The epileptology of alternating hemiplegia of childhood

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Abstract

Objective
To report our experience and investigate 5 original hypotheses: (1) multiple types of epileptic seizures occur in alternating hemiplegia of childhood (AHC), and these can be the initial presentation; (2) epileptiform abnormalities often appear well after clinical seizures; (3) nonepileptic reduced awareness spells (RAS) occur frequently; (4) epilepsy is commonly drug resistant but may respond to vagal nerve stimulation (VNS); and (5) status epilepticus (SE) is common and is usually refractory and recurrent.

Methods
We analyzed a cohort of 51 consecutive patients with AHC.

Results
Thirty-two of 51 patients had epilepsy: 18 focal seizures, frontal more frequently than temporal, and then posterior. Eleven had primary generalized seizures (tonic-clonic, myoclonic, and/or absence). Epileptic seizures preceded other AHC paroxysmal events in 8 (lag 5.63 ± 6.55 months; p = 0.0365). In 7 of 32, initial EEGs were normal, with the first epileptiform EEG lagging behind by 3.53 ± 4.65 years (p = 0.0484). RAS occurred equally in patients with epilepsy (16 of 32) and patients without epilepsy (10 of 19, p = 1.0). Twenty-eight patients had video-EEG; captured RAS showed no concomitant EEG changes. Nineteen patients (59%) were drug resistant. VNS resulted in >50% reduction in seizures in 5 of 6 (p < 0.04). Twelve patients (38%) had SE (9 of 12 multiple episodes), refractory/superrefractory in all (p < 0.001), and 4 of 12 had regression after SE.

Conclusions
Epilepsy in AHC can be focal or generalized. Epileptic seizures may be the first paroxysmal symptom. EEG may become epileptiform only on follow-up. Epilepsy, although frequently drug resistant, can respond to VNS. RAS are frequent and nonepileptic. SE often recurs and is usually refractory/superrefractory. Our observations are consistent with current data on AHC-ATP1A3 pathophysiology.
Alternating hemiplegia of childhood (AHC) is a rare neurologic disorder characterized by recurrent episodes of hemiplegia, double hemiplegia, dystonia, and frequently epilepsy.\textsuperscript{1} De novo mutations in the \textit{ATP1A3} gene are the cause of AHC in \textasciitilde75% of patients.\textsuperscript{2–5} AHC is diagnosed according to the Aicardi clinical criteria.\textsuperscript{1,3,6,7}

Epilepsy occurs in about half of all patients with AHC and is often drug resistant.\textsuperscript{8–10} However, a full characterization of the epilepsy of these patients, including seizure types and localizations, EEG characteristics, and other seizure-related manifestations, is still needed. Furthermore, status epilepticus (SE) is known to occur in AHC and is, at times, followed by developmental regression and psychomotor deterioration.\textsuperscript{11} However, the characteristics of SE in these patients remain to be fully described.

On the basis of our experience in managing epilepsy in patients with AHC, we generated the following original hypotheses that we aimed to investigate in our study: (1) epilepsy in AHC can be localization related (focal) or generalized, and epileptic seizures can be the initial presenting symptom; (2) the appearance of epileptiform abnormalities often lags behind epilepsy onset; (3) nonepileptic reduced awareness spells (RAS) occur frequently; (4) epilepsy is commonly drug resistant but may respond to vagal nerve stimulation (VNS); and (5) SE is common, usually refractory, and recurrent.

Methods

We analyzed the data of a cohort of 51 consecutive patients seen in our multidisciplinary AHC clinic who fulfilled the Aicardi criteria (see appendix e-1 available from Dryad, doi.org/10.5061/dryad.qn3287b).\textsuperscript{1,3,6,7} Patients underwent clinical evaluations and testing according to clinical need and our AHC clinical pathway\textsuperscript{1} (including genetic, EEG, and MRI investigations). Genetic testing was performed through whole-exome sequencing or through a targeted panel that included \textit{ATP1A3, ATP1A2, SLC2A1, SCN1A, PRRT2}, and \textit{CACN1A}, as well as other genes, performed with next-generation sequencing and then, when positive, confirmed by Sanger sequencing (table e-1 available from Dryad, doi.org/10.5061/dryad.qn3287b). Patients provided consent, and their prospectively collected data from our center and retrospectively available data from previous centers were entered into our Institutional Review Board–approved database.

Epilepsy and seizure types

Presence of epilepsy and epileptic seizures was defined according to the International League Against Epilepsy (ILAE) criteria.\textsuperscript{12–14} In addition, for the purposes of this study and because the AHC spells can often be difficult to distinguish from epileptic seizures, we used the following additional criteria. An epileptic seizure was considered to have occurred if at least one of the following conditions was satisfied: (1) a representative event recorded on video-EEG was proven to be an epileptic seizure by concurrent electrographic seizure activity; (2) according to the treating epileptologist, the semiology of the event is definitively indicative of an epileptic seizure (e.g., focal clonic seizure with motor march); or (3) according to the treating epileptologist, semiology of the event is consistent with an epileptic seizure and the patient also has definitive interictal EEG changes consistent with such a semiology (e.g., episode of staring with eyelid flutter and an interictal EEG of 3-Hz spike slow waves). Seizure types were defined according to ILAE definitions as focal, generalized, or unknown onset.\textsuperscript{14} Classification of seizure type and localization were performed according to the following procedure. First, we carefully analyzed the description of the seizure and correlated it with the EEG interictal findings. Semiology was, thus, classified as focal (with localization to a specific lobe) or generalized, as long as the EEG and semiology corresponded to each other and were clearly indicative of a specific classification and localization. Second, in patients on whom video-EEG monitoring was performed, monitoring information was used. Third, in those cases in whom it was not possible to classify the seizure type with the above 2 procedures, the seizure type was classified as unknown onset. The above procedures are fully consistent with the ILAE recommendations for the classification of seizures and epilepsy and for application of this classification.\textsuperscript{12,14} Focal seizures in which lobe localization was not possible were classified as undetermined localization. Severity of developmental disability was categorized as mild, moderate, severe, or profound on the basis of the neurologic and developmental examinations performed at the time of last follow-up as described and used in previous studies.\textsuperscript{1,15,16}

