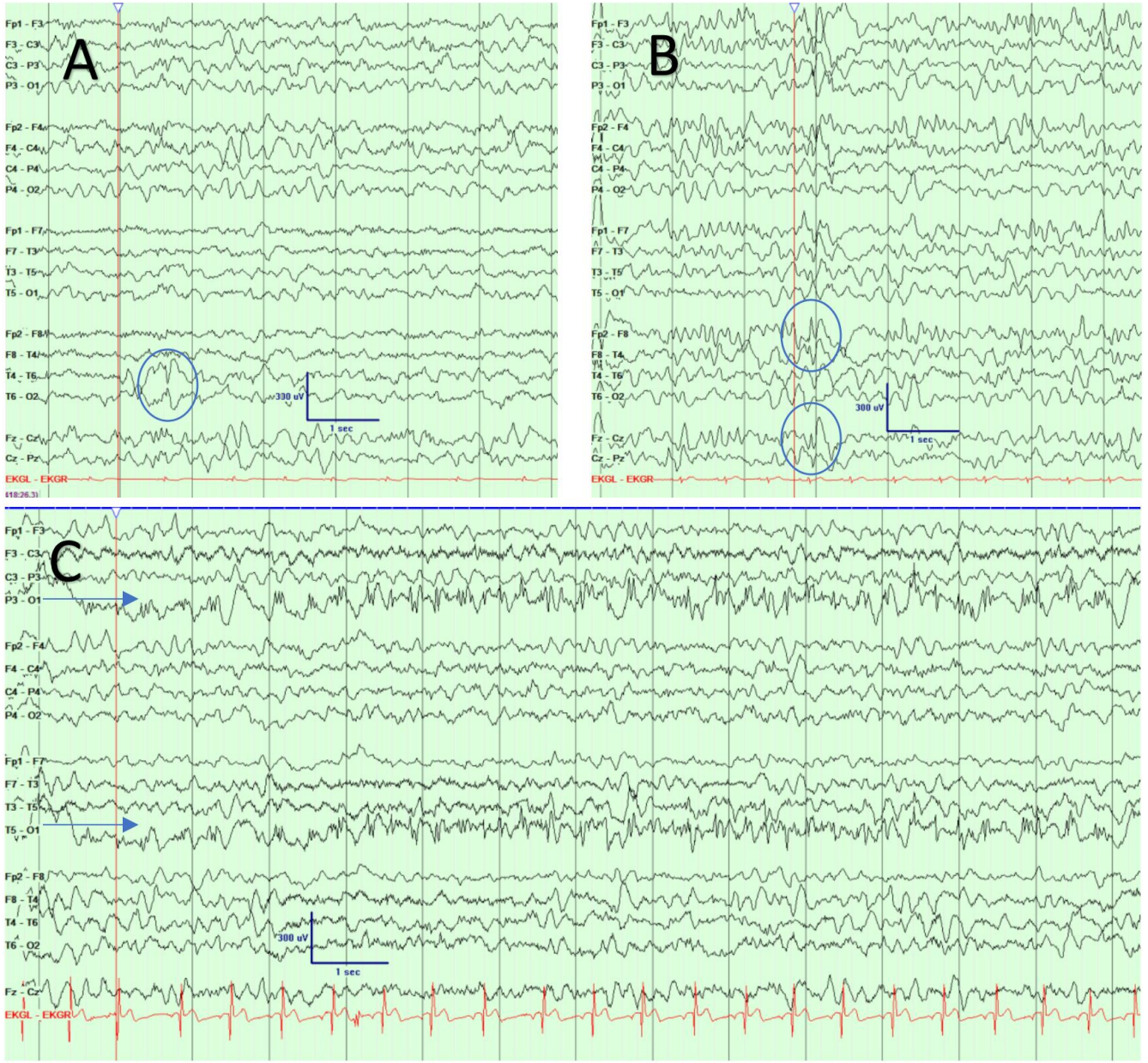
Case History:

- Admitted for video-EEG monitoring for spell characterization
- EEG now markedly different (Figure 2)
    - Generalized 4-Hz spike/slow-wave interictal discharges
    - Electrical status epilepticus in sleep (ESES) with 95-100% spike index
        - ESES in 2 distinct patterns
        - Pattern 1: continuous generalized spike/polyspike wave (observed first half of night)
        - Pattern 2: near-continuous bifrontal spikes/sharps (observed second half of night)
- Staring spells with/without atonia did not have epileptiform correlate and judged to be AHC-type events
- Due to clinical deterioration and worsening electrographic findings, she was considered to now have epileptic encephalopathy (EE)
- Updated brain MRI and MR spectroscopy now drastically different and suggestive of neuronal damage (Figure 3)
    - New significant cerebral and cerebellar atrophy
    - New depressed N-acetyl aspartate (NAA) peaks

- Carbamazepine weaned off, cannabidiol increased from 5mg/kg/day to 10 mg/kg/day, and lacosamide, topiramate, and monthly intravenous pulse steroids at 1gram/day for three consecutive days each month were continued
- Improvement of previously lost skills within one month of discharge; spike index improved to 22-28% at two months post-discharge, and she continued to have improvement of language and motor skills at four months of follow-up

EEG at age 4 years

A) Awake baseline with right temporal sharp waves best observed at T6 .
B) Awake baseline with right fronto-central spike and slow-wave discharge.
C) Left-occipital-onset focal seizure .



