RESEARCH ARTICLE OPEN ACCESS

# Characterization of Sleep in Alternating Hemiplegia of Childhood

## An International Survey

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## Abstract

### Background and Objectives

Few studies have investigated sleep features in people with alternating hemiplegia of childhood (AHC). In this study, we present a bespoke survey of individuals with AHC to characterize sleep disturbances in this condition.

### Methods

A cross-sectional survey was disseminated through the UK and Italian AHC family associations, addressing their registered families with at least 1 child or adult with a confirmed diagnosis of AHC by their national reference centers and who had consented to be contacted by email. The entire questionnaire implemented in the online surveys was organized into 3 main sections and included the Pittsburgh Sleep Quality Index (PSQI) scale. This scale ranges from 0 to 21, with higher scores indicating poorer sleep quality. Internal consistency of the questionnaire was assessed using Cronbach alpha statistic.

### Results

Forty-eight of 54 families with AHC (88.89%) filled out at least 1 item of the AHC-Sleep Questionnaire, and 36 of 54 (66.67%) completed the whole questionnaire. Eighteen of 44 people (40.91%) from our cohort reported having a problem with sleep, which was persistent for 10 of 44 (22.7%). Twenty-five of 44 people (56.82%) reported multiple arousals during a typical night, and for 9 of 25 (36%), these could be very prolonged. For 16 of 40 (40%) and 19 of 40 (47.5%), plegic spells resolved or improved, respectively, during sleep, whereas 5 of 40 (12.5%) reported no effect of sleep on these spells. The mean global PSQI score in 40 people was 5.40 (SD ± 4.69). Fifteen of 40 individuals (37.5%) had a global PSQI score ≥5. PSQI scores were significantly higher in those individuals who completed the questionnaire during summer (n = 6) compared with those who completed them during winter (n = 33) ($p = 0.011$, Mann-Whitney test). We found a strong correlation between AHC paroxysmal spell burden and PSQI score (Spearman $r = 0.39$, $p < 0.01$). The survey demonstrated a high degree of internal consistency, with a Cronbach alpha of 0.88 (95% CI 0.83–0.91).

### Discussion

We dissected sleep issues and reported sleep disruption, including elevated global PSQI scores, in a significant proportion of individuals with AHC. The main implication of this study is the importance of conducting comprehensive and regular assessments of sleep in both children and adults with AHC.

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**Supplementary Material**

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## Glossary

**AHC** = alternating hemiplegia of childhood; **FDR** = false discovery rate; **PSQI** = Pittsburgh Sleep Quality Index.

## Introduction

Alternating hemiplegia of childhood (AHC) is a rare lifelong neurodevelopmental disorder, usually presenting in early infancy, characterized by recurrent episodes of hemiplegia, which may alternate sides between attacks, and/or quadriplegia.[1,2] AHC is associated with a wide range of both paroxysmal and nonparoxysmal manifestations.[1-4] Paroxysmal events typically include epileptic seizures, dystonic and plegic spells, and abnormal eye movements, as well as autonomic dysfunction.[1-4] Nonparoxysmal manifestations typically include pervasive neurologic disabilities such as developmental delay with intellectual disability, choreoathetosis, and ataxia. Cardiac dysfunction is also part of the AHC spectrum and can be both paroxysmal and nonparoxysmal, accounting for some of the unexplained premature mortality.[3,5,6] Approximately 75% of individuals with AHC carry de novo pathogenic variants in *ATP1A3*.[1,4]

The diagnosis relies on clinical history, typically using the traditional Aicardi criteria,[7] which have been recently revised.[8]

Sleep has generally been regarded as having a unique effect in AHC because plegic and other paroxysmal events, but not seizures, have been reported to generally improve or resolve with sleep[1-4,8]: the improvement of plegic spells with sleep is 1 of the major criteria for clinical diagnosis.[8]

Few studies have investigated sleep features in people with AHC,[9,10] and no studies have incorporated qualitative information from those living with this rare disease. A recent study demonstrated altered sleep patterns in a cohort of 22 children with AHC: polysomnography revealed frequent apneas, insomnia, and arousals, with a mean arousal index of 15 events/hour.[9] Our group has also demonstrated disrupted sleep architecture in 5 adult individuals with AHC.[10] This preliminary evidence indicates that sleep disruption may be part of the core phenotypic spectrum in both children and adults with AHC.[9,10] A comprehensive evaluation of sleep features in AHC is important: first, for understanding its possible disruption in AHC per se, as a feature of a genetically driven condition, and second, for its relevance for AHC treatment, with potential impacts on other aspects of the condition. In addition, it is important to consider that sleep can be disrupted in anyone by external factors, including climate change, a key global health challenge that has important consequences for people with neurologic disorders[11] such as AHC.[12,13]

