Annals of the Child Neurology Society

Annals of the Child Neurology Society Open Access

RESEARCH ARTICLE OPEN ACCESS

Natural History of Alternating Hemiplegia of Childhood: Vulnerabilities in Early Childhood and Predictive Factors for Long-Term Outcomes

Shital H. Patel[1] | Eleni Panagiotakaki[2,3] | Beiyu Liu[4] | Carmen Fons[5] | Lyndsey Prange[1] | Maria T. Papadopoulou[2,6] | April Boggs[1] | Elisa De Grandis[7,8] | Aikaterini Vezyroglou[9] | Francesco Fortunato[10,11] | Simona Balestrini[10,11,12,13] | Francesca Ragona[14] | Eugenia Julia Tosi[14] | Claudio Zucca[15] | Giacomo Garone[16] | Andrey Megvinov[17] | Giosuè Lo Bosco[17,18] | Michela Stagnaro[7] | Julie Uchitel[1] | Marion Comajuan[2] | Matthildi Athina Papathanasiou Terzi[2] | Jennifer Anticona[5] | Joan M. Jasien[1] | Jeffrey Wuchich[19] | Sigurdur H. Johannesson[20] | J. Narayan[1] | J. Helen Cross[9] | Sanjay M. Sisodiya[10] | Hwanhee Hong[4] | Alexis Arzimanoglou[2,5] | Rosaria Vavassori[17,21] | Mohamad A. Mikati[1]

[1]Division of Pediatric Neurology and Developmental Medicine, Duke University Department of Pediatrics, Durham, North Carolina, USA | [2]Department of Pediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, Member of the ERN EpiCARE, University Hospitals of Lyon (HCL), Lyon, France | [3]Lyon Neuroscience Research Center, Lyon 1 University, French National Institute of Health and Medical Research (UMR 1028), French National Centre for Scientific Research (UMR5292), Lyon, France | [4]Department of Biostatistics & Bioinformatics, Duke University, Durham, North Carolina, USA | [5]Department of Child Neurology, Sant Joan de Déu Children's Hospital, Coordinating Member of the ERN EpiCARE, Barcelona, Spain | [6]CNRS, INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028 UMR5292, EDUWELL, Université Claude Bernard Lyon 1, Bron, France | [7]Child Neuropsychiatry Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy | [8]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy | [9]Department of Developmental Neurosciences, UCL NIHR BRC Great Ormond Street Institute of Child Health, Collaborating Partner of the ERN EpiCARE, London, UK | [10]Department of Clinical and Experimental Epilepsy, University College of London (UCL), Queen Square Institute of Neurology, Collaborating Partner of the ERN EpiCARE, London, UK | [11]Chalfont Centre for Epilepsy, Bucks, UK | [12]Neuroscience and Medical Genetics Department, Meyer Children's Hospital, Florence, Italy | [13]NEUROFARBA Department, University of Florence, Florence, Italy | [14]Department of Paediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Member of the ERN EpiCARE, Milan, Italy | [15]Clinical Neurophysiology Unit, Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini, Lecco, Italy | [16]Neurology, Epilepsy and Movement Disorders, Bambino Gesù Children's Hospital, Member of the ERN EpiCARE, IRCCS, Rome, Italy | [17]Euro Mediterranean Institute of Science and Technology I.E.ME.S.T., Palermo, Italy | [18]Department of Mathematics and Computer Science, University of Palermo, Italy | [19]Agape Pastoral Counseling, Rolesville, North Carolina, USA | [20]AHC Association of Iceland, Reykjavik, Iceland | [21]Association AHC18+ e.V., Germany, Member of the ERN EpiCARE Patient Advocacy Group (ePAG)

Correspondence: Mohamad A. Mikati (mohamad.mikati@duke.edu)

Received: 14 June 2025 | **Revised:** 17 August 2025 | **Accepted:** 19 August 2025

Funding: Funding for this study was provided by multiple family organizations. These include six national family organizations: USA (donations from Cure AHC), French (AFHA), Icelandic (AHC Samtökin), Dutch (AHC Vereniging Nederland), Spanish (AESHA), and UK (AHC UK), as well as by multiple funds from Duke University.

Keywords: AHC | development | epilepsy | genetics | natural history | rare disease

ABSTRACT

Objective: The natural history of the most common *ATP1A3*-related disease, alternating hemiplegia of childhood (AHC), has not been determined. We investigated three hypotheses: (1) AHC worsens over time; (2) several novel factors correlate with long-term outcomes; and (3) AHC manifests high mortality.

Methods: In a large cross-sectional study with a nested period of prospective 1–3-year follow-up, 115 patients (0.3–46.0 years old, 9 centers/5 countries) were evaluated using across-center-standardized protocol and validated scales. Univariable and

multivariable linear-mixed-effects models with random intercepts and random slopes for age, adjusted for confounding variables, allowed for the determination of the effect of age throughout the total age range of patients studied.
Results: Course: We identified a distinction between two periods, namely the period of early childhood (age 1–5 years) and the period of later childhood to mid-adulthood. Intellectual and non-paroxysmal disability indexes (IDS, NPDI) scores as well as the Vineland Adaptive Behavior Composite and its subscales worsened during early childhood, but not in the period after that. The extent of motor skills impairment did not differ with age in either period. Within the PDI (paroxysmal disability index) scores, dystonia severity scores did not differ with age in either period; however, plegia severity scores did improve with age after 5 years of age. **Prognostic variables** included the following: (1) Epilepsy was associated with worse NPDI, intellectual, and fine and gross motor skills. (2) Worse early life PDI and NPDI scores were significantly associated with worse respective scores at the latest follow-up. (3) Worse early life NPDI scores were also associated with worse IDS and fine and gross motor scores at the latest follow-up. (4) *D801N* mutation was associated with worse PDI. (4) *E815K* mutation was associated with worse IDS. **Mortality was** 1.12 deaths/100 patient-years and 6.5 sudden unexpected death in epilepsy (SUDEP) deaths/1000 patient-years.
Interpretation: AHC is a progressive disease, and early childhood is the vulnerable period. We identified several novel prognostic indicators and a mortality rate, which provide critical information not only regarding prognostication, counseling, and underlying pathophysiology but also for planning therapeutic studies.

1 | Introduction

Alternating hemiplegia of childhood (AHC), the most common *ATP1A3*-related disease, is a serious childhood-onset neurological disorder characterized by multisystem manifestations, most prominently hemiplegia and dystonia episodes and neurodevelopmental disability [1–5]. Approximately 80% of clinically diagnosed cases are due to de novo mutations in the *ATP1A3* gene [6–9]. Clinically, AHC is diagnosed according to specific criteria called the Aicardi criteria: (1) onset of symptoms before 18 months of age; (2) paroxysmal hemiplegia; (3) paroxysmal dystonia, nystagmus, or various autonomic symptoms; (4) episodic bilateral hemiplegia; (5) symptoms resolving with sleep; and (6) developmental delay or other neurological abnormalities [10]. Recently, in a revised version of the Aicardi criteria, the presence of an *ATP1A3* mutation has been considered as another major, though not an essential, diagnostic criterion [11].

The complexity and rarity of AHC require a multicenter approach to be able to study its natural history [12, 13]. Studying the natural history of this disease and its potential outcome predictors would allow determination of whether AHC is progressive or not, lead to improvements in prognostication, and help identify disease outcome trajectories and prognostic predictors to use in therapeutic trials.

A major question regarding AHC is whether it is progressive or not, and if so, whether this applies to the general AHC population and whether this affects different neurodevelopmental domains. Basic science investigations of the pathophysiological consequences of *ATP1A3* mutations, including animal models of these mutations, have indicated that progressive neuronal injury does occur [3, 6]. Whether there is convergence of basic science and clinical data regarding this issue is not yet known. In 2010, a large cross-sectional multicenter study, without prospective follow-up, of people with AHC did not detect evidence of a progressive course of AHC [14]. Subsequently, other studies reported catastrophic regression in a small number of people with AHC over time [15–17]. A large, more recent study from two centers reported that non-paroxysmal disability, but *not* paroxysmal disability, worsens over time [18].

Due to these apparently contradictory findings, we developed a novel standardized protocol in a multinational, multicenter study with a 1–3-year period of prospective follow-up to investigate the natural history of AHC and to identify potential outcome predictors beyond what is already known about the effects of the types of mutations on AHC clinical phenotype [8, 16, 19]. Our approach, detailed in our prior methodology article [13], involved using validated scales and statistical methods to analyze patients' disease from infancy to mid-adulthood by using the prospectively collected data of the follow-up period of 1–3 years. Additionally, cross-sectional studies without prospective follow-up have suggested increased mortality in AHC. However, the rates of mortality and sudden unexpected death in epilepsy (SUDEP) per year still need to be determined [14].

Given that, our overarching goal is to better understand the natural history of AHC, we tested the following hypotheses: (1) The severity of AHC, in its various clinical domains, follows a progressive course. (2) Several variables, not identified previously, correlate with long-term outcomes. (3) AHC manifests mortality comparable to that of other severe developmental encephalopathies.