EEG studies

Our pathway includes performance of a minimum of a 4-hour outpatient video-EEG on all patients with inpatient admission when clinically indicated.

Neuroradiologic studies

Brain MRI was performed on all patients. Magnetic resonance spectroscopy (MRS) was acquired on 7 patients according to clinical need to assess specific areas of interest. Interictal PET was performed on 3 patients.

Therapies

We classified epilepsy response to therapy by the ILAE classifications of drug resistant, seizure-free, epilepsy resolved, or...
undetermined response.\textsuperscript{13} To collect exploratory data on the response of seizures to specific medications, including antiepileptics, off-label use of repurposed drugs, steroids, or ketogenic diet, we used the following empirical definitions for this study. A medication was considered effective in a patient if that patient achieved seizure freedom (as per the ILAE definition) on it, possibly effective if both the physician and family agreed that the medication helped but did not result in seizure freedom, or ineffective otherwise. Off-label repurposed drugs were used in 11 patients due to their mechanisms of action. The intent was that they might reduce the severity of epileptic seizures and of other AHC manifestations. These included dextromethorphan, which reduces spreading depression, a presumed mechanism of increased excitability in AHC; amiloride, which has antiseizure effects in rodents and inhibitory effects of the Na\(^+/Ca\(^{2+}\) exchanger; and ATP, which has previously been reported to have helped 1 patient with AHC and can enhance ATPase pump activity.\textsuperscript{4,17–21} In a subgroup of 4 patients who underwent VNS implantation in our center, we documented response to VNS in a detailed way. To do this, we used seizure counts and an AHC spell index (based on 3 major variables that determine the extent of attacks: severity, frequency, and duration\textsuperscript{9}; see appendix e-2 available from Dryad, doi.org/10.5061/dryad.qn3287b) calculated for the 1-month baseline preceding VNS insertion and then at follow-up at the specific time points indicated below.

**Status epilepticus**

We categorized SE as defined in the literature. Refractory SE persists despite a sufficient dose of benzodiazepines and at least 1 antiepileptic drug regardless of time.\textsuperscript{22} Superrefractory SE continues for $\geq 24$ hours after the use of anesthetic therapy, including cases that recur on weaning of the anesthetic agent.\textsuperscript{12} We also categorized SE as focal or generalized and documented its duration, the medications needed to control it, whether subsequent regression occurred, and other clinical characteristics.

**Statistics**

We used the Kruskal-Wallis, Fisher exact test, binomial, and paired and unpaired Student $t$ tests as appropriate.

**Data availability**

Anonymized data will be shared by request from any qualified investigator.