The basis for sleep disorders in AHC could be multifactorial and, at least in part, related to the underlying genetic cause,[14] as well as the neurodevelopmental abnormalities, seizure activity, and other paroxysmal events. However, the few available sleep studies in AHC do not provide a detailed characterization of the sleep abnormalities nor investigate the possible causative factors.[9,10] During routine clinical appointments, sleep problems might be overlooked because of the complexity of the condition, with several other burdensome neurologic problems.[15]

People's voice surveys can be valuable for exploring unmet needs and understanding the lived experience, defined as the direct perspective of patients affected by the condition and their families, especially in rare neurodevelopmental disorders.[13,16] In this study, we present a survey of individuals with AHC and/or their families to better understand sleep disturbance and its impact in AHC.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

This research was approved by the relevant ethics committee. Individuals from the United Kingdom were recruited through a REC-approved study (REC 11/LO/2016), and all information was gathered under this approval. Individuals from Italy were recruited through a REC-approved study (REC Liguria: 256/2018 – approval code 4186). Individuals with AHC and their families were invited to complete the survey anonymously, with the stated purpose of obtaining an overview of their typical sleep pattern to help understand this monogenic condition in more detail. No personal information was collected through the survey nor included in the report of the survey results.

### Survey Development, Validation, and Administration

This study was a cross-sectional survey open between June 2021 and December 2023 and promoted by the AHCUK Charity and the IAHCRC International Consortium,[17] an international collaborative research initiative, established in 2015, whose goal is to unite researchers across several different countries to work toward a better understanding of the manifestations and natural history of AHC and related disorders and to develop more effective therapies.

The entire questionnaire implemented in the online surveys was organized into 3 main sections: form 01 "Welcome," form 02 "AHC-Sleep Questionnaire," and form 03 containing the PSQI scale.[18]

The survey was specifically designed in English by 3 neurologists with expertise in AHC and sleep (S.B., S.M.S., U.V.) and translated into Italian (M.S.). The survey was reviewed by AHC patient advocates for both the English (K.B.) and the Italian (R.V.) versions. The AHCUK patient association[19] committee piloted the survey and provided feedback. This iterative process was used to validate the survey. We added the Pittsburgh Sleep Quality Index (PSQI)[18] to the questionnaire after obtaining permission from the University of Pittsburgh for its use in noncommercial research. The PSQI is a questionnaire designed to assess sleep quality over a period of a month. It comprises 19 self-rated questions and 5 additional questions rated by the caregiver or bedpartner. Each item on the questionnaire is scored on a scale from 0 to 3, with higher scores reflecting greater difficulty with that specific aspect of sleep. The PSQI generates 7 component scores, which are totaled to create a "global" PSQI score ranging from 0 to 21. The developers of the PSQI proposed a cutoff score of 5, at or above which clinically significant sleep disturbances are likely present.

We also added detailed instructions to guide individuals with AHC and/or their caregivers in survey completion. The online survey was implemented on the IAHCRC-CLOUD Platform, the data collection and sharing service for collaborative studies of the IAHCRC International Consortium. The platform has been developed on the REDCap© system and is hosted by the I.E.ME.S.T. Institute, a member organization of the IAHCRC, and is managed by the IAHCRC Data Manager (R.V.).

We disseminated the survey through the UK and Italian AHC family associations via closed support groups, through newsletters for families, and by hosting a webinar organized by AHCUK with S. Balestrini. The link to the online survey was sent to those agreeing to participate. The Checklist for Reporting Results of Internet E-Survey (CHERRIES) was used to describe survey development, administration, analysis, and reporting,[20] as indicated in eAppendix 1.

## Data Handling and Reporting

The data collected through the online English and Italian surveys were stored in a specific database on the IAHCRC-CLOUD Platform, accessible online only by the study research team.

Families were given details of IAHCRC-CLOUD Platform's data handling policy as well as a contact email address for any questions arising.