2 | Methods

2.1 | Study Design and Procedures

2.1.1 | Inclusion Criteria

Patients had to meet the AHC diagnostic criteria listed in the Introduction [6, 11]. In addition, all had to have consent signed by their guardians. The protocol was approved in all the collaborating centers by their respective human institutional review boards. Patients were serially enrolled at multiple centers as described below.

2.1.2 | Study Procedures

The study, named OBSERV-AHC, was conducted as a collaborative study of the International AHC Consortium (IAHCRC). The details of the protocol and the approach have been described in a previous publication [13]. In brief, the IAHCRC consists of 38 centers in 13 countries of which 9 centers in five countries participated. The initiating-coordinating center is the Duke University Center (Durham, USA). The centralized online data collection service, the IAHCRC-CLOUD Platform, was developed and is hosted by the Euro-Mediterranean Institute for Sciences and Technology (IEMEST, Palermo, Italy). We used a collaborative and standardized protocol in all the participating institutions. Data collection forms were developed collegially, with all the variables needed to be collected at baseline and at follow-ups, as indicated below, including the following [13]:

- Demographics
- Physical examinations
- Genetic testing results
- PDI (paroxysmal disability index): This index, previously described and used in AHC [13, 14, 18, 20], was calculated by summing the scores of three components (frequency, severity, and duration) for two variables, plegia and dystonia episodes. The total score was then divided by the number of components of assessed variables, resulting in a range of 0–4 (0 = best, 4 = worst).
- NPDI (non-paroxysmal disability index): This index, also previously described and used in AHC [13, 14, 18, 20], was calculated by assigning a value to each of multiple motor, behavioral, communication, and cognitive impairments based on their presence and severity. The total score was then divided by the number of assessed variables, resulting in a range of 0–2.67 (0 = best, 2.67 = worst).
- IDS (intellectual disability assessment scale: This scale measures the severity of intellectual disability, with higher scores indicating greater impairment. It has been previously described and utilized, including for AHC, with a scoring range of 0–3 (0 = best, 3 = worst) [13, 18, 21–23].
- VAB-Composite (Vineland Adaptive Behavior II-Composite) and Vineland-II subscales, which include VAB-communication, VAB-daily living skills, VAB-socialization, and VAB-motor skills: These scales have also been used in AHC studies and are available in multiple languages and countries [13, 14, 24]. They provide total scores that are then converted to percentiles as compared with typically developing children (0%–100%). This conversion allows for comparisons over time.
- GMFCS (Gross Motor Function Classification System, range 0–5) and MACS (Manual Ability Classification System, range 0–3): Like the VAB, GMFCS and MACS are widely used scales and have also been used in AHC studies (0 = best, 5 = worst) [13, 22, 25].

The first phase of the study consisted of developing the protocol, establishing the OBSERV-AHC Study Database on the IAHCRC-CLOUD Platform, and standardizing the procedures across centers, which lasted approximately 2 years. The second phase (recruitment and follow-up phase) was planned for 2 years, during which patients would be prospectively enrolled sequentially in the first year and would be seen for a 1-year follow-up during the second year. Because of the extension of the study beyond the second year due to the COVID-19 pandemic, the recruitment time was extended, and, consequently, we had additional follow-up data for some patients at 2 and 3 years after enrollment.

2.2 | Statistics

Descriptive statistics were performed to summarize demographics and clinical characteristics. Continuous variables were summarized using means, medians, standard deviations, and interquartile 25th and 75th percentiles and ranges. Categorical variables were summarized with frequency counts and percentages of variables. Scatter plots, histograms, and spaghetti plots were created to visualize the data and results.

2.2.1 | Hypothesis 1

We analyzed, in our cross-sectional study with 1–3 years of follow-up, prospectively collected scores at enrollment and follow-up encounters to estimate the association between age and neurodevelopmental outcomes as assessed by these scores. Multivariable linear mixed-effects models with random intercepts and random slopes for age were fitted, adjusting for covariates including sex, epilepsy status (present or not), *ATP1A3* mutation type (D801N, E815K, other, or none), country, and early life (between ages 1 and 1.5 years) PDI and NPDI scores [12, 26–28]. Early life scores were determined at the initial enrollment visit through medical record review and family confirmation.

To examine potential nonlinear associations between age and outcomes, we fitted piecewise spline linear mixed-effects models to all scores and subscales. Model fit and visual inspection of the associations were compared with those from the linear mixed-effects models. As explained below, results are reported from the model with the best fit. These were the linear mixed-effects models for the PDI, MACS, and GMFCS outcomes and the spline linear mixed-effects models for the NPDI, IDS, and Vineland scores. Regression diagnostics were performed to assess the validity of model assumptions. The convergence criteria were examined to ensure proper model convergence. Multicollinearity was evaluated using the variance inflation factor (VIF) values, and we did not observe any collinearity among predictors (VIF < 2 for all covariates in the regression models).

In the spline regression, a knot is a point where the slope of the regression line changes. We allowed the relationship between outcomes and age to shift at one specific point to better capture changes in the data. We compared the model fit between candidate knot points. Based on the Akaike information criterion (AIC), spline models with a knot at age 5 years fitted the data better, and all spline regression results reported here are based on a knot at age 5.

2.2.2 | Hypothesis 2

Potential clinical predictors, including type of *ATP1A3* mutation, sex, presence of epilepsy, country, and early life PDI and early life NPDI scores, were studied each for correlation with specific long-term AHC outcome measures (including PDI, NPDI, VAB, IDS, MACS, GMFCS) using univariable and multivariable linear mixed-effects models with random intercepts and random slopes for age. To further explore potential interactions, we fitted models including interaction terms between age and the *ATP1A3* mutation group, as well as between age and epilepsy groups. Among these, only the interaction between age and epilepsy was statistically significant for NPDI scores and is therefore reported.

2.2.3 | Hypothesis 3

The profiles of the patients who died and the mortality rate per patient-year, of deaths that occurred during the study period, in the total study population, and in the subset with epilepsy patients were reported.

The significance of the tests was evaluated at an alpha level of 0.05. All statistical analyses were performed using RStudio Version 2023.12.0 + 369. For all models, the point estimates of the fixed effect coefficients, along with their 95% confidence intervals, were reported.

3 | Results

Patient demographics and clinical characteristics are presented in detail in Table 1. Briefly, a total of 115 patients with AHC were enrolled and prospectively followed for 1–3 years (one US and eight European centers, five countries, Table S1): 62 (54%) were female and 53 (46%) were male. The age at the initial visit ranged from 3.6 months to 46 years, with a mean age of 12.3 years (standard

TABLE 1 | Patient characteristics ($N = 115$).

	Categorical variables	***N* (%)**
Sex	Female	62 (54%)
	Male	53 (46%)
Epilepsy	No epilepsy	48 (42%)
	Presence of epilepsy without status	41 (36%)
	Presence of epilepsy with status	26 (23%)
ATP1A3 mutation[a]	D801N (c.2401 G>A, p.Asp801Asn)	30 (26%)
	E815K (c.2443 G>A, p.Glu815Lys)	20 (17%)
	G947R (c.2839 G>C, p.Gly947Arg)	11 (9.6%)
	Other	51 (44%)
	Negative	3 (2.6%)
Numerical variables		
	Mean (SD)	**Median (IQR)**
Baseline age (years)	12.3 (11.1)	9.6 (2.9, 19.5)
Early life PDI score at age 1–1.5 yrs	2.05 (0.84)	2.17 (1.67, 2.50)
Early life NPDI score at age 1–1.5 yrs	2.04 (0.95)	2.00 (1.50, 2.50)
Baseline PDI score	1.99 (0.73)	2.17 (1.82, 2.33)
Baseline NPDI score	1.22 (0.61)	1.14 (0.86, 1.57)
Baseline MACS score	1.35 (0.78)	1.00 (1.00, 2.00)
Baseline GMFCS score	2.27 (1.20)	2.00 (1.00, 3.00)
Baseline IDS score	1.84 (0.99)	2.00 (1.00, 3.00)
Baseline VAB-Composite percentile	5.72 (16.06)	0.20 (0.05, 2.50)
Baseline VAB-communication percentile	8.70 (20.28)	1.00 (0.05, 5.00)
Baseline VAB-daily living percentile	7.03 (16.46)	0.45 (0.05, 5.00)
Baseline VAB-socialization percentile	11.90 (21.02)	1.00 (0.05, 16.00)
Baseline VAB-motor percentile	6.33 (18.26)	0.20 (0.05, 1.00)

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a]Reference transcript for all: NM_152296.5 (*ATP1A3*).

deviation [SD] 11.1 years). Of the 115 patients, 30 (26%) had the most common pathogenic variant, *ATP1A3* D801N-NM_152296.5(*ATP1A3*):c.2401G>A, (p.Asp801Asn), followed by 20 patients (17%) with E815K-NM_152296.5(*ATP1A3*):c.2443G>A, (p.Glu815Lys), 11 (9.6%) with G947R-NM_152296.5(*ATP1A3*):c.2839G>C (p.Gly947Arg), 51 patients (44%) with other variants, and three patients who did not carry a pathogenic variant in *ATP1A3*. Table 1 also presents baseline scores (mean, SD, median, and interquartile range) for the PDI, NPDI, IDS, GMFCS, MACS, and VAB-C and its subscales.