**Results**

**Epilepsy and seizures of various types occur in AHC**

Of the 51 patients, 32 had epilepsy starting at a mean age of 1.83 ± 3.00 years (range 1 day–14 years, median 9 months) (figure 1 and tables 1 and 2). Mean age at AHC spell onset was not significantly different between patients with epilepsy and patients without epilepsy ($p = 0.2595$). However, 8 patients had onset of epilepsy before onset of AHC spells (average age at onset of seizures 2.12 ± 2.74 months, average age at onset of AHC spells 7.75 ± 6.32 months; $p = 0.0365$). The characteristics of these patients are shown in table 1. Characteristics of all 32 patients, seizures, epilepsy, and gene mutations are shown in table 2. Twenty-seven were classified on the basis of semiology and interictal EEG and 5 on the basis of ictal EEG recordings. Seizure types were as follows (figure 1). (1) Eighteen had focal seizures: 7 were localized to the frontal lobe, 2 to the temporal lobe, 2 to the parietal lobe, and 2 to the occipital lobe; 4 were bifocal (frontal and temporal in all 4); and 1 could not be localized. Of the 18, 15 had focal seizures with impaired awareness, 3 with preserved awareness, and 16 with focal to bilateral tonic-clonic seizures; 2 had gelastic seizures. (2) Eleven had primary generalized seizures; all had primary generalized tonic-clonic seizures, 3 had myoclonic seizures, 2 had atonic seizures, and 2 had absence seizures. (3) Three had generalized tonic-clonic seizures of unknown onset (unknown if primary or secondary). Nineteen patients (59%) had drug-resistant epilepsy; 7 patients achieved seizure freedom; and 6 patients had undetermined responses (figure e-1A available from Dryad, doi.org/10.5061/dryad.qn3287b, shows the time course of patients’ responses to medications). Seizures were often reported to occur in the context of AHC spells. Nonepileptic events were categorized according to the psychogenic nonepileptic seizures classification system.\textsuperscript{23,24} One patient had spells of arm shaking and repetitive stepping (documented by video-EEG); another had repetitive stepping only (clinically established by video recording); a third had arm weakness that the mother could abort.
Epileptiform activity onset often lags behind epileptic seizure onset
Abnormalities included diffuse slowing in 9 patients, focal slowing in 6, and epileptiform activity in 19 (figure 2 and figure e-1B available from Dryad, doi.org/10.5061/dryad.qn3287b). Seven of the 19 patients had an initially normal EEG that later became abnormal (lag 3.53 ± 4.65 years, median 3, range 1–14). This supported the notion that the yield for abnormal and epileptiform activity onset often lags behind epileptic seizure onset significantly with increasing number of EEGs performed. EEG was categorized into 4 categories: normal, diffuse slowing, localized slowing, and epileptiform (spikes, spike slow waves, and sharp waves). Of our 32 patients (138 EEG studies; 4.31 ± 3.37 EEGs per patient, median 3, range 1–14), 19 had at least 1 epileptiform EEG (5.26 ± 3.48 EEGs per patient, range 1–14), and 3 had all of their EEGs as epileptiform (1.33 ± 0.57 EEGs per patient, range 1–2). Twenty-six had at least 1 abnormal EEG (5.00 ± 3.37 EEGs per patient, range 1–14), and 8 had all abnormal EEGs (3.38 ± 2.97 EEGs per patient, range 1–8). Six had all normal EEGs (1.33 ± 0.82 EEGs per patient, range 1–3). There were significantly fewer EEGs performed per patient for the 6 patients with all normal EEGs compared to those 19 with at least 1 epileptiform EEG and to those 26 with at least 1 abnormal EEG (p = 0.0126 and p = 0.0137, respectively). Figure e-1B (available from Dryad, doi.org/10.5061/dryad.qn3287b) shows the time course of the EEG findings for each of these patients. Twenty-nine of 32 patients with epilepsy had long-term video-EEG monitoring (>24 hours) of an average duration of 6.96 ± 7.71 days (average 3.38 ± 2.66 monitorings per patient, median 3, range 1–10). During monitoring, numerous AHC spells (hemiplegia, double hemiplegia, dystonia, autonomic dysfunction, myoclonus, and abnormal eye movements) were recorded without any significant concurrent EEG changes. Five patients had electromyographic seizures captured on video-EEG: 2 from the left frontal region, right temporal in 1, and generalized spike and slow wave in 1 (figure 2D). The fifth patient had 6 seizures captured on video-EEG: 1 from the left frontotemporal region, 3 from the right temporal-parasagittal area, and 2 from the left temporal region. An additional patient was recorded in the postictal period after SE and demonstrated diffuse background slowing (figure 2F).

RAS are common and nonepileptic in nature
RAS consisted of isolated lethargy and drowsiness with staring and reduced responsiveness, usually lasting minutes to hours (table 3). Twenty-six of the 51 patients in this study had episodes of RAS. No significant difference was noted between the number of patients with epilepsy who had RAS (16 of 32) and those without epilepsy who had RAS (10 of 19) (p = 1.000). Most episodes of RAS were not associated with other symptoms; however, in about one-third of RAS episodes, there were also brief superimposed additional manifestations such as minimal hemiplegia, dystonia, autonomic dysfunction, agitation, atonia of the neck, atonia of the body, pain, or abnormal eye movements during part of the spell. Each of these occurred only as a minor feature with the predominant symptom being reduced awareness. No symptom indicative of seizures was noted by calling him out of them (documented by video-EEG); and a fourth had generalized tremors that the mother recognized as attention seeking (clinically established by video recording). The first 2 patients were diagnosed as stereotypies; the last 2 were diagnosed as psychogenic nonepileptic seizures.

Table 1 Characteristics of 8 patients with onset of epilepsy before AHC spells

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at last FU, y</th>
<th>Epilepsy onset/age at other AHC manifestations onset</th>
<th>Developmental delay classification</th>
<th>Description of epilepsy onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7</td>
<td>DOL 1/12 mo</td>
<td>Moderate</td>
<td>Seizures began at DOL 1, left-sided stiffening, head deviated to the left, confirmed by EEG to be epileptic seizures</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>2 mo/3 mo</td>
<td>Mild</td>
<td>Left upper-extremity clonic jerking</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>1 mo/4 mo</td>
<td>Severe</td>
<td>GTC started at age 4 wk</td>
</tr>
<tr>
<td>11</td>
<td>8.5</td>
<td>8 mo/10 mo</td>
<td>Moderate</td>
<td>At 8 mo had seizure consisting of eye deviation to the left with nystagmus and left arm tonic and clonic activity</td>
</tr>
<tr>
<td>19</td>
<td>7</td>
<td>DOL 1/3 mo</td>
<td>Moderate</td>
<td>During DOL 1, cyanotic and had a seizure characterized by eye deviation to the left with clonic shaking of left arm</td>
</tr>
<tr>
<td>22</td>
<td>7</td>
<td>4 mo/4 mo</td>
<td>Moderate</td>
<td>Right-sided clonic seizures started at 4 mo of age, occurred every 2 wk</td>
</tr>
<tr>
<td>29</td>
<td>3</td>
<td>2 mo/7 mo</td>
<td>Profound</td>
<td>Tonic-clonic seizures first noted at 2 mo of age</td>
</tr>
<tr>
<td>49</td>
<td>26</td>
<td>DOL 1/5 mo</td>
<td>Mild</td>
<td>Generalized seizures noted at DOL 1</td>
</tr>
</tbody>
</table>