Responses to the Italian surveys were first translated to English by F. Fortunato and S. Balestrini. Data from all individual surveys were exported from the IAHCRC-CLOUD Platform by the study research team in a Microsoft Excel format; checked for inconsistencies, missing data, and duplicates; and merged into a single Excel spreadsheet. Missing data were omitted, with no other correction or interpolation undertaken. Two authors (F.F. and S.B.) also independently checked and adjudicated any ambiguities in the final spreadsheet.

## Data Analysis

The full list of variables included as well as the online survey is available in eAppendix 2.

The denominator for each question was the aggregate number of participants who replied to that specific question.

Internal consistency of the questionnaire was assessed using Cronbach alpha statistic and corrected component-total correlation coefficients.

The Pearson $\chi^2$ or Fisher exact tests, as appropriate, for binary or categorical variables, and the $t$ test for continuous variables were used for association tests. The nonparametric Wilcoxon signed-rank test was also used to compare data that were not normally distributed. Association between variables was quantified using the Spearman rho nonparametric rank correlation coefficient. A multiple logistic regression model was also developed using PSQI as the dependent variable.

The threshold for statistical significance was set at $p < 0.05$, which was considered significant after correction for multiple comparisons using the false discovery rate (FDR) or Bonferroni method.

Data analysis was performed using IBM Statistical Package for Social Science Software (SPSS, version 29.0.2.0, Chicago, IL) for Mac.

## Data Availability

The data can be requested by emailing the corresponding author. Data will be shared with bona fide researchers after approval of proposals with signed data access agreements as required by, and subject to, institutional and national regulations.

# Results

## Form 01: Welcome

Sixty-six individuals were originally contacted. Fifty-four of 66 participants (84.4%) completed form 01 while 12 started but did not finish (further details in eFigure 1). Of the 54 respondents, 39 (72.2%) were AHC families from Italy and 15 (27.8%) were from the United Kingdom.

## Form 02: AHC-Sleep Questionnaire

### AHC Cohort Description

Forty-eight of 54 AHC families (88.9%) completed at least 1 item of form 02, and 36 (66.7%) completed the entire questionnaire. We did not observe any significant difference between AHC families who fully completed the questionnaire and those who only partially completed it for any of the analyzed variables (further details in eTable 1).

A comprehensive listing of all the survey responses is provided in eAppendix 3. Most of the responses (45/48, 93.8%) were completed by a parent or relative of individuals with AHC. Only 1 adult with AHC completed the questionnaire, while for the remaining 2 children with AHC, the responses were submitted by individuals other than a parent or relative.

Table 1 provides the demographic and clinical data of our AHC cohort. Most affected individuals were adult (28/46, 60.9%) and female (28/46, 60.9%). Age ranges were as follows: 1.5–2 years (n = 2/46, 4.4%), 3–5 years (n = 2/46, 4.3%), 5–12 years (n = 9/46, 19.6%), 12–18 years (n = 5/46, 10.9%), and more than 18 years (n = 28/46, 60.9%).

Epilepsy was present in 22 of 46 individuals (47.8%); 33 of 40 (82.5%) experienced plegic spells, and 32 of 41 (78%) had dystonic spells.

Figure 1 shows the medications regularly used by our cohort at the time of questionnaire. The 3 most common prescribed medications were flunarizine (n = 24/46, 52.2%), benzodiazepines (n = 18/46, 39.1%), and melatonin (n = 7/46, 15.2%). Benzodiazepines were used as baseline treatment (n = 8/18, 44.4%) or as rescue therapy (6/18, 33.3%), or both (4/18, 22.2%).

## Sleep Items

Eighteen of 44 people (40.9%) reported having a problem with sleep, which was persistent for 10 of 44 (22.7%) (further details in eAppendix 3). Twenty-five of 44 people (56.8%) reported multiple arousals during a typical night, and for 9 of 25 (36%), these could be very prolonged. When a cause was reported, arousals were frequently attributed to AHC-related paroxysmal events, including plegic spells (n = 3), seizures (n = 3), dystonic spells (n = 4), and other combinations of AHC spells (n = 3). In the remaining people with AHC, the cause of nocturnal arousals was unknown (n = 10). For 30 of 44 individuals (68.2%), the sleep features were reported to be "always the same" (i.e., meaning no change in sleep phenotype over time).