Three patients without pathogenic *ATP1A3* variants were included in our study. This represented only 2.6% of our study population. These patients did not clinically differ from those with *ATP1A3* disease–causing variants: All three met the clinical diagnostic criteria of AHC and had consistent clinical profiles as seen in the Supporting Information Table 2: S1.

3.1 | Age Adversely Affects AHC Manifestations

3.1.1 | Age Adversely Affected NPDI and IDS (Figure 1a,b)

Using the linear spline regression model, we determined there was a significant association between NPDI and age in

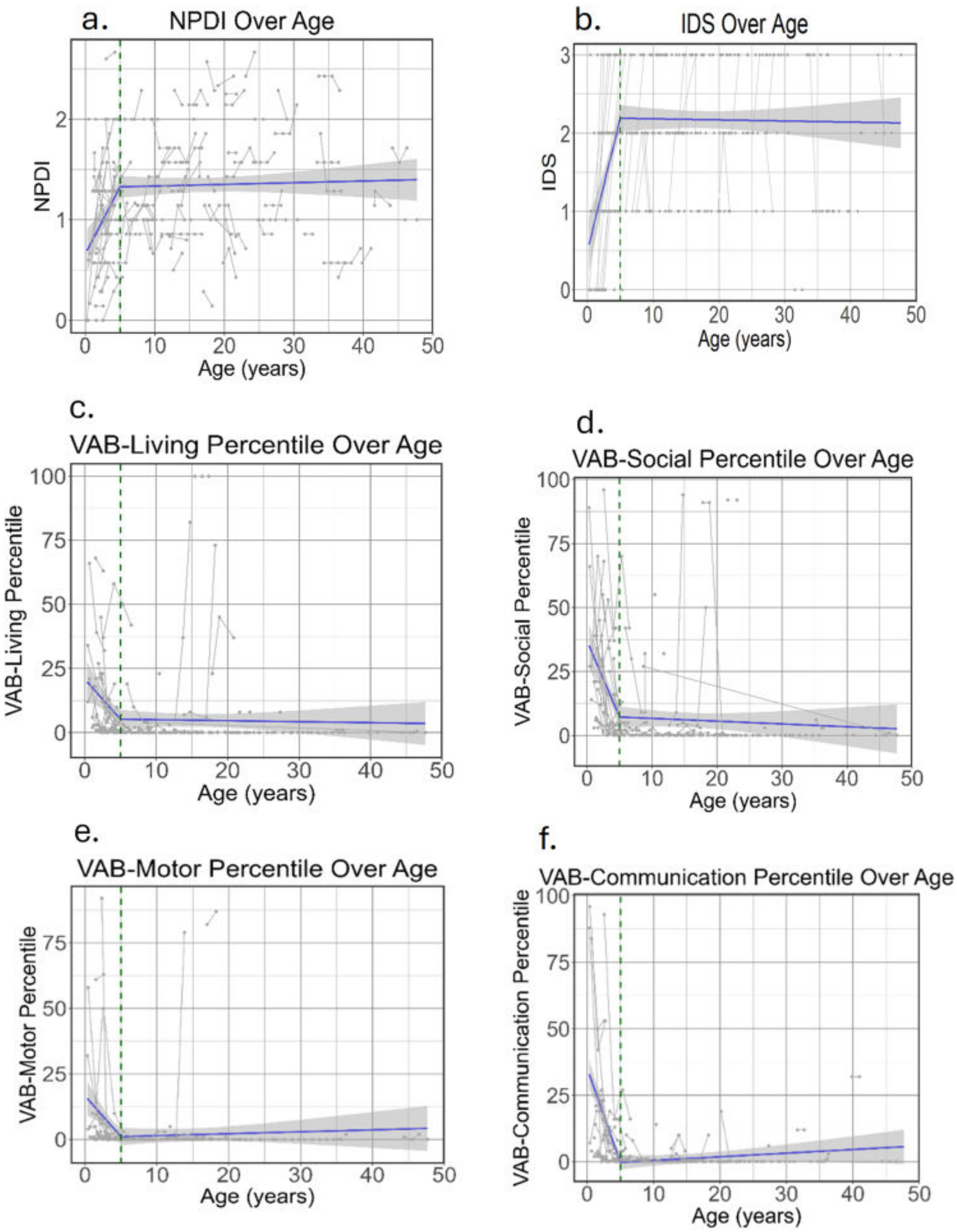

FIGURE 1 | Spaghetti diagrams of parameters that worsened with age. These show that up to the age of 5 years, there are steep increases (worsening) in the NPDI and IDS scores and steep declines (worsening) in the Vineland scale and subscale percentiles before stabilizing, with the prominent vulnerable period being early childhood up to age 5 years. (a) Non-paroxysmal disability index score (NPDI) ($p < 0.001$) and (b) intellectual disability index score (IDS) ($p < 0.001$) both show worsening only during the period of 1–5 years (please see results section for details). (c–f) are the Vineland subscales. (c) Vineland-daily living skills percentile ($p < 0.001$). (d) Vineland-social percentile ($p < 0.001$). (e) Vineland-motor percentile ($p < 0.001$). (f) Vineland-communication percentile ($p < 0.001$).

children aged 5 years or younger; the 1-year age change in the slope was 0.10 points (CI: 0.06, 0.14) ($p < 0.001$). However, the slope of the relationship changed significantly after age 5 ($p < 0.001$), and no significant association was observed between NPDI and age beyond 5 years ($p = 0.59$, Figure 1a and Table 2).

Similarly, we determined there was a significant association between IDS and age in children aged 5 years or younger; the 1-year age change in the slope was 0.30 points (CI: 0.22, 0.38) ($p < 0.001$). However, the slope of the relationship changed significantly after age 5 ($p < 0.001$), and no significant association was observed between IDS and age beyond 5 years ($p = 0.97$, Figure 1b and Table 2).

This analysis was possible because the statistics that we used make it possible to compare effects of age on different measures even though the follow-up was for a range of 1–3 years [12, 25, 26].

3.1.2 | Age Also Adversely Affected VAB-Composite and Its Subscales, Namely VAB-Communications, VAB-Living, VAB-Social, and VAB-Motor (Figure 1c–f and Table 2)

Multivariable linear spline mixed-effects models showed that for children younger than 5 years, age is significantly negatively associated with VAB-Composite and all its subscales, with annual decreases of 3.98%, 6.03%, 3.13%, 4.95%, and 3.98% for VAB-Composite, VAB-communications, VAB-living, VAB-social, and VAB-motor, respectively ($p < 0.001$ for all, Table 2). However, for children older than 5 years and adults, there is no significant association between age and any of the VAB-Composite or subscale score percentiles.

3.1.3 | PDI Showed a Trend Toward Improvement With Age (Figure 2a,d and Table 2)

Although PDI appeared to improve with age, this trend did not reach statistical significance when adjusted for covariates ($p = 0.1$). To further investigate the observed trend toward improvement in PDI scores over time, we calculated plegia and dystonia scores from the PDI and assessed their associations with age using piece-wise linear regression models, incorporating intercept as random effects, each with a knot at age 5 years. Plegia scores showed a statistically significant association with age beyond 5 years of age, with an estimated change of −0.02 points per year (95% CI: −0.04 to −0.0002, $p = 0.03$). In contrast, dystonia scores were not significantly associated with age either before or after age 5 ($p = 0.82$, 0.59). These findings suggest that the observed trend toward improvement in PDI over time is primarily driven by changes in plegia, which tends to improve after age 5.

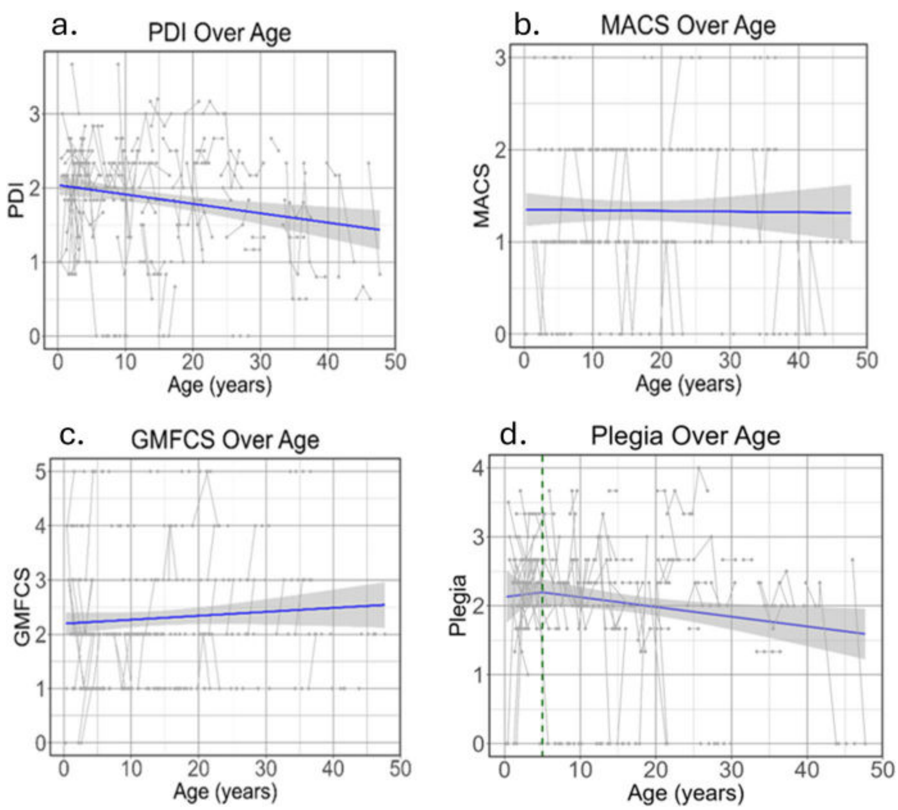

FIGURE 2 | Spaghetti diagrams of parameters that did not worsen with age. Age did not affect the following: (a) PDI, (b) MACS, or (c) GMFCS ($p = 0.1$, 0.78, 0.42, respectively). (d) Plegia of PDI, which showed improvement > 5 years of age ($p = 0.03$). GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; PDI, paroxysmal disability index.