Summary:
Mean: 10.03 ± 8.47
Mean onset of epilepsy: 2.12 ± 2.74 mo (range DOL 1–8 mo)
Mean onset of other AHC spells: 7.75 ± 6.32 mo (range 3–12 mo)
Mean onset of epilepsy/age at other AHC spells: 8.47 ± 10.03 ± 12 mo

Assessment:
Mean onset of other AHC spells: 8.47 ± 10.03 ± 12 mo

Abbreviations: AHC = alternating hemiplegia of childhood; DOL = day of life; FU = follow-up; GTC = generalized tonic-clonic.
during such spells. Altogether, 10 (8 with epilepsy, 2 without epilepsy) patients of the 26 had 28 RAS captured on video-EEG, all without EEG correlate (table 3 for details).

**Neuroradiologic abnormalities occur in severe cases**

Of the 32 patients with epilepsy, 23 had normal MRIs and 9 had abnormalities: diffuse usually more frontal and cerebellar atrophy in 4, nonspecific abnormalities in 4, and a postictal (within 24 hours after SE) hyperintense fluid-attenuated inversion recovery signal in the right parietal cortex in 1 (figure 3B) (details of all patients in appendix e-3 available from Dryad, doi.org/10.5061/dryad.qn3287b). This patient also had residual long-term left hemiparesis after this episode of SE (see section on SE below). Four of the 7 patients who had MRS had an abnormal MRS study,

### Table 2 Characteristics of epilepsy in 32 patients with AHC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of seizures</strong></td>
<td>Focal seizures with impaired awareness (15), focal seizures with preserved awareness (3), PGTS (11), focal to bilateral tonic-clonic (16), GTC with unknown onset (3), myoclonic (3), absence (2), tonic (2), febrile (2). In the patients with focal seizures, 2 had gelastic seizures, and 1 was described to have a Jacksonian motor march. 93.8% (30/32) of patients had either GTC seizures or SE.</td>
</tr>
<tr>
<td><strong>Localization</strong></td>
<td>Frontal (7), frontal and temporal (4), temporal (2), occipital (2), parietal (2), primary generalized (11), unknown if primary or focal to bilateral (3).</td>
</tr>
<tr>
<td><strong>Age at onset, y</strong></td>
<td>Mean 1.83 ± 3.00, range 0–14</td>
</tr>
<tr>
<td><strong>Developmental delay</strong></td>
<td>In 32 patients with epilepsy: none (1, 3%), mild (8, 25%), moderate (6, 19%), severe (15, 47%), profound (2, 6%). In 19 patients without epilepsy: none (1, 5%), mild (8, 42%), moderate (6, 32%), severe (4, 21%), profound (0, 0%).</td>
</tr>
<tr>
<td><strong>Seizure frequency</strong></td>
<td>In 11 patients with drug-resistant focal seizures: range 4× per day—once per year, median 2–3 times per month. In 6 patients with drug-resistant primary GTC seizures: range once per week—once every few months, median 2–3 times per month. In 2 patients with absence of seizures: several times per day in 1, several times per month in the other. In 2 patients with drug-resistant GTC seizures of unknown onset: 2–3 times per week in 1, 2 times per month in 1. Myoclonic and atonic seizure frequency ranged between once per week and 3 times in the lifetime.</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>19 were drug resistant, 7 achieved seizure freedom, 6 were undetermined.</td>
</tr>
<tr>
<td><strong>Interictal EEG findings</strong></td>
<td>Normal EEGs: 19% (6/32) have only ever had normal EEGs, 72% (23/32) has at least 1 normal EEG. Diffuse slowing: 3% (1/32) have only had EEGs with diffuse slowing, 31% (10/32) had at least 1 EEG with diffuse slowing. Focal slowing: 0% (0/32) have only had EEGs with focal slowing, 22% (7/32) had at least 1 EEG with focal slowing. Epileptiform/paroxysmal activity: 9% (3/32) have had all EEGs with epileptiform/paroxysmal activity, 59% (19/32) had at least 1 EEG with epileptiform/paroxysmal activity.</td>
</tr>
<tr>
<td><strong>Neuroradiologic studies</strong></td>
<td>MRI: normal in 72% (23/32), abnormal in 28% (9/32). MRS: abnormal in 80% of those tested (1/5 normal and 4/5 abnormal), MRS was normal in 2/2 patients with no prior epilepsy or SE.</td>
</tr>
<tr>
<td><strong>Video-EEG ictal and postictal recordings</strong></td>
<td>Clinical seizures ictal recordings: 5 patients (5/32, 16%), focal onset in 4 and generalized in 1. Clinical seizures postictal recordings: 1 patient with diffuse slowing of background. RAS captured: 28 in 10/32 patients, no EEG change in any.</td>
</tr>
<tr>
<td><strong>Genotype-phenotype correlation</strong></td>
<td>E815K: 3/5 (60) Mean age at epilepsy onset (y) = 2.18 ± 2.55, Drug resistant, n (%) = 2/3 (66), SE, n (%) = 2/3 (66), Mean age at first SE, y = 1.5 ± 2.12, Range age at first SE, y = Neonate–7. D801N: 5/9 (56) Mean age at epilepsy onset (y) = 4.07 ± 6.11, Drug resistant, n (%) = 2/5 (40), SE, n (%) = 3/5 (60), Mean age at first SE, y = 8.33 ± 6.81, Range age at first SE, y = 3–24.</td>
</tr>
</tbody>
</table>

