Non-Stationary Outcome of Alternating Hemiplegia of Childhood into Adulthood

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ABSTRACT: Background: Although described as non-progressive, alternating hemiplegia of childhood (AHC) can display a sudden deterioration, anecdotally reported mainly in childhood. Outcome in adulthood is uncertain.

Objectives: Aim of this study is to describe the long-term follow-up of neurological function in adults with AHC.

Methods: Seven adults with AHC were included in this retrospective single-center study. Clinical history and previous investigation data were gathered from the review of medical records. Video-documented neurological examination was performed at the last follow-up visit in four out of the seven reported individuals.

Results: Over a median follow-up of 16 years, neurological outcome and trajectories were heterogeneous. All individuals showed new neurological signs or symptoms. Three experienced a serious irreversible neurological deterioration after prolonged quadriplegic episodes and/or status epilepticus in their second or third decade. One patient died at age 29.

Conclusions: This video-series suggests that AHC in adulthood is not stationary; larger cohorts are needed to identify genotype-phenotype correlations and clinically useful outcome predictors.

Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental condition with onset before 18 months of age, characterized by recurrent attacks of hemiplegia involving one or both sides of the body that typically resolve on sleep, and other paroxysmal disturbances including epilepsy, paroxysmal dystonic attacks, oculomotor abnormalities, and autonomic phenomena. Subsequently, non-paroxysmal neurological signs appear, such as cognitive impairment and movement disorders including choreoathetosis, dystonia, or ataxia. Mutations in the ATP1A3 gene, encoding the α3 isoform of the Na+/K+ ATPase pump, are reported in ~85% of individuals.1,2 Mutations in the same gene are also associated with other clinical syndromes.3-7

Disease course and progression in AHC is now a matter of debate. A non-progressive course has been described in the past, whereas in a more recent case series, seven patients, aged 12 years and below, were reported to have experienced abrupt and irreversible regression along with significant acquired cortical and cerebellar atrophy.9 Slow and mild progression of non-paroxysmal disability were recently observed in a multicentric cohort of 94 children and young adults.10

The only case of regression in adulthood described so far happened in concomitance with frequent episodes of status epilepticus, but few details regarding neurological function are given and the time course is unprecise.11

We report seven adult patients with AHC with detailed clinical history and long-term follow-up, adding data on the natural history of the disease and its phenotypic variability. Three of them presented acute regression, which we characterize with...
| Patient N | Age (mo) | Gender | Clinical features, diagnostic findings and treatment | Age of onset | Symptoms at onset | Paroxysmal features | Non-paroxysmal features | Psychiatric features | Other | Baseline GMFCS score | Last GMFCS score | Intellectual and SE | History of epilepsy and SE | History of acute regression | Treatment | EEG (age in yr) | MRI (age in yr) |
|-----------|---------|--------|--------------------------------------------------|-------------|------------------|--------------------|---------------------|---------------------|-------|----------------------|----------------|-----------------|-------------------------|---------------------------|-----------|----------------|----------------|
| 1         | 42      | F      | c.3839G>A; p.G947R, Paroxysmal nystagmus and hemipLEGic episodes | 39          | G > A; p.G947R    | Ataxia, hypotonia | Headaches | Visual and auditory hallucinations, onset in her 30s | 2            | Mild | 23 | 23 | | Bac | Eeg (2, 18, 33, 30) | VT (34) some changes in G1 activity | Mild cortical and ventricular atrophy (34) |
| 2         | 34      | F      | c.2411 T > C; p.S811P, Paroxysmal eye fluttering | 23          | T > C; p.S811P    | Hypotonia, spastic torsion, dystonia | Headaches | Depression | 2            | 5            | Moderate-severe | Yes, last GTC seizure at age 35 yr | Yes (23 yr) after prolonged quadriplegic episode triggered by febrile illness | PHT, TPM, FLN, Bac | Eeg (1) VT (26, 31) abnormal bursts of sharp and slow waves | Normal (19) |
| 3         | 27      | M      | c.2214 A > C; p.S722R, Paroxysmal quadriplegic epis | 12          | A > C; p.S722R    | Ataxia, dystonia | No | No | 1            | 10            | Mild | Yes, SE at age 15 yr | No | Tpm, Fln, Pzt | Eeg (11, 16) normal | Normal (19) |
| 4         | 25      | F      | c.3839G>A; p.G947R, Dystonic attacks, hypotonia | 3            | G > A; p.G947R    | Ataxia, mild dystonia | Headaches | Normal | 1            | 10            | Mild | No | No | No | Eeg (1) normal | Normal (19) |
| 5         | 37      | F      | None | 4 | Hemiplegic, hypotonia | Mild ataxia, leggomenous lary | No | No | 1            | 10            | Mild | No | No | No | Eeg (9) VT (20) normal | Non-specific theta abnormalities | Normal (19) |
| 6         | 29      | F      | c.2413 G>A; p.G947R, Dystonic attacks, hypotonia | 2            | G > A; p.G947R    | Dystonia, choreoathetosis | No | No | 4            | 10            | Moderate-severe | Yes, focal or secondary during sleep at age 24 yr | Yes (19 yr) after febrile illness | Lcs, Fln, Clb | Eeg (2) normal VT (24) focal spikes | Normal (19) |
| 7         | 34      | F      | c.410 C>T; p.S133F, Paroxysmal eye fluttering, hypotonia | 1 | C>T; p.S133F | Ataxia, dystonia | No | No | 1            | 10            | Moderate | Yes, SE at age 34 | Yes (34 yr) after febrile illness and SE | Lev, Fln, Pzt, CBz | VT (23) diffuse slowing of background and generalized spike and slow waves (frontal dominance) | Left hippocampal sclerosis (5, 23) |