3.1.4 | Age Did Not Affect MACS or GMFCS (Figure 2b,c)

Our analysis showed no statistically significant changes with age (MACS $p = 0.78$, GMFCS $p = 0.42$).

3.2 | Multiple Parameters Adversely Affect Outcome in AHC

We documented that several variables independently affected outcome, including presence of epilepsy, type of *ATP1A3* mutation, and early life PDI and NPDI scores (at age 1–1.5 years), through fixed effects coefficients are as follows (Figure 3).

3.2.1 | Presence of Epilepsy

This was the most pervasive of the observed indicators adversely affecting more outcome variables than any other indicator. Patients with epilepsy, as compared with patients who had otherwise similar characteristics but no epilepsy, had, at any age within the range of ages studied, worse IDS ($p = 0.003$), GMFCS ($p = 0.015$), and MACS ($p = 0.003$) scores than those without epilepsy. Importantly, the presence of epilepsy resulted in a range of 9.2%–16% worse scores in these parameters: an increase of 0.48 (CI: 0.19, 0.78) in the IDS score (maximum score is 3, 16%), an increase of 0.49 (CI: 0.12, 0.84) in the GMFCS score, and an increase of 0.46 (CI: 0.19, 0.75) in the MACS score (maximum score is 5 for each, 9.8% and 9.2%, respectively). This means that for two patients who are of the same age with all other parameters being the same, the one with epilepsy would have higher IDS, GMFCS, and MACS scores by the increments mentioned above.

FIGURE 3 | Sunburst diagram showing outcome measures (inner circle) and the corresponding risk factors for each (outer circle).

3.2.2 | Effect of Age on NPDI Differs Based on Presence of Epilepsy

We did a piecewise linear regression model, which showed that age 5 years or less and epilepsy status (present or not) interaction was significant ($p = 0.028$). Among children aged 5 years or less, for each additional year of age in those without epilepsy the NPDI score increased by 0.06 (CI: 0.02–0.12, $p = 0.012$). In contrast, for those with epilepsy in the same age group, each year an increase in age was associated with a more pronounced 0.15-unit increase in NPDI (CI: 0.09–0.20, $p < 0.001$). After age 5, age was not significantly associated with NPDI ($p = 0.73$). This is shown in Figure 4.

3.2.3 | *ATP1A3* D801N Mutation (NM_152296.5(*ATP1A3*):C.2401 G>A, p.Asp801Asn)

As compared with patients with other *ATP1A3* mutations or no mutations of *ATP1A3*, those with the D801N mutation had a 0.35 higher PDI score ($p = 0.017$, CI: 0.06, 0.62), maximum PDI score is 4).

3.2.4 | *ATP1A3* E815K Mutation (NM_152296.5(*ATP1A3*):c.2443 G>A, p.Glu815Lys)

Patients with the E815K mutation had a 0.39 higher IDS score than other patients ($p = 0.035$, CI: 0.03, 0.77), maximum IDS score is 3).

3.2.5 | Early Life NPDI and PDI Scores (1–1.5 Years of Age)

Early life PDI and NPDI scores were associated, respectively, with the later worse PDI ($p = 0.01$) and NPDI scores ($p < 0.001$). Specifically, with a 1-point increase in early life NPDI score, the NPDI score during the study was higher by an additional 0.27 points (NPDI scale range 0–2.67, CI: 0.17–0.38). Similarly, with a 1-point increase in early life PDI, there was an increase of an additional 0.2 points of the PDI score during the study (PDI scale range 0–4, CI: 0.06, 0.36).

In addition, early life NPDI scores also predicted worst IDS scores, GMFCS scores, and MACS scores. Specifically, with a 1-point increase in early life NPDI score, IDS, GMFCS, and MACS scores increased by an additional 0.28 [0.12, 0.44] (< 0.001), 0.74 [0.53, 0.95] (< 0.001), and 0.4 [0.26, 0.53] (< 0.001), respectively.

3.3 | Mortality Is High in AHC

Three patients died during the follow-up period of this study at 19, 21, and 33 years of age. All three were males who had epilepsy. One died of SUDEP and the other two from post-status epilepticus respiratory failure. All three had a history of status epilepticus episodes (see below). This constituted a mortality rate of 1.12/100 patient-years in this study's AHC population, a rate of 19.5/1000 patient-years in those with epilepsy, and a SUDEP rate of 6.5/1000 patient-years in those with epilepsy as a feature of AHC.

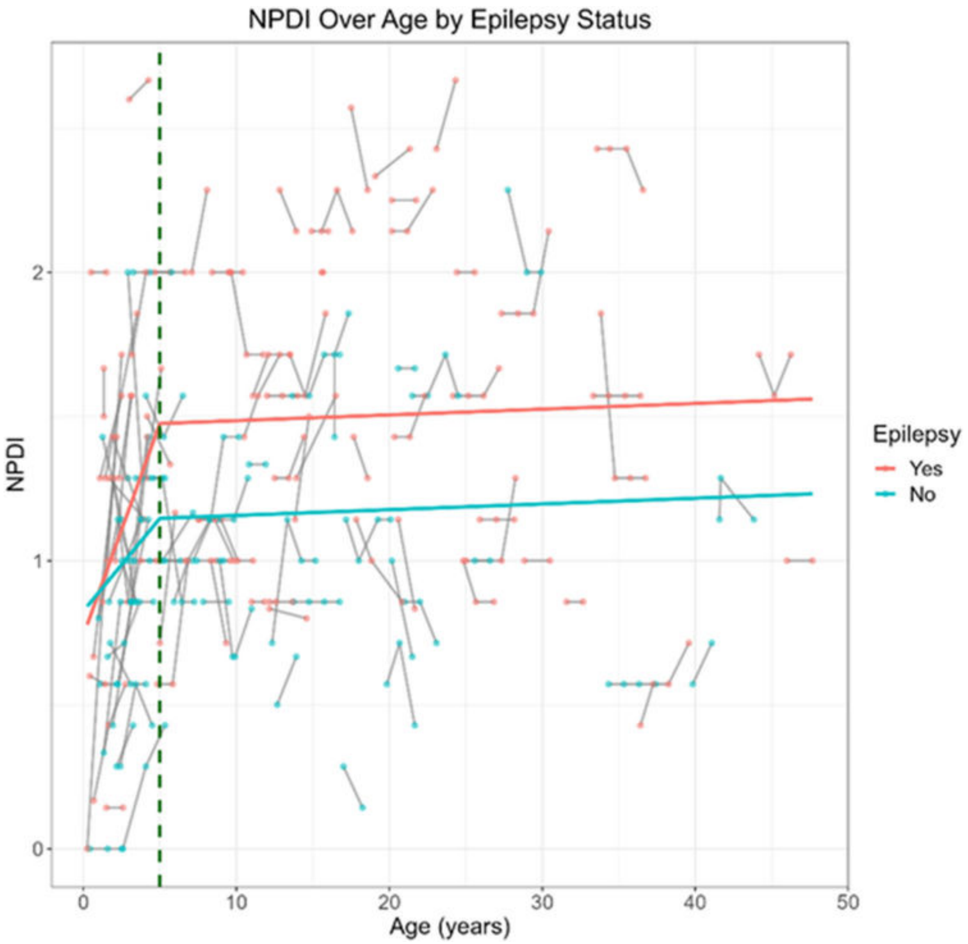

FIGURE 4 | How non-paroxysmal disability index (NPDI) is affected by age based on the presence or absence of epilepsy. Among children aged 5 years and younger without epilepsy, each additional year of age had a 0.06 increase in coefficient of the score (CI: 0.02–0.12, $p = 0.012$). In contrast, for those with epilepsy in the same age group, each year an increase in age was associated with a more pronounced 0.15 coefficient increase in NPDI (CI: 0.09–0.20, $p < 0.001$). After age 5, age was not significantly associated with NPDI ($p = 0.73$).

3.3.1 | Patient 1 (NM_152296.5(*ATP1A3*):c.2263 G>A-G755S, Age 33)

This patient had recurrent status epilepticus over a period of 2 months. Despite pharmacologic treatment, seizures persisted. Death was due to respiratory failure, and status epilepticus occurred the day before death.