Abbreviations: AHC = alternating hemiplegia of childhood; GTC = generalized tonic-clonic; MRS = magnetic resonance spectroscopy; PGTC = primary generalized tonic-clonic; RAS = reduced awareness spells; SE = status epilepticus. Other less frequent mutations seen (total 20 different ATP1A3 mutations) included G89D, G775C, Y768H, A333T, P336S, Q851R, G947R, D923Y, C609Y, E828K, L326R, R756H, L839P, V589F, V859F, A330T, E828K, and L939P. The numbers of patients with each were less than the above 2 mutations and thus were not enough to meaningfully perform additional correlations.
and all 4 had a history of SE and epilepsy (details presented in appendix e-3 available from Dryad, doi.org/10.5061/dryad.qn3287b). Three had normal MRS: 1 patient had a history of SE, and 2 did not have epilepsy. Three patients had PET scans, 2 of which were normal and 1 showed hypometabolism in the right temporal lobe in a patient with known temporal lobe epilepsy.

**Epilepsy in AHC is often drug resistant but can respond to VNS**

Of 22 antiepileptic drugs, we could not observe any definitive specific pattern of better response with certain medications or classes of medications (table e-2 available from Dryad, doi.org/10.5061/dryad.qn3287b). The 19 drug-resistant patients were on 2.95 ± 1.21 (range 1–5) medications as of the last follow-up (mean age when last seen 11.40 ± 10.53 years, range 1.5–26 years). For the 11 patients on off-label repurposed drugs, the number of patients and doses used were as follows: dextromethorphan n = 4, dose range 2 to 4 mg/kg/d; ATP n = 2, doses 1.5 mg/kg/d; and amiloride n = 3, dose range 0.2 to 0.3 mg/kg/d. None of these agents were associated with a favorable response for seizures or hemiplegia. Of the 4 patients who received dextromethorphan, 1 patient had a decrease in the number of dystonia spells from 7 per day (10-minute duration each). In addition, pulse steroids (30 mg/kg/d × 3 d/mo) were used in 2 patients. One 8-year-old patient reported hemiplegia frequency to be reduced to one-fourth the original frequency and from hours to minutes in duration. This patient has continued to receive monthly pulse steroids for the past 2 years. The other patient did not tolerate treatment due to behavioral side effects. Two of 6 patients benefited from the ketogenic diet. One patient experienced a reduction in seizure and AHC spell frequency (baseline: seizures once per month, hemiplegia 2 times per month, dystonia 3 times per day; at the 4-month follow-up: no seizures, no hemiplegia, dystonia 2 times per week), and 1 patient became more vocal.

![Figure 2 EEGs of 5 patients with alternating hemiplegia of childhood with epilepsy](image-url)
and alert during the 6 months of follow-up on the diet without a change in seizure or spell frequency. All 4 patients who had the VNS device inserted in our center reported a >50% reduction in seizure frequency (mean follow-up, 22.2 ± 5.42 months, range 9–36 months). Pre-VNS seizure frequency at baseline was 99.5 ± 59.2 per month; at 1 month, 8.50 ± 4.97; at 6 months, 4.25 ± 0.90; p = 0.036). The change in the spell index score for dys tonic attacks did not achieve statistical significance (baseline before VNS 7.63 ± 0.55, 1 month 6.5 ± 0.20, 6 months 5.38 ± 0.8, last follow-up [12–29 months] 4.88 ± 0.90; p = 0.036). The change in the spell index score for dystonic attacks did not achieve statistical significance (baseline before VNS 6.13 ± 1.05, 1 month 5.5 ± 1.02, 6 months 3.63 ± 0.97, last follow-up 3.63 ± 1.13; p = 0.167). One patient had episodes of atonia associated with output current settings >1 mA that resolved by reducing the output current. Of the 2 patients in whom the VNS was inserted elsewhere, 1 patient reported >50% reduction in seizure and AHC spell frequency, and the other did not report improvement. In both patients, the VNS stimulation was discontinued; in the first due to an inability to reimplant after the first implantation became nonfunctional and in the second due to lack of efficacy.