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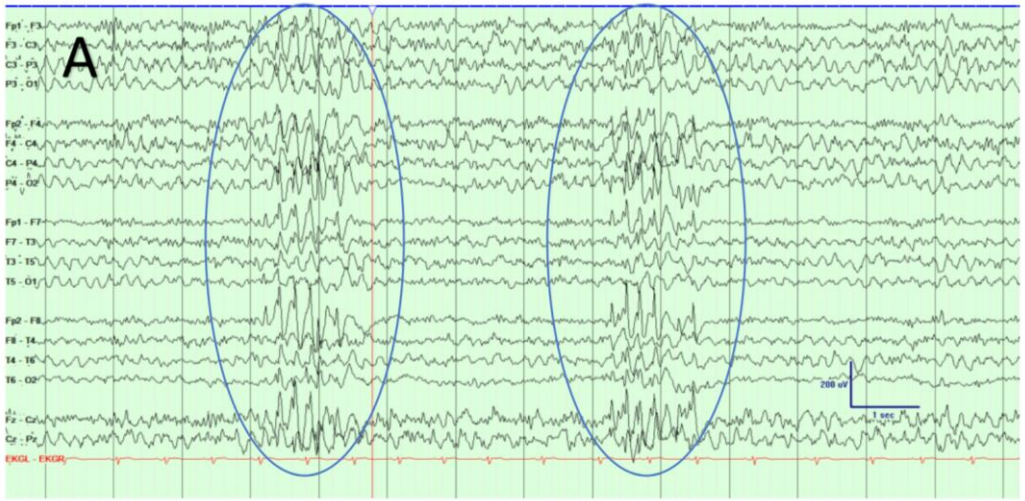
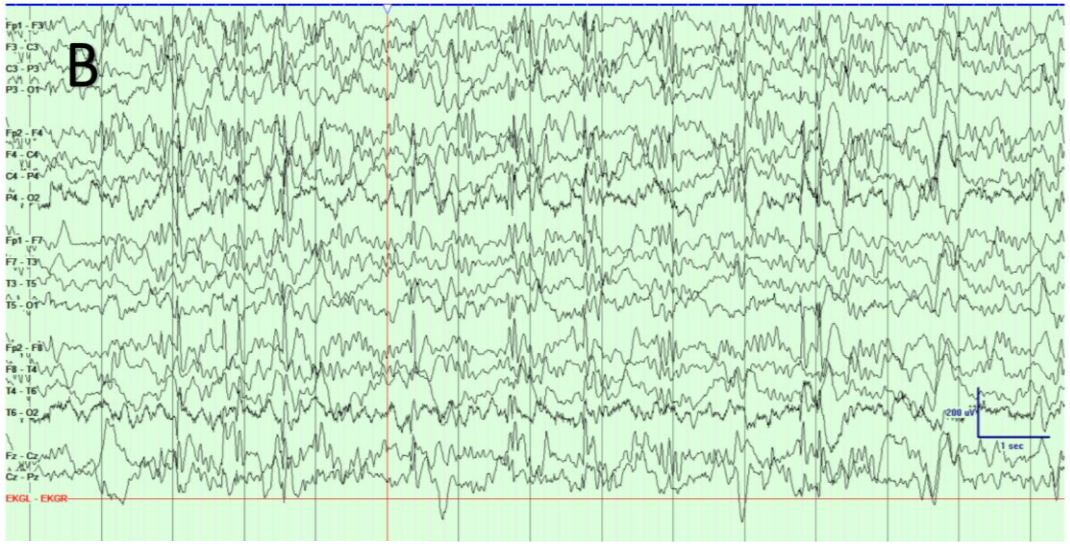
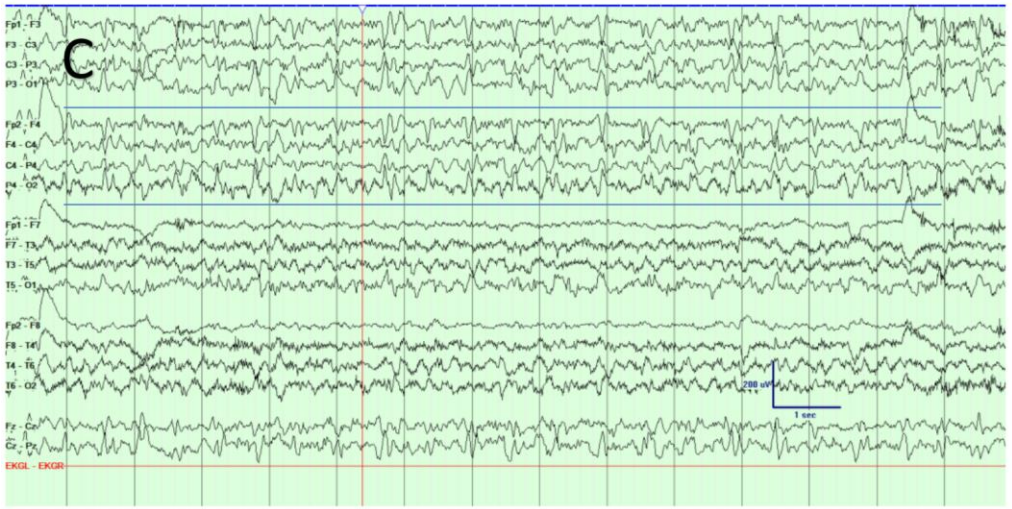
EEG at 10.5 years old

- A) Awake EEG shows diffuse slow ~5-Hz background with rare generalized 4-Hz spike-and –low-wave discharges, slightly 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).