*Baseline motor performance as observed in the first encounter.

†Formal neuropsychometry assessment was not available, intellectual disability severity was based on adaptive behavior according to the ICD-10 classification.

Abbreviations: GMFCS, gross motor function classification system; SE, status epilepticus; VT, video-telemetry; GTC sz, generalized tonic–clonic seizure; Baclofen; PHT, phenytoin; TPM, topiramate; FLN, flunarizine; PZT, pizotifen; ZNS, zonisamide; LCS, lacosamide; CBZ, carbamazepine; CLB, clonazepam; LEV, levetiracetam; yr, years.
respect to clinical features, precipitating factors, genotype, and treatment.

Methods

All patients and/or their parents/legal guardians gave informed consent/assent, including for video-recordings. This study was approved by the local Ethics Committee. Clinical records of patients attending University College London Hospitals (UCLH), with a clinical diagnosis of AHC according to the Aicardi criteria, were reviewed. Video-recordings of the neurological examination were acquired between May and September 2019.

Sequencing of the \textit{ATP1A3} gene was performed in all individuals with the identification of a pathogenic \textit{ATP1A3} mutation in six out of seven. One patient had whole-exome sequencing, which did not identify any \textit{ATP1A3} or other gene pathogenic variants.

Results

We describe seven adult patients (six female, one male; age range, 25–42 years), diagnosed with AHC and followed-up at our center for a median of 16 years (range, 7–24 years). The disease course for each individual is detailed in Table 1 and Video 1. During follow-up, 3 of 7 patients experienced an episode of abrupt neurological deterioration in adulthood (age range at onset of deterioration, 19–34 years), following a febrile illness that triggered an extremely prolonged quadriplegic episode at onset of deterioration, 19 years of abrupt neurological deterioration in adulthood (age

Video 1. Patient 1. At rest, she shows mild dystonic features, more prominent on the right side and a few generalised jerky movements. Her speech is mildly dysarthric. With arms outstretched, dystonia of upper limbs becomes more evident. At the finger-to-nose test, there is some dysmetria on the right. Fine movements are impaired, more on the right, with great asymmetry. There is no true bradykinesia but some clumsiness bilaterally. Handwriting is legible but clearly dystonic. When walking, there is in-turning of the feet, mainly on the right and abnormal posturing of both arms, flexed and with hands in a clenched fist. Posture is impaired, with mild antecollis. Patient 2. She is wheelchair-bound with permanent right-sided hemiplegia. She has also bilateral foot in-turning with reduced articular mobility. When repeatedly stimulated, she can keep eye contact. Reaching movements are possible with the left arm. Head control is impaired, with limited ability to follow an object and sudden head drops. She has striatal toes and extension at the planar reflex. Patient 3. When seated, he has mild truncal deviation towards the left. With arms outstretched, mild dystonia of the upper limbs becomes more prominent. There is some clumsiness during pronosupination of the arms, along with mobile dystonia. A slight bilateral dysmetria is seen at the finger-to-nose test. At finger tapping there is no true bradykinesia, but the fluidity of the movement is bilaterally reduced due to the dystonia. In this segment of the video it is also possible to notice a reduced blink rate and a mild antecollis. Handwriting is barely intelligible, and severe dystonic posturing of the right hand while holding the pen is shown. While walking, hands are both held in clenched fist, with some involuntary proximal jerky movement of the arms. There is mild antecollis. He complains about fatigue, however he can walk independently for few meters. Patient 4. She is examined at the end of a prolonged right hemiplegic episode which evolved into paroxysmal dystonic attack. The right arm is still flexed, held in front of the body with the hand raised upwards. The rest of the examination is typical of her interictal condition. Her speech is clearly dysarthric. When asked to outstretch her arms and protrude/supinate the hands, she shows a bilateral, distal mobile dystonia with overflow phenomenon. No clear dysmetria at the finger-to-nose test, while fine hand movements are severely impaired on the right, due to the dystonia. However, handwriting is clear. Gait is independent with mild antecollis and some jerky movements of the left upper limb. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13388