**SE is often refractory, recurrent, and followed by regression**

High frequency, drug resistance, and developmental regression were noteworthy characteristics of SE (table 4). Twelve patients had 32 episodes of SE, ranging from 30 minutes to 4.5 days (mean age 5.58 ± 6.07 years, range neonate–24 years, median 3.50 years). Characteristics of SE are shown in table 4. One had 8 episodes; 5 had 3 episodes; 3 had 2 episodes; and 3 had 1 episode. All episodes were refractory and 3 were superrefractory. Seven had focal to bilateral convulsive SE; 3 had primary generalized convulsive SE; 1 had nonconvulsive SE of focal etiology; and 1 had both focal to bilateral convulsive SE and nonconvulsive SE of focal etiology. In 5 of 32 episodes, there was an initial recognizable focal impaired awareness seizure phase before generalization. Patients required 2 to 5 medications to halt SE: diazepam, lacosamide, topiramate, phenobarbital, midazolam, lorazepam, levetiracetam, fosphenytoin, and/or propofol. Nine SE episodes in 5 patients required intubation. Four SE episodes in 3 different patients were immediately preceded by nonepileptic AHC spells. Two other SE episodes were precipitated by attempts to taper phenobarbital in 1 patient and levetiracetam in another. Four of 12 patients had regression after SE. Regression was reversible in 2 of the 4 (patients 15 and 18) but not in the other 2 (patients 21 and 51). Patient 15 had weakness on the left side for 12 hours following SE and was poorly coordinated for 2 to 3 days, but then fully recovered. Patient 18, at age 18 months, lost the ability to walk after 4 hours of SE and then regained this ability 1 month later. She then, that same year, regressed in swallowing and fine motor movements after 1.5 hours of SE and regained these in 1 month. Then at age 4 years, after 1.5 hours of SE, she lost her ability to comprehend speech and her 30 words of sign language and only regained these 6 months later. Patient 21 lost the ability to feed herself and the ability to walk and developed diffuse left-sided greater than right-sided weakness. By 3 months, she recovered all these except for residual

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**Table 3 Characteristics of RAS**

<table>
<thead>
<tr>
<th>RAS manifestation</th>
<th>Patients with spells, n</th>
<th>Additional superimposed manifestations (total patients, n)</th>
<th>Spells recorded on video-EEG/patients, n</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced awareness alone as the only manifestation in all RAS of that patient</td>
<td>8</td>
<td>None</td>
<td>19/6</td>
<td>Few times a day–few times in life</td>
<td>10 s–30 min</td>
</tr>
<tr>
<td>Reduced awareness alone in some spells and in other spells reduced awareness with other manifestations</td>
<td>18*</td>
<td>Reduced awareness with abnormal eye movements (3)</td>
<td>0/0</td>
<td>Few times per day–few times per week</td>
<td>10 s–3 min</td>
</tr>
<tr>
<td></td>
<td>Reduced awareness with agitation (2)</td>
<td>1/1</td>
<td>Few times per week</td>
<td>5–10 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced awareness with autonomic changes (4)</td>
<td>1/1</td>
<td>Multiple times per day</td>
<td>10 s–10 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced awareness with dystonia (6)</td>
<td>3/1</td>
<td>Few times per month</td>
<td>10 seconds–30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced awareness with pain (2: head in 1; feet, eyes, and stomach in 1)</td>
<td>4/1</td>
<td>Few times per day–few times per week</td>
<td>10 s</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RAS = reduced awareness spells.

*Eighteen of 26 patients had both types of RAS: reduced awareness with no other accompanying manifestations and, in the same patient at other times, reduced awareness as the main manifestation of the spell with accompanying minor manifestations. The rows to the right detail the most common accompanying manifestations that occurred during RAS and the number of patients who had them. Many of these patients had multiple types of accompanying manifestations. Some of the 18 patients had additional accompanying manifestations not listed in these rows, including myoclonus, repetitive speech, enuresis, mouthing movements, and vision loss.
weakness that persisted even at last follow-up 1 year later. The fourth, patient 32, regressed, losing the previously established ability to sit up, roll over, reach for objects, play, smile, and take food by mouth, none of which returned as of the latest follow-up after 18 months, at which time he was still being fed through a gastrostomy tube. For further details on regression after SE, see appendix e-4 available from Dryad (doi.org/10.5061/dryad.qn3287b). These patients are reported in table 4 as patients 15, 18, 21, and 32. The MRI performed on patient 21 within 24 hours after the SE episode is presented in figure 3B.

Discussion

Seizure and epilepsy characteristics

Epilepsy in our patients with AHC was characterized by multiple seizure types and localizations, drug resistance, and high frequency and high recurrence rate of refractory SE. Prior studies have reported a 15% to 77% range of occurrence of epilepsy in AHC. The observed prevalence in our study (62%) is on the upper end of this range, possibly due to potential referral bias: patients with AHC may have been referred to us because we are also a level 4 epilepsy center. Our findings extend the knowledge about epilepsy in AHC by demonstrating that it can be focal or generalized, that it can also be multifocal, and that the anterior lobes are more affected than the posterior lobes. This is consistent with the prior finding that cerebral hypometabolism in AHC is more severe in the frontal lobes. Of note, we observed a higher incidence of epilepsy and SE in the patients with E815K as previously reported. In addition, we demonstrated that in a significant subset of patients (8 of 32, 25%) with epilepsy, epileptic seizures and even SE can occur before other types of AHC spells, with the epileptic seizures often starting in the neonatal period. Physicians taking care of neonates and infants with new-onset epileptic seizures of unknown etiology...
should consider AHC as a potential cause and be vigilant about recognizing the development of its symptoms.