3.3.2 | Patient 2 (NM_152296.5(*ATP1A3*):c.1825G>T-D609Y, Age 19)

This patient developed status epilepticus with dystonia, complicated by sepsis and pulmonary infection. Despite treatment, the patient died under palliative care.

3.3.3 | Patient 3 (NM_152296.5(*ATP1A3*):c.2443 G>A-E815K, Age 21)

This patient had epilepsy and status epilepticus; he was found deceased in bed at night, consistent with SUDEP.

4 | Discussion

We demonstrate that AHC is a progressive disease, and early childhood is the vulnerable period. We also identified several novel prognostic indicators and a mortality rate. These findings provide critical information not only regarding prognostication, counseling, and underlying pathophysiology but also for planning therapeutic studies. This multinational, multicenter study is a unique cross-sectional study with a distinctive period of 1–3 years of prospective follow-up protocol of people with AHC. The patient population is similar to that of prior AHC studies in terms of the distribution of mutations, sex, and occurrence of epilepsy [7–9, 16, 19, 29–31], which strengthens the relevance of our findings as it supports that our study population is representative of the known AHC general population.

4.1 | The Effects of Age

One of the main questions regarding AHC has been whether it is a progressive disease, whether this applies to the general AHC population, and whether this affects different neurodevelopmental domains [14–17, 22]. Our findings clearly show that AHC has a progressive course in the early age. Even more importantly, this study demonstrates for the first time that as a group, people with AHC at an older age have persistence of neurodevelopmental impairment across a range of domains, particularly in adaptive and intellectual skills that had progressed during the first 5 years of life to the levels that persist after age 5 years. This highlights this period of early childhood before the age of 5 years as a particularly vulnerable period. Another meaningful finding is the demonstration of the mathematical relationships of the effects of age and of other predictors on various neurodevelopmental variables, as shown in Tables 2 and 3. These relationships should prove to be valuable in counseling families and in planning clinical studies. Finally, our findings support prior proposals [2] that the clinical course of AHC may fit into four distinct phases (Figure 5): (1) birth to early infancy (a phase we did not investigate in this study); (2) early childhood, in which there is a worsening of NPDI, adaptive, and intellectual skills; (3) late childhood to mid-adulthood, during which there is an improvement in plegia episodes but continued impairment of the other skills; (4) and later adulthood (which also was not investigated in this study). Future studies are needed not only for the first period of early infancy but also for the last period of later adulthood due to obvious prognostic and pathophysiological implications.

4.2 | Potential Clinical Predictors

4.2.1 | Epilepsy

Another important original finding is the pervasive effect of the presence of epilepsy on many neurodevelopmental domains: these include cognitive and motor dysfunction (fine and gross motor). This association possibly stems, at least in part, from the effects of recurrent seizures and/or status epilepticus, which can significantly impact long-term prognosis in a brain already impaired by the underlying AHC pathophysiology. Furthermore, this study shows the impact that epilepsy has on early neurodevelopment, as scores of multiple variables including NPDI worsen in patients with epilepsy compared with those without epilepsy in early childhood. This is particularly relevant since epilepsy, which was present in 52% of our patients, has been reported to be drug-resistant in a large proportion of people with AHC (59%), with a high proportion of those (38%) often experiencing recurrent episodes of status epilepticus [22]. Due to these rates, many patients are on multiple antiseizure medications, and these medications may negatively impact their neurodevelopmental trajectory. Furthermore, our previous research has indicated that epilepsy can also be associated with autism in patients with AHC, which also impacts social and adaptive skills [22, 32].

TABLE 2 | Magnitude of effect of age on NPDI, IDS, PDI Vineland-Composite, and its subscales.

Effect of age on NPDI, IDS, PDI			
	1-year age change	**Confidence interval**	***p* value**
NPDI (range 0–2.67)			
Age ≤ 5	+0.10	0.06, 0.14	$p < 0.001$
Age > 5	+0.003	−0.01, 0.01	$p = 0.59$
IDS (range 0–3)			
Age ≤ 5	+0.30	0.22, 0.38	$p < 0.001$
Age > 5	+0.0003	−0.02, 0.02	$p = 0.97$
	10-year age change	Confidence interval	*p* value
PDI (range 0–3.67)	−0.1	−0.3, 0.02	$p = 0.1$
PDI–plegia score[a]	−0.2	−0.3, −0.03	$p = 0.029$
PDI–dsytonia score	−0.03	−0.2, 0.1	$p = 0.73$
Effect of age (< 5 years) on Vineland-Composite and its subscales			
	Percentage drop per year up to the age of 5 years (no drops after that)	**Confidence interval**	***p* value**
VAB-Composite	3.98%	2.73%–5.25%	$p < 0.001$
VAB-communications	6.03%	4.64%–7.41%	$p < 0.001$
VAB-living	3.13%	1.68%–4.55%	$p < 0.001$
VAB-ocial	4.95%	2.72%–7.17%	$p < 0.001$
VAB-motor	3.98%	2.17%–5.79%	$p < 0.001$

Note: Ranges for the NPDI, IDS, and PDI are provided in the first column, while the ranges for the VAB-Composite and its subscales percentiles are 0–100%. Note that the NPDI, IDS, and Vineland Composite and its subscales declined only within the first 5 years. Beyond the age of 5, there is no significant association between these parameters and age. Note that the PDI total score shows a trend toward improvement but is not statistically significant. When viewed based on its parts, it shows that the PDI-plegia score improves with age with statistical significance.

[a]Please also see Figure 2d and the Results section for related analysis that showed that the improvement with age of the plegia score occurred after age of 5 years and not before.

TABLE 3 | Magnitude of the effect of each of the specific clinical predictors (top row) on the various outcome parameters (listed in first column) scores.

Clinical predictor Outcome parameter	D801N versus other patients: effect on parameter	E815K versus other patients: effect on parameter	Early life PDI: effect on parameter	Early life NPDI: effect on parameter	Presence of epilepsy: effect on parameter
PDI[a] (range 0–4)	+0.35 [0.06, 0.62] (0.017)		+0.2 [0.06, 0.36] (0.01)		
NPDI (spline regression with a knot at age = 5)				+0.27 [0.17, 0.38] (< 0.001)	+0.25 [0.05, 0.44] (0.012)
NPDI (spline regression) with interaction of age and epilepsy				+0.28 [0.18, 0.39] (< 0.001)	Age $\leq$ 5 years Not constant (0.99)
					Age > 5 years 0.33 [0.12, 0.53] (0.002)
IDS (spline regression with a knot at age = 5) (range 0–3)		0.39 [0.03, 0.77] (0.035)		0.33 [0.17, 0.48] (< 0.001)	0.49 [0.22, 0.76] (0.001)
GMFCS[a] (range 0–5)				+0.74 [0.53, 0.95] (< 0.001)	+0.49 [0.12, 0.84] (0.015)
MACS[a] (range 0–3)				+0.4 [0.26, 0.53] (< 0.001)	+0.46 [0.19, 0.75] (0.003)

Note: Results of the multivariable regression models are presented below the top row in the respective cells (CI in brackets; *p* values in parentheses). Blank cells indicate no significant effects. The increments in the cells indicate that for two patients who differ by the presence or absence of the clinical predictor at the top of that column but are otherwise similar with other characteristics, the patient with predictor will have the listed increment in the score of the outcome parameter listed in that row.

[a]Increases in PDI, NPDI, IDS, GMFCS, and MACS scores indicate worsening in those scores.

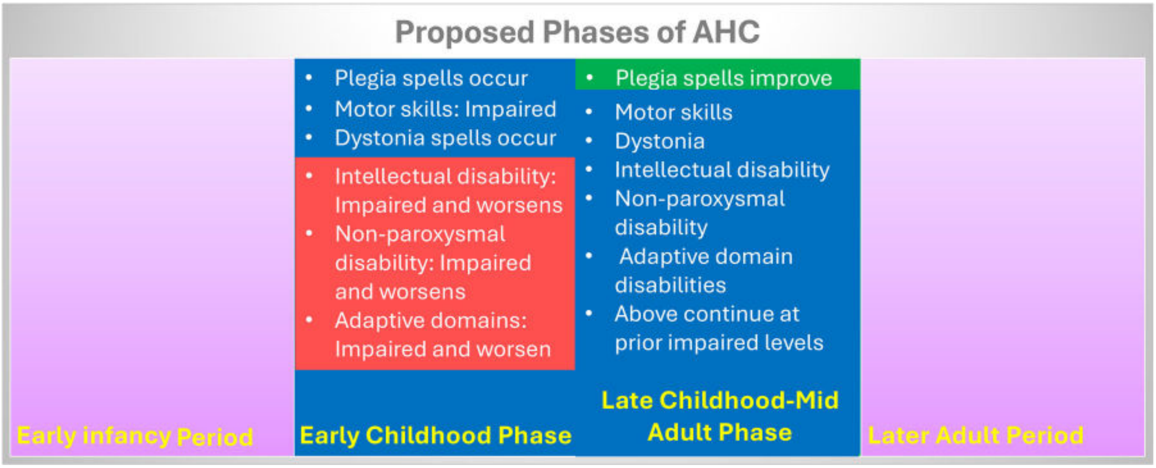

FIGURE 5 | Proposed phases of alternating hemiplegia of childhood (AHC). This figure illustrates the proposed four phases of the AHC clinical course: birth to early infancy (a phase we did not investigate in this study); early childhood, in which intellectual, non-paroxysmal, and social adaptive skills worsen; late childhood to mid-adulthood, in which plegia episodes improve and there is no further decline in these skills; and later adulthood (which also was not investigated in this study). Please see the Discussion section for further details. Green indicates improvement, and red indicates worsening of corresponding parameters in that box.