Our cohort suggests that individuals with AHC may experience either abrupt or slowly progressive worsening of their symptoms on a background of low mood. To date, these symptoms have been relatively stable without the need for psychiatric treatment. One patient is awaiting psychiatric assessment.

Discussion

Our cohort suggests that individuals with AHC may experience either abrupt or slowly progressive worsening of their symptoms on a background of low mood. To date, these symptoms have been relatively stable without the need for psychiatric treatment. One patient is awaiting psychiatric assessment.
TABLE 2 Clinical and genetic features of patients with acute clinical regression

| ID      | Mutation | Age at regression (y) | Language regression | Motor function impairment | Precipitating events | Flunarizine treatment with respect to onset of clinical regression | References |
|---------|----------|-----------------------|---------------------|---------------------------|----------------------|---------------------------------------------------------------|-------------|
| Sasaki-1| p.E815K  | 5                     | Words → absent      | Stand → bed               | SE, fever           | Discontinued 2 years before                                   | 17          |
| Sasaki-2| p.E815K  | 10                    | Absent              | Bed                       | SE                   | Discontinued same year                                          | 17          |
| Sasaki-3| p.E815K  | 6                     | Sentence → words    | Sit → bed                 | SE, fever           | Discontinued 1 year before                                    | 17          |
| Sasaki-4| p.E815K  | 7                     | Words               | Stand → bed               | SE                   | Discontinued 1 year before                                    | 17          |
| Sasaki-5| p.E815K  | 4                     | Words → absent      | Stand → bed               | SE                   | Discontinued 1 year before                                    | 17          |
| Sasaki-6| p.G755S  | 12                    | Words → absent      | Stand → bed               | SE                   | Ongoing treatment                                              | 17          |
| Sasaki-7| p.G755S  | 3                     | Words → absent      | Sit → bed                 | SE                   | Never used                                                     | 17          |
| Uchitel-21| Not identified | 8                  | Sentence             | Residual hemiparesis     | SE                   | Never used                                                     | 19          |
| Uchitel-32| p.V589F   | 2                     | –                   | Walk → bed                | SE                   | Never used                                                     | 19          |
| Ito     | p.G755S  | 38                    | –                   | Walk → bed                | SE                   | Discontinued 13 years before                                   | 20          |
| #2      | p.S811P  | 23                    | Sentence → words    | Walk → bed                | Fever followed by quadriplegia | Ongoing treatment                                              | Current study |
| #6      | p.E815K  | 19                    | Words → absent      | Crawl → bed               | Fever followed by SE/quadriplegia | Ongoing treatment                                              | Current study |
| #7      | p.S137F  | 34                    | Sentence → words    | Walk → sit                | Fever followed by SE/quadriplegia | Ongoing treatment                                              | Current study |

1Information on whether fever preceded SE was not provided by the authors.

2Difficult to distinguish between the two with the data reported, more detailed information available in the Supplementary data.

Abbreviations: Bed, bedridden; sit, sit without support; stand, stand with support; walk, walk unassisted; SE, status epilepticus. For the seven patients reported in Panagiotakaki et al17 the only information provided is that the regression was typically triggered by a “stressful event”.

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19. Uchitel et al. J Neurosci 2019; 39(13): 4225-4230.
neurological function and for most adults the hemiplegic episodes may no longer be the main clinical issue.

A previous longitudinal characterization of large AHC cohorts suggested a generally non-progressive course of AHC, but adult patients represented a small proportion of the group (14/157). Review of the data in that report shows that 5 of 14 adults developed fine motor abnormalities after infancy (three in childhood, one in adolescence, and one in adulthood), 3 of 14 developed chorea and/or dystonia after infancy (two in late childhood, one in adulthood) and 2 of 14 developed new-onset hypotonia and gross motor abnormalities after the age of 24 years. More recently, Uchitel et al described a large cohort of 94 children and young adults that they studied retrospectively and partly prospectively with a linear mixed effects model and observed a mild decline in non-paroxysmal disability. Their methodological approach allowed to detect subtle degrees of progression and their cohort included 7 of 42 adults (age range, 20–43 years; mean follow-up, 3.4 years) prospectively evaluated, and 23 of 52 adults in the retrospective analysis (19–39 years, mean follow up 9.9 years). In this cohort, a “catastrophic” regression is described in one subject, who did not have an ATP1A3 mutation.