We explored the need for daytime napping, which varied as follows: several times per day (n = 8/40, 20%), once a day (n = 8/40, 20%), less than once a day (n = 2/40, 5%), never (n = 8/40, 20%), and "it varies" (n = 14/40, 35%).

We also examined several additional contributors to sleep disruption in AHC, such as regular meal and bedtime routines, jet lag, weather, and effects of artificial lighting. Most AHC families tended to have regular meal and bedtime routines, and they found changes of daily routine disruptive. For the 17 of 33 individuals (51.5%) who found changes of daily routine disruptive, the main consequences were as follows: 8 of 17 (47.1%) experienced more AHC-related spells, 5 of 17 (29.4%) reported behavioral symptoms such as irritability, and 3 of 17 (17.6%) reported insomnia. Some individuals also experienced adverse impacts of traveling to a different timezone: 4 of 10 (40%) reported taking measures to reduce the impact of jet lag. For 28 of 40 respondents (70%), weather did not significantly affect sleep; however, 5 of 40 (12.5%) reported finding it harder to sleep during warmer weather.

Finally, most people with AHC people reported that having a bad night's sleep could affect them the next day. From the open comment section (those that are most relevant are summarized in Table 2), additional points emerged. Indeed, the open comment section further emphasizes the kaleidoscope of sleep disorders that may affect people with AHC, highlighting the persistence of sleep issues over time. As an example, a relative of 1 individual with AHC stated, "the older he gets, the more problematic his sleep becomes." Another emerging point is the impact of paroxysmal AHC spells on sleep: "plegic episodes & dystonia waking her up; dystonia in particular causing pain" (Table 2).

We further explored the impact of sleep on paroxysmal spells. Plegic spells resolved (16/40 (40%)) or improved (19/40) during sleep, whereas 5 of 40 (12.5%) reported no effect of sleep on these spells. Furthermore, more than one-third of people with AHC reported that only plegic spells were improved by sleep. The chance of AHC spells resolving during sleep could vary dependent on sleep length. Spells resolved with any sleep duration in 15 of 40 (37.5%), only when sleep lasted for more than 1 hour in 6 of 40 (15%), variably in 12 of 40 (30%), and finally only during nocturnal sleep in 1 of 40 (2.5%). Furthermore, 9 of 15 respondents (60%) reported a major improvement in spells with a longer sleep, whereas for 6 of 15 (40%), there was no difference between long sleep and a short nap.

## Pittsburgh Sleep Quality Index

Forty AHC families completed form 03 (Pittsburgh Sleep Quality Index, PSQI). PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month interval. The score ranges from 0 to 21, with 0–4 indicating "good" sleep and 5–21 indicating "poor" sleep.[18] The global PSQI score mean in our cohort was 5.40 (SD ± 4.69; range 0–16). Fifteen of 40 individuals (37.5%) had a global PSQI score ≥5. Sex did not influence the global PSQI score [$p = 0.858$, Mann-Whitney test]. The global PSQI score was higher (mean 6.8 ± 4.9) among individuals taking benzodiazepines compared with those who were not (mean 4.3 ± 4.3) [Mann–Whitney test, $p = 0.045$]. Moreover, the PSQI score was further elevated (mean 7.5 ± 5.2) in individuals who were taking benzodiazepines and were on multiple antiseizure medications.

The PSQI includes an additional section for individuals with a bedpartner or roommate, containing 5 questions about observed sleep behaviors. Of the 40 individuals with AHC, 26 (65%) had a bedpartner or roommate who could answer these questions. The most frequently reported behaviors were "legs twitching or jerking during sleep" (n = 16), "loud snoring" (n = 8), "long pauses between breaths" (n = 6), "episodes of