4.2.2 | Gene Mutations and Early Life Parameters

Prior studies have shown that the E815K mutation is associated with severe developmental delay, earlier onset of AHC, and a higher incidence of status epilepticus and epilepsy, while D801N results in an intermediate phenotype and G947R a milder phenotype, characterized by more prominent dystonia [8, 16, 19, 29, 30]. Our study is consistent with this, showing worse IDS in patients with the E815K mutation. Significant findings of our study are that not only did we confirm prior previous findings but that we also demonstrated that the D801N mutation exhibits the highest levels of paroxysmal disability (hemiplegia and dystonia), and even more importantly, we quantitated the effect of these gene mutations on outcome using specific AHC relevant scales, as summarized in Table 3. These findings, too, will be valuable in prognostication and in clinical trial planning along with other parameters, including the quantification of the effects of the early life PDI and early life NPDI scores on various variables, as described in Figure 5 and Table 3.

4.3 | Mortality

The observed mortality rates, 11.2/1000 patient-years in all our AHC studied patients and 19.5/1000 patient-years in those with epilepsy with a rate of SUDEP of 6.5/1000 patient-years, are very comparable to recently documented mortality and SUDEP rates in developmental and epileptic encephalopathies [33, 34]. As an example, the mortality rate in Dravet syndrome has been reported to be 15.84/1000 person-years and the SUDEP rate 9.32/1000 person-years [34]. Given the small number of mortality events observed ($n = 3$), the interpretation of mortality and of SUDEP rates must be approached with caution, as the limited sample size constrains the statistical precision and generalizability of these estimates. Our findings should incentivize active studies to understand the underlying pathophysiology of SUDEP, of the increased mortality in AHC, and of strategies to prevent such deaths. These findings will also be useful in counseling patients' families.

4.4 | Potential Mechanisms and Conclusions

There are many potential underlying pathophysiological mechanisms that could underlie our observations. These include abnormal protein folding, programmed cell death, markedly abnormal neuronal physiology, and the effect of recurrent seizures [35–38]. The distinctive drop in VAB-Composite and VAB subscales during early childhood is consistent with the particular vulnerabilities of the brain during early childhood and to the increased importance of *ATP1A3* protein during this period as described previously: (1) There is increased expression of *ATP1A3* in early life [39, 40]. (2) There is also increased occurrence of apneas and hypoxic episodes during early childhood in AHC patients [41]. (3) Given that Na^+/K^+ ATPase is dependent on ATP generation and is very vulnerable to hypoxia, the combination of the above two factors are likely to predispose neurons to increased risk of hypoxic injury during early childhood [42]. (4) Of note also is that injury from intermittent hypoxia due to the resulting reactive oxygen species is known to adversely impact the development of brain regions critical to adaptive, cognitive, and social functions (including the ventromedial and ventrolateral prefrontal cortex and superior temporal sulcus), which undergo greater maturation in early childhood, than areas of motor development [43–45].

The causes of death in our study were attributed to post–status epilepticus respiratory failure in two patients and SUDEP in another. There are several potential underlying mechanisms based on AHC mouse models as well as human pathophysiological studies: (1) ATP1A3 is important for the function of brainstem respiratory control centers. The D801N mouse model has abnormal central respiratory and cardiac rate control, which lead to SUDEP and seizure-related deaths [46, 47]. (2) Patients with AHC are known to have autonomic dysfunction with predisposition to apneas and cardiac arrhythmias [4, 41]. These factors have been incriminated as contributing to the pathophysiology of SUDEP in general [2, 31, 41]. Our findings underscore the importance of expanding the lines of research in the above increased mortality areas, particularly because data from the above mouse model show that predisposition to increased mortality can be rescued by *ATP1A3* gene supplementation therapy that is administered postnatally [48].

The differences in manifestations between the E815K and D801N mutations may be due to the different types of impairment in the Na^{+}–K^{+}–ATPase activity caused by each of these two muations [36, 49].

We acknowledge there are limitations to our study. While this study focuses on AHC as a clinically defined entity, AHC represents one part of the broader, genetically defined spectrum of *ATP1A3*-related disorders, which are phenotypically diverse; therefore, current findings may not be generalizable to other *ATP1A3*-associated phenotypes. The duration of the prospective follow-up was 1–3 years, and the age range studied did not include early infancy or late adulthood. In addition, there is also possible referral bias and the potential for unrecognized, confounding variables for which we could not control, including the retrospective nature of determining early life scores that were obtained by caregiver recall and chart review. Whereas the progressions we observed are likely to be due to biological and underlying pathophysiology mechanisms, they could also be related to the possibility that older individuals with AHC may have had a different level of care as younger individuals. However, this may be applicable to any disease and is a potential limitation in any natural history study. We also note that in our patients, the progression was domain specific, not global, which would argue against care-related progressions. In addition, mouse animal models of AHC and prior, albeit smaller, AHC patient series, all reviewed above, also show progression and worsening of AHC over time. Moreover, the duration of our study of a follow-up period of 1–3 years makes it unlikely that there were major changes in care practices over time during that period. Finally, although we did not measure the level of care directly, our clinical experience suggests no major age-related patient care disparities. Nevertheless, we acknowledge that this is a potential confounding variable that is worthy of future investigation. However, our study does provide original clinical data with convergence of our clinical findings with the pathophysiology, as detailed above, and with data from the two respective mouse models carrying the D801N and E815K mutations, which both also show worsening neurological status with age [18, 50].

In conclusion, this multinational, multicenter study used methodologies specifically designed to enhance our understanding of the natural history of the rare and complex disorder of AHC. As a result, we have gained insights into the progression of AHC across different domains, its stages, its prognostic indicators, and its mortality risks. All this will aid prognostication, counseling, and clinical trial planning, while hopefully helping to guide and concentrate future basic science research on areas relevant to patient management.

Author Contributions

Shital H. Patel: visualization, writing – original draft, writing – review and editing, methodology, formal analysis. **Eleni Panagiotakaki:** conceptualization, investigation, methodology, data curation, supervision, funding acquisition, writing – review and editing; validation. **Beiyu Liu:** formal analysis, software, writing – review and editing, methodology. **Carmen Fons:** writing – review and editing, conceptualization, investigation, methodology, data curation, funding acquisition, validation. **Lyndsey Prange:** data curation, conceptualization, methodology, writing – review and editing, validation. **Maria T. Papadopoulou:** writing – review and editing, data curation, investigation, validation. **April Boggs:** data curation, writing – review and editing, validation. **Elisa De Grandis:** data curation, validation, conceptualization, investigation, methodology, writing – review and editing. **Aikaterini Vezyroglou:** data curation, investigation, validation, writing – review and editing. **Francesco Fortunato:** data curation, writing – review and editing. **Simona Balestrini:** investigation, validation, writing – review and editing, data curation. **Francesca Ragona:** writing – review and editing, investigation, data curation. **Eugenia Julia Tosi:** investigation, writing – review and editing, data curation. **Claudio Zucca:** data curation, writing – review and editing, investigation. **Giacomo Garone:** investigation, writing – review and editing, data curation. **Andrey Megvinov:** software, writing – review and editing. **Giosuè Lo Bosco:** software, writing – review and editing. **Michela Stagnaro:** investigation, data curation, writing – review and editing, validation. **Julie Uchitel:** conceptualization, writing – review and editing; methodology; investigation. **Marion Comajuan:** data curation, writing – review and editing, validation. **Matthildi Athina Papathanasiou Terzi:** data curation, validation, writing – review and editing. **Jennifer Anticona:** data curation, validation, writing – review and editing. **Joan M. Jasien:** investigation, conceptualization, writing – review and editing, methodology. **Jeffrey Wuchich:** funding acquisition, writing – review and editing, conceptualization, methodology. **Sigurdur H. Johannesson:** funding acquisition, writing – review and editing, conceptualization, methodology. **J. Helen Cross:** funding acquisition, writing – review and editing, conceptualization. **Sanjay M. Sisodiya:** writing – review and editing, funding acquisition, conceptualization. **Hwanhee Hong:** formal analysis, methodology, supervision, writing – review and editing, software. **Alexis Arzimanoglou:** conceptualization, investigation, methodology, funding acquisition, writing – review and editing, supervision. **Rosaria Vavassori:** software, supervision, conceptualization, investigation, methodology, writing – review and editing, funding acquisition, validation, formal analysis, project administration, data curation, resources. **Mohamad A. Mikati:** conceptualization, investigation, funding acquisition, writing – original draft, writing – review and editing, supervision, resources, project administration, formal analysis, software, methodology, validation, visualization, data curation.