Other authors have already noted that movement disorders and spasticity can appear at a later stage, but, to the best of our knowledge, this is the first report of fatigue and muscle spasms in adults with AHC. Although muscle spasms could be interpreted as painful paroxysmal dystonic attacks, their predominance at night and their response to baclofen suggest they may be associated with chronic spasticity (as in multiple sclerosis). The same parallel with multiple sclerosis can be proposed for fatigue, the most common disorder where this symptom presents along with chronic spasticity. Fatigue could be also associated with the fear of exercise-induced paroxysmal events.

In terms of psychiatric features, in a recent publication, 20/25 individuals with AHC had a neuropsychiatric diagnosis including attention deficit/hyperactivity disorder (ADHD), disruptive behavior, and mood disorders, but only three individuals were adults. Additionally, two individuals with a severe AHC phenotype and childhood-onset schizophrenia have been reported. Milder adult-onset psychiatric features have been described in two adult individuals with difficulties in social integration. It is not clear whether these psychiatric manifestations are independent comorbidities or if they are a new feature directly linked to the genetic mutation. We cannot exclude that psychiatric disorders in adults with AHC might be under-reported.

Of our seven patients, three experienced an abrupt neurological regression in adulthood, following a febrile illness that triggered either or both an extremely prolonged quadriplegic episode and status epilepticus. There are at least 17 reports of abrupt neurological regression, although these were not always fully characterized (Table 2). Median age at regression was 6.5 years and only one patient was an adult. Of the 10 patients with available genetic data, six had the E815K mutation, which was proposed as a risk factor for acute regression. It was also observed that only one patient was on flunarizine, whereas the others had either recently discontinued it or never used it. In all these reported patients, catastrophic events were preceded by status or very frequent seizures. In our cohort, one of the three adult patients who experienced an acute regression had the E815K variant, whereas the others did not, and all were on flunarizine; regression was triggered by prolonged quadriplegia and fever and not only by seizure activity. Notably, none of the 13 patients (10 previously reported and three from our series) with a history of acute regression had the most common (D801N) recurrent mutation.

In addition, there are 11 reports of sudden unexpected death, an outcome that has recently been grouped together with regression as “catastrophic events in AHC.” The cause of these events and in particular the role of paroxysmal events and fever remain elusive. In 8 of 11 patients with sudden death, there were preceding prolonged paroxysmal episodes, either seizures or quadriplegic episodes. Conversely, in a large clinical cohort, the previous degree of fixed disability emerged as the only significant risk factor for mortality, whereas the severity of paroxysmal events was not associated with early death. Episodes of abrupt onset or worsening of neurological signs triggered by fever or other stressors have been reported in other ATP1A3-related conditions such as rapid-onset dystonia parkinsonism and relapsing encephalopathy with cerebellar ataxia, where paroxysmal events are not a feature. This suggests that paroxysmal events and catastrophic events may be provoked by the same trigger, but are not causally linked.

Compared with the existing literature, we add here further characterization of the AHC course in adulthood and new information on genotype–phenotype correlation: we did not find an association between acute regression and mutation type or lack of flunarizine treatment as previously reported, although we acknowledge the small sample size of our cohort. In conclusion, our case series of patients with long follow-up in adulthood provides useful insights on the natural history of AHC. In the long term, most patients have reduced frequency of paroxysmal events. However, adult patients may present with new onset of fatigue, muscle spasms, psychotic symptoms, and aggravation of movement disorders, all of which have a detrimental impact in their quality of life and level of independence. Finally, a sudden and irreversible deterioration of their condition, mainly with pyramidal and bulbar signs, may occur not only after status epilepticus, but also after prolonged non-epileptic spells, which should, therefore, be promptly treated. Our report expands the spectrum of clinical and genetic factors associated with neurological regression in AHC. Understanding the evolution of disease in adulthood and its associated pathophysiology will help to design targeted interventions.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,
Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This study was approved by the UCLH Ethics Committee. Patients and families have signed consent for video acquisition and publication. Any research involving human participants was approved by the UCLH Ethics Committee. The study was approved by the UCLH Ethics Committee. Patients and family members have signed consent for video acquisition and publication. The study was approved by the UCLH Ethics Committee.

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Supporting Information

Supporting information may be found in the online version of this article.

Summary of patients clinical history and investigations.