**EEG and video-EEG studies**

We identified a range of EEG abnormalities in patients with AHC with epilepsy, including focal discharges and generalized spike slow wave discharges. Our observations indicate that while most patients had abnormal and epileptiform EEGs, many did not initially manifest those abnormalities. In addition, 6 patients had only normal EEGs. This is likely due to the significantly fewer number of EEGs performed in these patients (1.33 ± 0.82) compared to patients with epileptiform EEGs (5.26 ± 3.48). Physicians need to be aware of these observations, with a low threshold to repeat EEGs if epileptic seizures are still suspected. In addition, our observation that patients with AHC can have a variety of seizure types and other spells not previously described or emphasized, particularly RAS, underscores the fact that physicians should be vigilant for various semiologies with obvious implications on therapy. For example, one of the patients was investigated in another center for epilepsy surgery candidacy with subdural electrode monitoring before the diagnosis of AHC was made. This also includes not only multiple types of focal seizures and various types of generalized seizures but also RAS, stereotypies, and psychogenic nonepileptic seizure episodes that are distinct from other known paroxysmal events of AHC. This is the first study to explicitly define and describe RAS as a distinct and common type of spells in AHC that often mimics seizures. It is possible that the underlying pathophysiologic mechanism of RAS is similar to that of confusional migraine and that this involves spreading depression. The fact that both confusional migraine and AHC animal models are

### Table 4 Characteristics of SE in AHC

<table>
<thead>
<tr>
<th>Patient/sex</th>
<th>ATP1A3 mutation</th>
<th>Seizure types/localization</th>
<th>SE episodes, n</th>
<th>Age at SE episode, y</th>
<th>Age at last follow-up, y</th>
<th>Regression</th>
<th>Duration of each episode</th>
<th>Average duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>E815K</td>
<td>PGTC/primary generalized</td>
<td>3</td>
<td>Neonate, 1, 2</td>
<td>8</td>
<td>No</td>
<td>At least 30 min, 1 h, 3 h</td>
<td>2 h</td>
</tr>
<tr>
<td>2/M</td>
<td>E815K</td>
<td>FBTC, FIA/fron tal</td>
<td>3</td>
<td>3, 4, 7</td>
<td>9</td>
<td>No</td>
<td>45 min each</td>
<td>45 min</td>
</tr>
<tr>
<td>4/F</td>
<td>D801N</td>
<td>FBTC, FIA, gelastic/fron tal and temporal</td>
<td>3</td>
<td>3, 5, 5</td>
<td>7</td>
<td>No</td>
<td>2 h, 30 min, 30 min</td>
<td>1 h</td>
</tr>
<tr>
<td>7/M</td>
<td>D801N</td>
<td>FBTC, FPA/occipital</td>
<td>2</td>
<td>6, 7</td>
<td>11</td>
<td>No</td>
<td>30 min, 1 h</td>
<td>45 min</td>
</tr>
<tr>
<td>8/M</td>
<td>D810N</td>
<td>FBTC, FIA/ fron tal and temporal</td>
<td>3</td>
<td>16, 23, 24</td>
<td>24</td>
<td>No</td>
<td>9 h, 1 h, 15 min</td>
<td>3.75 h</td>
</tr>
<tr>
<td>9/M</td>
<td>Y768H</td>
<td>FIA, FPA, FBTC, nonconvulsive SE/fron tal</td>
<td>1a</td>
<td>13</td>
<td>23</td>
<td>No</td>
<td>30 min</td>
<td>30 min</td>
</tr>
<tr>
<td>11/F</td>
<td>L326R</td>
<td>FBTC, FIA/ temporal</td>
<td>2</td>
<td>6, 7</td>
<td>8.5</td>
<td>No</td>
<td>48 h, 24 h</td>
<td>36 h</td>
</tr>
<tr>
<td>15/F</td>
<td>D923Y</td>
<td>PGTC/primary generalized</td>
<td>2</td>
<td>3, 5</td>
<td>6</td>
<td>Yes; motor and language with full recovery</td>
<td>180 min, 30 min</td>
<td>105 min</td>
</tr>
<tr>
<td>18/F</td>
<td>Negative</td>
<td>PGTC, myoclonic, atonic/primary generalized</td>
<td>3</td>
<td>1.5, 1.5, 4</td>
<td>6</td>
<td>Yes; motor and language with full recovery</td>
<td>4 h, 1.5 h, 1.5 h</td>
<td>140 min</td>
</tr>
<tr>
<td>21/F</td>
<td>Negative</td>
<td>FBTC, FIA, febrile/parietal</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>Yes; motor and language without full recovery</td>
<td>4.5 d</td>
<td>4.5 d</td>
</tr>
<tr>
<td>27/M</td>
<td>Negative</td>
<td>FBTC, FIA, tonic/ fron tal and temporal</td>
<td>1</td>
<td>13</td>
<td>16</td>
<td>No</td>
<td>36 h</td>
<td>36 h</td>
</tr>
<tr>
<td>32/M</td>
<td>V589F</td>
<td>FBTC/ fron tal and temporal</td>
<td>8</td>
<td>0.5, 0.66, 1.25, 1.25, 1.5, 2, 2.5</td>
<td>4</td>
<td>Yes; motor (gross motor and feeding) interaction, and speech without recovery</td>
<td>30 min, 40 min, 45 min, 30 min, 45 min, 40 min</td>
<td>36 min</td>
</tr>
</tbody>
</table>

Abbreviations: AHC = alternating hemiplegia of childhood; FIA = focal seizures with impaired awareness, FPA = focal seizures with preserved awareness, FBTC = focal to bilateral tonic-clonic seizures, PGTC = primary generalized tonic-clonic seizures; SE = status epilepticus.

*Patient 9 had, FIA, FPA, and FBTC followed by nonconvulsive SE.*
predisposed to spreading depression supports the hypothesis that RAS are migrainous in nature.\textsuperscript{4,30} Physicians should be aware that RAS and nonepileptic events are not uncommon in AHC. In such cases, video-EEG monitoring can be helpful to distinguish various seizure and spell types.