Acknowledgments

We thank the patients and their families who inspired this study and particularly those caregivers who provided material for the study procedures. We thank the following AHC patient organizations for their support of the OBSERV-AHC study (including this and other related studies that included Videolibrary, Event-calendar, and e-Diary–related projects) and of the IAHCRC-CLOUD Platform, serving as the data collection platform for the OBSERV-AHC study and related studies (listed above): USA Cure AHC, French (AFHA), Icelandic (AHC Samtökin), Dutch (AHC Vereniging Nederland), Spanish (AESHA), UK (AHC UK), German (AHC18+ e.V.), Polish (AHC-PL), and Italian (AISEA) associations. Our work was also extensively supported by funds from Duke University. We also deeply thank all the caregivers of AHC patients who over the years have given repeated input that further motivated our study and helped refine its procedures. We thank the multiple providers who contributed to the care of the AHC patients and to the administrative staff, particularly Dona Tran Woodlief for the excellent administrative support she gives to the AHC program at Duke and to Ceci Chamorro and Haley Neese of the Duke Office of Clinical Research for their invaluable help with the RED Cap database. Funding for this study was provided by multiple family organizations. These include six national family organizations: USA (donations from Cure AHC), French (AFHA), Icelandic (AHC Samtökin), Dutch (AHC

Vereniging Nederland), Spanish (AESHA), and UK (AHC UK) as well as by multiple funds from Duke University. The IAHCRC-CLOUD Platform, the data input, hosting, and sharing service for the studies of the IAHCRC Consortium, has been developed by IEMEST based on the REDCap System provided by Vanderbilt University. We also thank Mrs. Sébile Tchaicha, research project manager of the European Reference Network for Rare and Complex Epilepsies, ERN EpiCARE, for her contribution to the OBSERV-AHC study design and implementation in European centers and for ensuring a regular liaison with all ERN EpiCARE centers that contributed to the work. We acknowledge support from the Biostatistics, Epidemiology, and Research Design (BERD) Methods Core funded through Grant Award Number UL1TR002553 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. S.B. and S.M.S. are supported by the Epilepsy Society, UK. All research of J.H.C. and A.V. is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre.

Conflicts of Interest

M.A.M. has intellectual property interest in the therapy of *ATP1A3*-related disease (patent number WO2020232297). J.H.C. has received research grants from Zogenix (now a part of UCB), Marinus, GW Pharma (now Jazz Pharmaceuticals), Vitaflo, Longboard (now Lundbeck), Stoke Therapeutics, Ultragenyx, UCB, National Institute of Health Research (NIHR), EPSRC, GOSH Charity, ERUK, the Waterloo Foundation, and the NIHR Great Ormond Street Hospital Biomedical Research Centre; has served as consultant/advisor for UCB, GW Pharma (now Jazz Pharmaceuticals), Longboard (Lundbeck), and Biocodex, for which remuneration was made to the department outside of the submitted work; and serves as chair of the medical board for Dravet Syndrome UK, Hope for Hypothalamic Hamartomas, and Matthew's Friends and endowed chair at UCL Great Ormond Street Institute of Child Health.

References

1. M. Bourgeois, J. Aicardi, and F. Goutières, "Alternating Hemiplegia of Childhood," *Journal of Pediatrics* 122, no. 5 (Pt 1) (1993): 673–679, https://doi.org/10.1016/s0022-3476(06)80003-x.

2. M. A. Mikati, U. Kramer, M. L. Zupanc, and R. J. Shanahan, "Alternating Hemiplegia of Childhood: Clinical Manifestations and Long-Term Outcome," *Pediatric Neurology* 23, no. 2 (2000): 134–141, https://doi.org/10.1016/s0887-8994(00)00157-0.

3. M. Masoud, L. Prange, J. Wuchich, A. Hunanyan, and M. A. Mikati, "Diagnosis and Treatment of Alternating Hemiplegia of Childhood," *Current Treatment Options in Neurology* 19, no. 2 (2017): 8, https://doi.org/10.1007/s11940-017-0444-7.

4. S. Balestrini, M. A. Mikati, R. Álvarez-García-Rovés, et al., "Cardiac Phenotype in ATP1A3-Related Syndromes: A Multicenter Cohort Study," *Neurology* 95, no. 21 (2020): 2866, https://doi.org/10.1212/WNL.0000000000010794.

5. S. Kansagra, R. Ghusayni, B. Kherallah, et al., "Polysomnography Findings and Sleep Disorders in Children With Alternating Hemiplegia of Childhood," *Journal of Clinical Sleep Medicine* 15, no. 1 (2019): 65–70, https://doi.org/10.5664/jcsm.7572.

6. E. L. Heinzen, K. J. Swoboda, Y. Hitomi, et al., "De Novo Mutations in ATP1A3 Cause Alternating Hemiplegia of Childhood," *Nature Genetics* 44, no. 9 (2012): 1030–1034, https://doi.org/10.1038/ng.2358.

7. H. Rosewich, H. Thiele, A. Ohlenbusch, et al., "Heterozygous De-Novo Mutations in ATP1A3 in Patients With Alternating Hemiplegia of Childhood: A Whole-Exome Sequencing Gene-Identification Study," *Lancet Neurology* 11, no. 9 (2012): 764–773, https://doi.org/10.1016/S1474-4422(12)70182-5.

8. L. Viollet, G. Glusman, K. J. Murphy, et al., "Alternating Hemiplegia of Childhood: Retrospective Genetic Study and Genotype-Phenotype Correlations in 187 Subjects From the US AHCF Registry," *PLoS One* 10, no. 5 (2015): e0127045, https://doi.org/10.1371/journal.pone.0127045.

9. A. Capuano, G. Garone, G. Tiralongo, and F. Graziola, "Alternating Hemiplegia of Childhood: Understanding the Genotype-Phenotype Relationship of ATP1A3 Variations," *Application of Clinical Genetics* 13 (2020): 71–81, https://doi.org/10.2147/TACG.S210325.

10. E. L. Heinzen, A. Arzimanoglou, A. Brashear, et al., "Distinct Neurological Disorders With ATP1A3 Mutations," *Lancet Neurology* 13, no. 5 (2014): 503–514, https://doi.org/10.1016/S1474-4422(14)70011-0.

11. M. A. Mikati, E. Panagiotakaki, and A. Arzimanoglou, "Revision of the Diagnostic Criteria of Alternating Hemiplegia of Childhood," *European Journal of Paediatric Neurology* 32 (2021): A4–A5, https://doi.org/10.1016/j.ejpn.2021.05.004.

12. J. Liu, J. S. Barrett, E. T. Leonardi, et al., "Natural History and Real-World Data in Rare Diseases: Applications, Limitations, and Future Perspectives," *Journal of Clinical Pharmacology* 62, Suppl 2 (2022): S38–S55, https://doi.org/10.1002/jcph.2134.

13. S. H. Patel, E. Panagiotakaki, M. T. Papadopoulou, et al., "Methodology of a Natural History Study of a Rare Neurodevelopmental Disorder: Alternating Hemiplegia of Childhood as a Prototype Disease," *Journal of Child Neurology* 38, no. 10–12 (2023): 597–610, https://doi.org/10.1177/08830738231197861.

14. E. Panagiotakaki, G. Gobbi, B. Neville, et al., "Evidence of a Non-Progressive Course of Alternating Hemiplegia of Childhood: Study of a Large Cohort of Children and Adults," *Brain* 133, no. 12 (2010): 3598–3610, https://doi.org/10.1093/brain/awq295.

15. Y. Saito, T. Inui, T. Sakakibara, K. Sugai, H. Sakuma, and M. Sasaki, "Evolution of Hemiplegic Attacks and Epileptic Seizures in Alternating Hemiplegia of Childhood," *Epilepsy Research* 90, no. 3 (2010): 248–258, https://doi.org/10.1016/j.eplepsyres.2010.05.013.

16. M. Sasaki, A. Ishii, Y. Saito, et al., "Genotype-Phenotype Correlations in Alternating Hemiplegia of Childhood," *Neurology* 82, no. 6 (2014): 482–490, https://doi.org/10.1212/WNL.0000000000000102.

17. M. Perulli, J. Poole, G. Di Lazzaro, et al., "Non-Stationary Outcome of Alternating Hemiplegia of Childhood into Adulthood," *Movement Disorders Clinical Practice* 9, no. 2 (2022): 206–211, https://doi.org/10.1002/mdc3.13388.

18. J. Uchitel, K. Wallace, L. Tran, et al., "Alternating Hemiplegia of Childhood: Evolution Over Time and Mouse Model Corroboration," *Brain Communications* 3, no. 3 (2021): fcab128, https://doi.org/10.1093/braincomms/fcab128.

19. E. Panagiotakaki, E. De Grandis, M. Stagnaro, et al., "Clinical Profile of Patients With ATP1A3 Mutations in Alternating Hemiplegia of Childhood—A Study of 155 Patients," *Orphanet Journal of Rare Diseases* 10, no. 123 (2015), https://doi.org/10.1186/s13023-015-0335-5.

20. M. Pratt, J. Uchitel, N. McGreal, et al., "Alternating Hemiplegia of Childhood: Gastrointestinal Manifestations and Correlation With Neurological Impairments," *Orphanet Journal of Rare Diseases* 15, no. 1 (2020): 231, https://doi.org/10.1186/s13023-020-01474-w.