**Table 1** Clinical and Demographic Data of the AHC Cohort

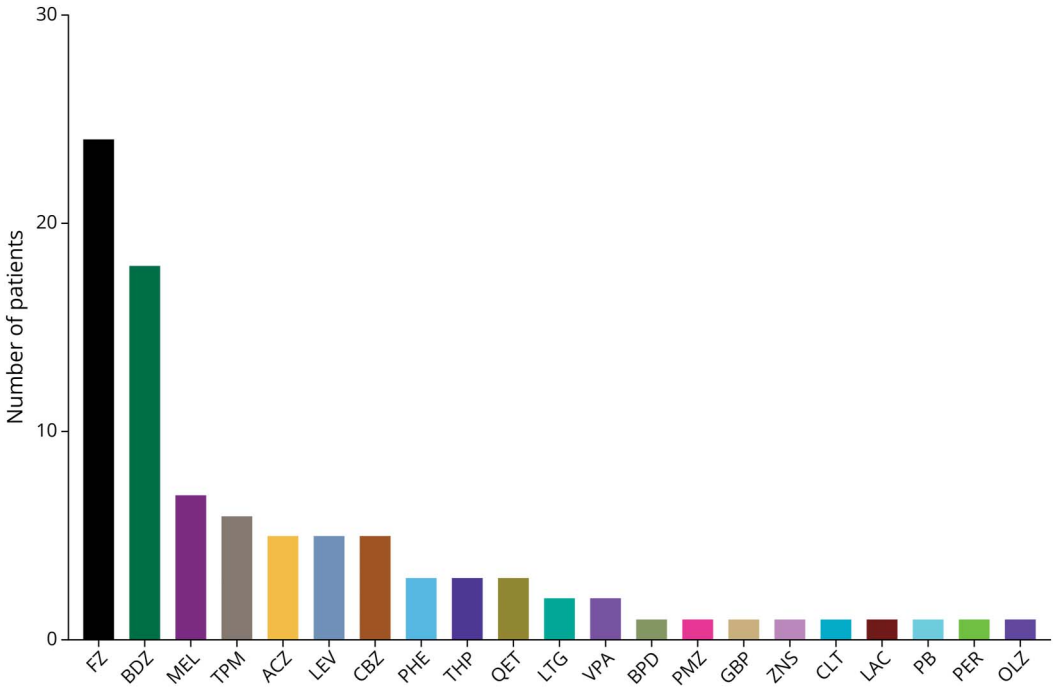
| Data | AHC cohort |
|---|---|
| **Sex (M/F)** | 18/28 |
| **Age at survey, y**[a] | 23.94 ± 15.51 |
| **Epilepsy**[b] | 22/46 (47.8%) |
| **Epileptic seizures** | |
| **More than once daily** | 2/46 (4.3%) |
| **Daily** | 0/46 |
| **Several times a week** | 3/46 (6.5%) |
| **Weekly** | 8/46 (17.4%) |
| **Monthly** | 6/46 (13%) |
| **Less than once monthly** | 0/46 |
| **Do not have seizures/epilepsy** | 24/46 (52.2%) |
| **Not sure/not relevant** | 3/46 (6.5%) |
| **Plegic spells**[c] | |
| **More than once daily** | 0/45 |
| **Daily** | 0/45 |
| **Several times a week** | 6/45 (13.3%) |
| **Weekly** | 9/45 (20%) |
| **Monthly** | 11/45 (24.4%) |
| **Less than once monthly** | 5/45 (11.1%) |
| **Do not have plegic spells, neither isolated nor in combination** | 5/45 (11.1%) |
| **Not sure/not relevant** | 9/45 (20%) |
| **Dystonic spells**[d] | |
| **More than once daily** | 2/44 (4.5%) |
| **Daily** | 5/44 (11.4%) |
| **Several times a week** | 6/44 (13.6%) |
| **Weekly** | 4/44 (9.1%) |
| **Monthly** | 13/44 (29.5%) |
| **Less than once monthly** | 1/44 (22.7%) |
| **Do not have dystonic spells, neither isolated nor in combination** | 6/44 (13.6%) |
| **Not sure/not relevant** | 7/44 (15.9%) |

Abbreviation: AHC = alternating hemiplegia of childhood.
[a] Data are expressed as mean ± SD.
[b] Data are expressed as counts.
[c] This question has 45 responders.
[d] This question has 44 responders.

disorientation or confusion" (n = 5), and "other restlessness" (n = 8) (eFigure 2). In addition, 3 individuals mentioned frequent nightmares or anxiety as causes of sleep disturbance. A "Bedpartner PSQI Score" was created by combining the ordinal values for each item in this section, which showed a strong positive correlation with the overall PSQI score (Spearman $r = 0.80$, $p < 0.0001$).