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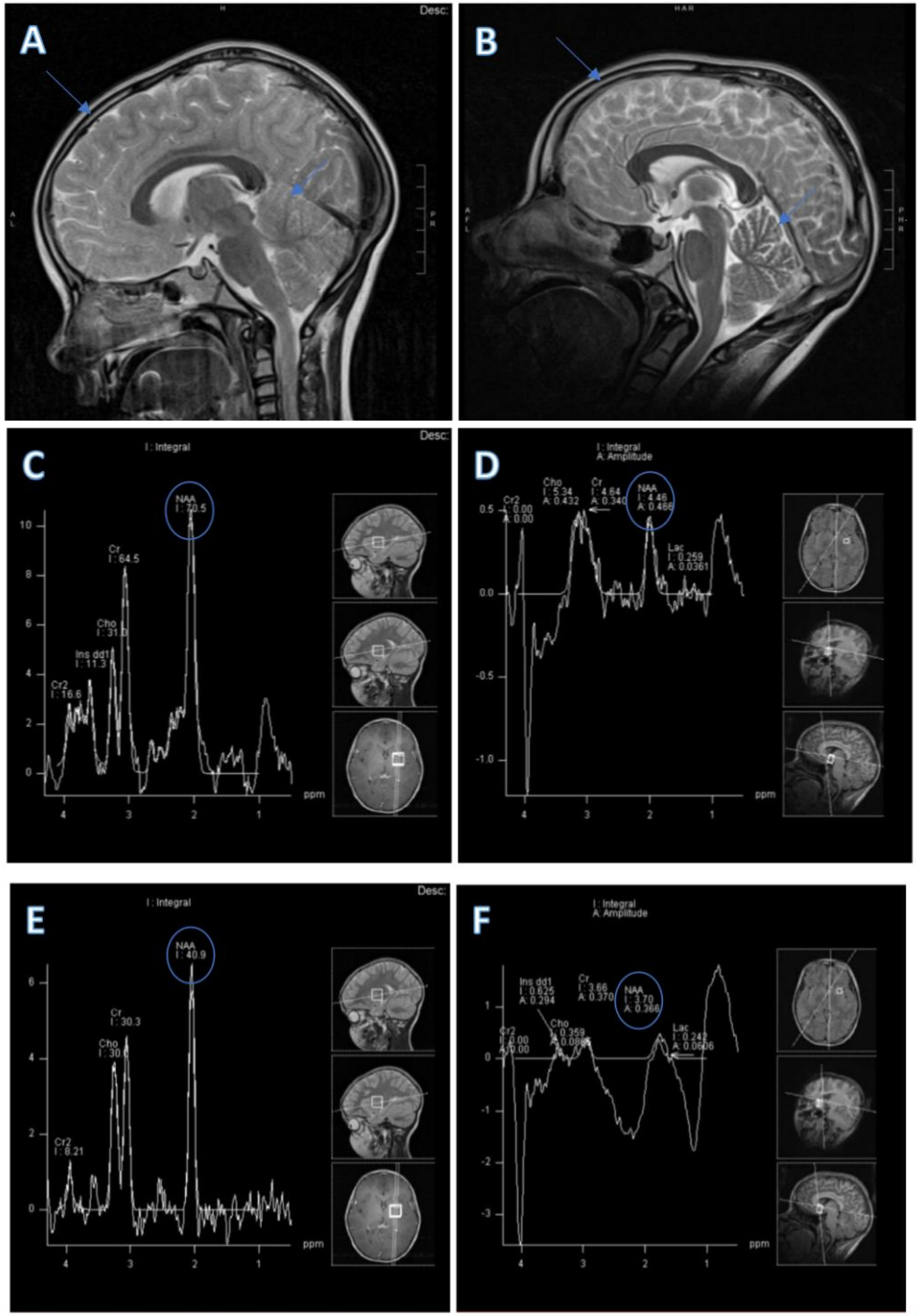
MRI and MRI spectroscopy at 5 years (left) and 10.5 years (right)

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).

MRI spectroscopy: normal at age five years (C, E) and interval depressed NAA peaks at age 10 years (D, F).



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Conclusions:

- To our knowledge, this is a unique case with novel observations due to the following:
  - Progression of focal epilepsy to ESES with generalized discharges in a patient with AHC due to *ATP1A3* mutation
  - Development of neurologic regression consistent with EE that correlates with the onset of ESES and generalized discharges
  - Accompanying evidence of neuronal damage as illustrated by significant change in MRI and MR spectroscopy despite normal studies 5 years prior
  - Improvement of neurologic regression with reversing of ESES via medical antiepileptic management. Physicians taking care of AHC patients need to be aware that regression in AHC may be due to ESES which can be reversible

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