21. G. Katz and E. Lazcano-Ponce, "Intellectual Disability: Definition, Etiological Factors, Classification, Diagnosis, Treatment and Prognosis," *Salud Publica de Mexico* 50, no. Suppl 2 (2008): 132–141, https://doi.org/10.1590/s0036-36342008000800005.

22. J. Uchitel, A. Helseth, L. Prange, et al., "The Epileptology of Alternating Hemiplegia of Childhood," *Neurology* 93, no. 13 (2019): 1248, https://doi.org/10.1212/WNL.0000000000008159.

23. X. Yang, C. Liu, Y. Liu, et al., "The Global Burden, Trends, and Inequalities of Individuals With Developmental and Intellectual Disabilities Attributable to Iodine Deficiency From 1990 to 2019 and Its

Prediction Up to 2030," *Frontiers in Nutrition* 11 (2024): 1366525, https://doi.org/10.3389/fnut.2024.1366525.

24. J. M. Jasien, M. Bonner, R. D'alli, et al., "Cognitive, Adaptive, and Behavioral Profiles and Management of Alternating Hemiplegia of Childhood," *Developmental Medicine & Child Neurology* 61, no. 5 (2019): 547–554, https://doi.org/10.1111/dmcn.14077.

25. M. Masoud, K. Gordon, A. Hall, et al., "Motor Function Domains in Alternating Hemiplegia of Childhood," *Developmental Medicine & Child Neurology* 59, no. 8 (2017): 822–828, https://doi.org/10.1111/dmcn.13443.

26. A. G. Hamedani, L. A. Hauser, S. Perlman, et al., "Longitudinal Analysis of Contrast Acuity in Friedreich Ataxia," *Neurology: Genetics* 4, no. 4 (2018): e250, https://doi.org/10.1212/NXG.0000000000000250.

27. C. Janson, S. McPhee, J. Francis, et al., "Natural History of Canavan Disease Revealed by Proton Magnetic Resonance Spectroscopy (1H-MRS) and Diffusion-Weighted MRI," *Neuropediatrics* 37, no. 4 (2006): 209–221, https://doi.org/10.1055/s-2006-924734.

28. K. E. King, S. Kim, C. B. Whitley, and J. R. Jarnes-Utz, "The Juvenile Gangliosidoses: A Timeline of Clinical Change," *Molecular Genetics and Metabolism Reports* 25 (2020): 100676, https://doi.org/10.1016/j.ymgmr.2020.100676.

29. R. Cordani, M. Stagnaro, L. Pisciotta, et al., "Alternating Hemiplegia of Childhood: Genotype-Phenotype Correlations in a Cohort of 39 Italian Patients," *Frontiers in Neurology* 12 (2021): 658451, https://doi.org/10.3389/fneur.2021.658451.

30. X. Yang, H. Gao, J. Zhang, et al., "ATP1A3 Mutations and Genotype-Phenotype Correlation of Alternating Hemiplegia of Childhood in Chinese Patients," *PLoS One* 9, no. 5 (2014): e97274, https://doi.org/10.1371/journal.pone.0097274.

31. S. Kansagra, M. A. Mikati, and F. Vigevano, "Alternating Hemiplegia of Childhood," in *Handbook of Clinical Neurology*, Vol. 112 (2013), 821–826, https://doi.org/10.1016/B978-0-444-52910-7.00001-5.

32. J. Uchitel, E. Abdelnour, A. Boggs, et al., "Social Impairments in Alternating Hemiplegia of Childhood," *Developmental Medicine & Child Neurology* 62, no. 7 (2020): 820–826, https://doi.org/10.1111/dmcn.14473.

33. A. M. Donnan, A. L. Schneider, S. Russ-Hall, L. Churilov, and I. E. Scheffer, "Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies," *Neurology* 100, no. 16 (2023): 1712, https://doi.org/10.1212/WNL.0000000000207080.

34. M. S. Cooper, A. McIntosh, D. E. Crompton, et al., "Mortality in Dravet Syndrome," *Epilepsy Research* 128 (2016): 43–47, https://doi.org/10.1016/j.eplepsyres.2016.10.006.

35. E. Arystarkhova, L. J. Ozelius, A. Brashear, and K. J. Sweadner, "Misfolding, Altered Membrane Distributions, and the Unfolded Protein Response Contribute to Pathogenicity Differences in Na,K−Atpase ATP1A3 Mutations," *Journal of Biological Chemistry* 296 (2021): 100019, https://doi.org/10.1074/jbc.RA120.015271.

36. T. H. Holm and K. Lykke-Hartmann, "Insights into the Pathology of the alpha3 Na(+)/K(+)−Atpase Ion Pump in Neurological Disorders; Lessons From Animal Models," *Frontiers in Physiology* 7 (2016): 209, https://doi.org/10.3389/fphys.2016.00209.

37. A. S. Hunanyan, N. A. Fainberg, M. Linabarger, et al., "Knock-in Mouse Model of Alternating Hemiplegia of Childhood: Behavioral and Electrophysiologic Characterization," *Epilepsia* 56, no. 1 (2015): 82–93, https://doi.org/10.1111/epi.12878.

38. A. S. Hunanyan, A. R. Helseth, E. Abdelnour, et al., "Mechanisms of Increased Hippocampal Excitability in the Mashl(+/−) Mouse Model of Na(+)/K(+)−Atpase Dysfunction," *Epilepsia* 59, no. 7 (2018): 1455–1468, https://doi.org/10.1111/epi.14441.

39. M. Cardoso-Moreira, J. Halbert, D. Valloton, et al., "Gene Expression Across Mammalian Organ Development," *Nature* 571, no. 7766 (2019): 505–509, https://doi.org/10.1038/s41586-019-1338-5.

40. Science TAIfB. Allen Brain Map. 2024.

41. J. Thamby, L. Prange, A. Boggs, et al., "Characteristics of Non-Sleep Related Apneas in Children With Alternating Hemiplegia of Childhood," *European Journal of Paediatric Neurology* 48 (2024): 101–108, https://doi.org/10.1016/j.ejpn.2023.12.002.

42. P. Depierre, V. Ginet, A. C. Truttmann, and J. Puyal, "Neuronal Autosis Is Na(+)/K(+)−Atpase Alpha 3-Dependent and Involved in Hypoxic-Ischemic Neuronal Death," *Cell Death & Disease* 15, no. 5 (2024): 363, https://doi.org/10.1038/s41419-024-06750-2.

43. V. S. Ten and A. Starkov, "Hypoxic-Ischemic Injury in the Developing Brain: The Role of Reactive Oxygen Species Originating in Mitochondria," *Neurology Research International* 2012 (2012): 542976, https://doi.org/10.1155/2012/542976.

44. U. M. Krämer, B. Mohammadi, N. Doñamayor, A. Samii, and T. F. Münte, "Emotional and Cognitive Aspects of Empathy and Their Relation to Social Cognition—An fMRI-Study," *Brain Research* 1311 (2010): 110–120, https://doi.org/10.1016/j.brainres.2009.11.043.

45. M. B. Potts, S. E. Koh, W. D. Whetstone, et al., "Traumatic Injury to the Immature Brain: Inflammation, Oxidative Injury, and Iron-Mediated Damage as Potential Therapeutic Targets," *NeuroRx* 3, no. 2 (2006): 143–153, https://doi.org/10.1016/j.nurx.2006.01.006.

46. R. L. Holt, E. Arehart, A. Hunanyan, N. A. Fainberg, and M. A. Mikati, "Pediatric Sudden Unexpected Death in Epilepsy: What Have We Learned From Animal and Human Studies, and Can We Prevent It?," *Seminars in Pediatric Neurology* 23, no. 2 (2016): 127–133, https://doi.org/10.1016/j.spen.2016.05.002.

47. A. S. Hunanyan, A. Verma, M. T. Bidzimou, et al., "Progressive Central Cardiorespiratory Rate Downregulation and Intensifying Epilepsy Lead to Sudden Unexpected Death in Epilepsy in Mouse Model of the Most Common Human ATP1A3 Mutation," *Epilepsia* 66, no. 3 (2025): 899–913, https://doi.org/10.1111/epi.18236.

48. A. S. Hunanyan, B. Kantor, R. S. Puranam, et al., "Adeno-Associated Virus-Mediated Gene Therapy in the Mashlool, Atp1a3(Mashl/+), Mouse Model of Alternating Hemiplegia of Childhood," *Human Gene Therapy* 32, no. 7–8 (2021): 405–419, https://doi.org/10.1089/hum.2020.191.

49. K. M. Weigand, M. Messchaert, H. G. P. Swarts, F. G. M. Russel, and J. B. Koenderink, "Alternating Hemiplegia of Childhood Mutations Have a Differential Effect on Na(+),K(+)−Atpase Activity and Ouabain Binding," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 1842, no. 7 (2014): 1010–1016, https://doi.org/10.1016/j.bbadis.2014.03.002.

50. A. R. Helseth, A. S. Hunanyan, S. Adil, et al., "Novel E815K Knock-In Mouse Model of Alternating Hemiplegia of Childhood," *Neurobiology of Disease* 119 (2018): 100–112, https://doi.org/10.1016/j.nbd.2018.07.028.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supplementary Table 1: Patients per country/center. **Supplementary Table 2:** Baseline data of the three patients without *ATP1A3* mutations.