Comprehensive results of PSQI among children and adult AHC cases are summarized in eTable 2. No significant

**Figure 1** Medications Used by Individuals With Alternating Hemiplegia of Childhood Included in This Study




FZ = flunarizine, BDZ* = benzodiazepines, MEL = melatonin, TPM= topiramate, ACZ= acetazolamide, LEV= levetiracetam, CBZ = carbamazepine, PHE = phenytoin, THP= trihexyphenidyl, QET= quetiapine, VPA= valproate, LTG= lamotrigine, BPD= biperiden, PMZ = Promethazine, GBP= gabapentin; ZNS= zonisamide, CLT= clotiapine, LAC= lacosamide, PB= phenobarbital, PER= perampanel, OLZ= olanzapine. *= please note that BDZ were used as baseline therapy, rescue therapy or both.

**Table 2** Most Relevant Comments, Reported From the Open Comment Section (Reported as Original Comments,[a] Anonymized)

| Original comments |
|---|
| "At night, even if he doesn't sleep during the day, waking up is a constant" |
| "The older he gets, the more problematic his sleep becomes" |
| "As an infant, we dealt with nighttime feedings and diaper changes, but as he grew and we eliminated those, the situation did not improve; his sleep remains restless" |
| "His sleep is erratic; he requires position changes. He also has episodes of agitation where he cannot fall asleep. He can go 24 h no sleep or sleep for 24 h" |
| "Every night his sleep is troubled. Sometimes he falls back asleep immediately if rocked, but then he keeps tossing and turning in bed. When he sleeps with us in the parents' bed, we are forced to keep rocking him. Other times, less frequently, he wants to get out of bed, cries, and stays awake for more than an hour or two" |
| "Irritability, bad dreams, fear, paranoia" |
| "He cannot always sleep deeply" |
| "She wakes up several times a night and seems to struggle to get back to sleep; even though she is clearly tired. At one point; she would wake 10 or more times a night; sometimes only sleeping for a couple of hours. She rarely naps in the day; even when very tired. She now takes melatonin and promethezine at bedtime- she is prescribed chloral; but it seems to make her more awake" |
| "Fragmented sleep; nighttime agitation in childhood; difficulty falling back asleep." |
| "Waking up frequently (once in 3–4 hours); sometimes difficult to get back to sleep but most of the times it is only mummy that can get me back to sleep. Others try to get me back to sleep but it's difficult and it carries on for around an hour and sometimes can lead to paralysis; dystonia or even other AHC complications." |
| "Plegic episodes & dystonia waking her up; dystonia in particular causing pain" |
| "Whilst sleep changes day to day. When he is unwell he has more sleep disturbance" |

[a] Comments from Italian AHC families have been translated to English by 2 Italian investigators (F.F. and S.B.).

differences in the global PSQI score, or its components, emerged between children and adults.

We also explored the effect of seasons on PSQI changes. We tracked the season at questionnaire compilation from timestamp data extracted from each questionnaire and compared PSQI score results across different seasons. PSQI scores were significantly higher in those individuals who completed the questionnaire during summer (n = 6) compared with those who completed it during winter (n = 33) [$p = 0.011$, Mann-Whitney test] (Figure 2). All people who filled questionnaires during summer had a PSQI score higher than 5 (Figure 2).

## Comprehensive Analysis of All Survey Items

### Internal Consistency of the Questionnaire

We tested the internal consistency of 13 sleep-related variables from our survey: number of arousals per night (question "sq08"), duration of arousals (question "sq8b"), lifelong burden of sleep problems (question "sq12"), sleep variability (question "sq13"), need for napping during daytime (question "sq26"), and sleep medications (question "sq27"), as well as the 7 subcomponents of the PSQI score (e.g., sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medications, and daytime dysfunction). These items showed a very high overall reliability coefficient [Cronbach alpha of 0.88, 95% CI 0.83–0.91], indicating a high degree of internal consistency.