**Neuroradiologic studies**

We note that our results are consistent with the previous observations of usually normal MRI, except for occasional cerebral and cerebellar atrophy noted in $\approx$10% of cases.\textsuperscript{25–29,31–38} However, our findings extend prior findings with a number of novel observations. First, we observed that 1 patient had, on an MRI done within 24 hours after SE (patient 21), postictal changes of focal increased T2 signal that correlated with the epileptic focus documented on ictal EEG and with the long-term post-SE deficit of contralateral hemiplegia. Second, our findings extended prior MRS observations by demonstrating increased lactate peaks postictally in 2 patients, suggesting anaerobic metabolism (novel). We also observed an increased choline peak in another patient, suggesting increased cellular turnover (confirms a prior observation).\textsuperscript{39} Finally, the reduced N-acetyl aspartate peak seen in the 4 of 5 patients who experienced prior SE and in 0 of 2 who had not had prior SE suggests that neuronal loss may be associated with a history of SE (novel). These observations support further investigation of a potential relationship between SE and MRS changes and of MRS as a potential biomarker in AHC.

**Therapies and observed responses**

Our findings are consistent with prior studies that have noted drug resistance of epilepsy in AHC.\textsuperscript{4,10} We found in our cohort that as many as 37% (19 of 51 patients) had drug-resistant epilepsy. We did not observe any apparently more effective antiepileptic medication(s). In addition, our data, albeit limited, did not support that ATP or amiloride had definitive antiseizure or other beneficial effects in AHC. For ATP therapy, our doses were much lower, due to cost issues, than those previously used in the prior case report (25 mg/kg/d).\textsuperscript{17} Our observations of a potentially beneficial effect of dextromethorphan warrant further investigation. VNS therapy appeared to help seizures and plegic spells in AHC. Our patient who appeared to respond to steroid therapy is the second such case in the literature.\textsuperscript{40} The other case, however, was treated with continuous steroids rather than pulse steroids. Our data on the above agents should be interpreted very cautiously due to their open-label and observational nature. In the literature, 2 studies and 3 case reports have described the use of the ketogenic diet in AHC.\textsuperscript{41–45} All 7 treated patients were reported to respond to the diet for paroxysmal spells, 1 of whom was also reported to have epilepsy and noted disappearance of seizures. In our study, 2 of 6 patients appeared to benefit from diet.

**Status epilepticus**

Overall, high frequency (39% of patients with epilepsy had SE), high recurrence rate (75% of patients with SE had multiple episodes), drug resistance, and possible regression characterize SE in AHC. Regression was noted in 4 of 12 (33%) of our patients, which is similar to previous reports of 33% (3 of 9) and 32% (6 of 19).\textsuperscript{11,25} Two of the 4 did not fully recover from this regression. Of note is that recent data have highlighted that there is very frequently a delay in the initiation of therapy for SE in children.\textsuperscript{46} This would be particularly troublesome for patients with AHC who are predisposed to regression after SE. In addition, many of our patients had SE start in the context of prolonged AHC spells or after stress or during antiepileptic drug taper. Thus, physicians should have a low threshold for admitting patients if there is a prolonged AHC spell with associated seizures because this could be followed by SE.

**Correlations with underlying pathophysiology**

The multiple types of seizures, drug resistance, and increased predisposition to SE are consistent with the recently uncovered pathophysiology of AHC. ATP1A3 is diffusely expressed in brain neurons, predominantly in GABAergic interneurons.\textsuperscript{47} In the mouse model carrying the D801N mutation, there is increased excitability of hippocampal CA1 pyramidal cells, which is easily demonstrable with high-frequency, but not with low-frequency, Schaffer collateral stimulation.\textsuperscript{4,5} This is due largely to reduced firing rate of fast-spiking interneurons.\textsuperscript{5} It appears that the brain of patients with AHC not only has increased pyramidal cell excitability but also is often unable to stop ongoing seizure activity once initiated, presumably leading to drug resistance and to SE, because of the following: the ATP1A3 sodium potassium ATPase pump is specifically important in maintaining the sodium potassium gradient during periods of rapid firing\textsuperscript{5,48} and fast-spiking interneurons are also important in such situations.\textsuperscript{5}

**Limitations**

Patients in this study may have been specifically referred to our center because they may have had more severe disease. In addition, not all patients underwent all tests. We have also commented above on the limitations and exploratory nature of our drug response data. Nonetheless, this study has the advantage of a hypothesis-driven, comprehensive analysis of the available epilepsy-related manifestations and data of an informative cohort of consecutive patients with AHC.

Epilepsy in AHC can be generalized or localization related. Onset of epileptic seizures is usually after, but may be before, the onset of AHC spells. For seizures of focal origin, frontal lobes and, less frequently, temporal lobes tend to be more commonly affected than posterior lobes, and multiple lobes may be involved. EEG can be initially normal and then become epileptiform. Epilepsy in AHC is also characterized by drug resistance and by high risk of refractory SE that can occur in the context of attempts of drug withdrawal, stress, or prolonged episodes of AHC spells. Regression after SE is not uncommon. We also found that distinct RAS, which do not have EEG correlate, are likely of nonepileptic pathophysiology and occur commonly. Our findings are consistent with the recently characterized mechanisms of inhibitory-excitatory imbalance leading to enhanced neuronal excitability in AHC animal models.
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Disclosure

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<thead>
<tr>
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<th>Role</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

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