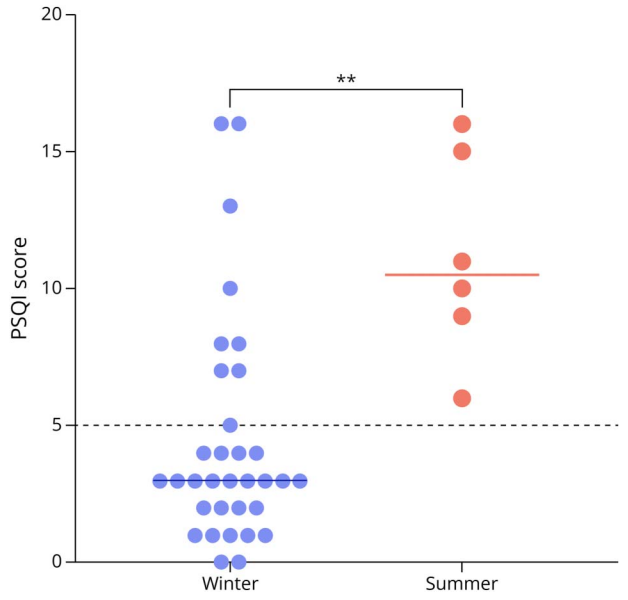
### Correlations Between Clinical and Sleep Variables

We derived a variable, referred to as the "AHC paroxysmal spell burden," by summing the scores from 3 survey questions: sq04 (i.e., epileptic seizures), sq05 (i.e., plegic spells), and sq06 (i.e., dystonic spells). Each of these items was scored as follows: 6 for "more than once daily," 5 for "daily," 4 for "multiple times per week," 3 for "weekly," 2 for "monthly," and 1 for "less than once per month," with higher values indicating a greater overall frequency of paroxysmal spells. There was a strong correlation between "AHC paroxysmal spell burden" and PSQI score [Spearman $r = 0.39$, $p < 0.01$] (Figure 3).

We also aimed to explore granular correlations between all clinical variables and sleep items of the questionnaire. Correlation matrices between clinical variables (e.g., age, seizure frequency, frequency of plegic, and dystonic spells) and sleep items from form 02 and form 03 are shown in Figure 4.

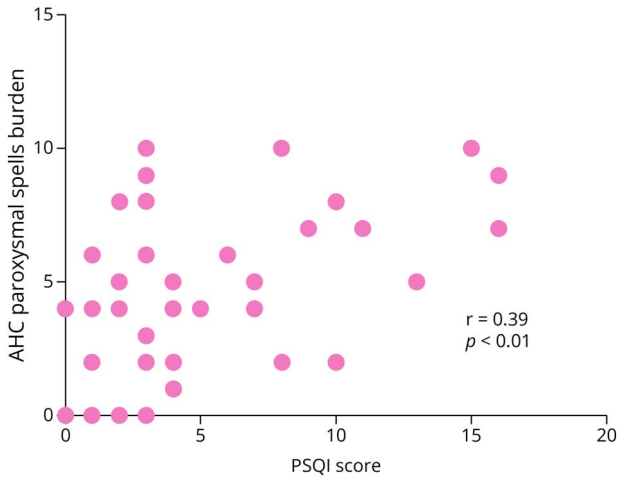
In the first correlation matrix (Figure 4A), only 2 correlations survived after multiple FDR correction. However, some interesting trends regarding clinical variables emerged. Higher seizure frequency (sq04) positively correlated with greater variability of sleep (sq13) [Spearman $r = 0.364$, $p = 0.04$]. Higher frequency of plegic spells at any point in the sleep-wake cycle (sq05) positively correlated with higher frequency of nocturnal arousals (Spearman $r = 0.391$, $p = 0.027$), and it had a negative correlation with age (Spearman $r = -0.43$, $p = 0.008$). Higher number of plegic spells during sleep (sq24) was also correlated with higher frequency of nocturnal arousals (Spearman $r = 0.40$, $p = 0.02$, $q$ value = 0.019). Higher frequency of dystonic spells (sq06) correlated with duration of nocturnal arousals (Spearman $r = 0.688$, $p = 0.003$, $q$ value = 0.03) and need for napping during daytime (Spearman $r = 0.548$, $p = 0.01$, $q$ value = 0.047). Moreover, higher frequency of dystonic spells had a positive correlation

**Figure 2** Effect of Seasonality on PSQI Scores in the AHC Cohort



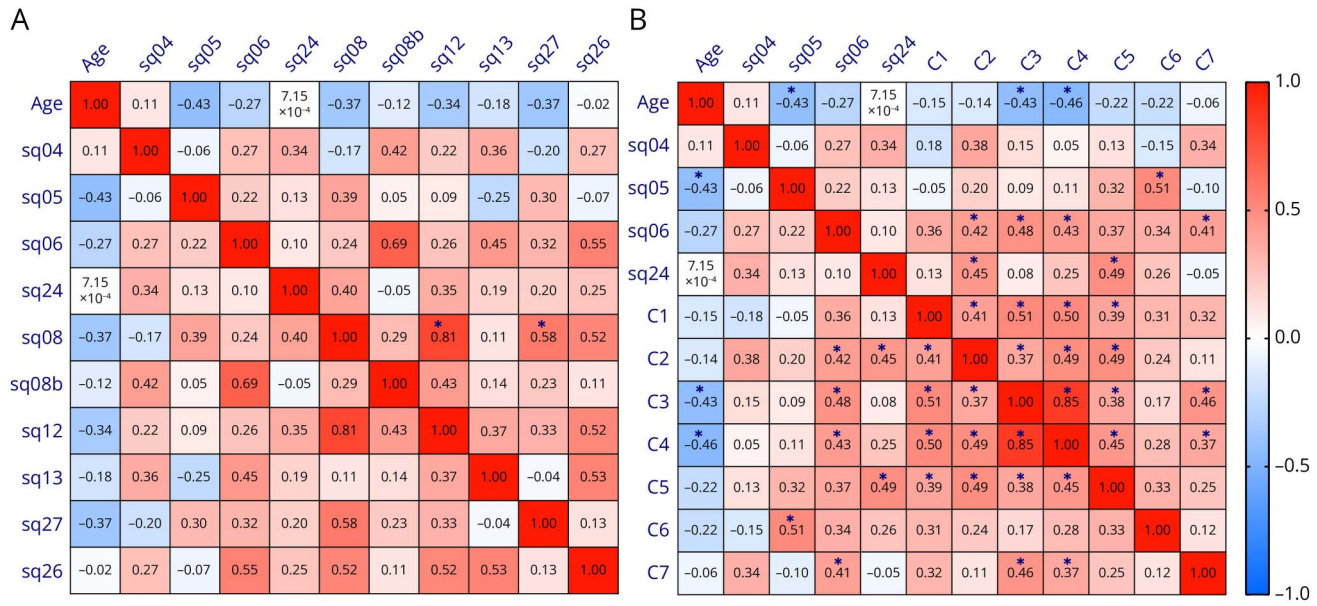

AHC = alternating hemiplegia of childhood; PSQI = Pittsburgh Sleep Quality Index.

**Figure 3** Correlation Between AHC Paroxysmal Spell Burden and Pittsburgh Sleep Quality Index Score




AHC paroxysmal spell burden is a variable derived by summing sq04 (i.e. epileptic seizures), sq05 (i.e., plegic spells), and sq06 (i.e., dystonic spells). AHC = alternating hemiplegia of childhood.

**Figure 4** Correlation Matrix Between Clinical Variables and Ordinal Sleep Items




Correlation matrix between clinical variables and ordinal sleep items of both "form 02-AHC-Sleep Questionnaire" (A) and "form 03-Pittsburgh Sleep Quality Index" (B). Numbers in the cells indicate the Spearman *r* coefficient (*significant correlations after false discovery rate at 5% correction). AHC = alternating hemiplegia of childhood.

with higher variability of sleep (sq13) (Spearman $r = 0.447$, $p = 0.022$, $q$ value = 0.069).

In the second correlation matrix (Figure 4B), 22 correlations survived after multiple FDR correction. Higher frequency of plegic spells (sq05) significantly correlated with age (Spearman $r = -0.43$, $p = 0.00008$, q value = 0.015) and with use of sleep medications (Spearman $r = 0.51$, $p = 0.003$, $q$ value = 0.02).

The frequency of dystonic spells (sq06) was significantly correlated with PSQI-C2 sleep latency (Spearman $r = 0.42$, $p = 0.013$, $q$ value = 0.04), PSQI-C3 sleep duration (Spearman $r = 0.48$, $p = 0.004$, $q$ value = 0.019), PSQI-C4 sleep efficiency (Spearman $r = 0.43$, $p = 0.013$, $q$ value = 0.04), and PSQI-C7 daytime dysfunction (Spearman $r = 0.41$, $p = 0.018$, $q$ value = 0.047).

Plegic spells occurring during sleep (sq24) were significantly correlated with PSQI-C2 sleep latency (Spearman $r = 0.45$, $p = 0.004$, $q$ value = 0.01) and PSQI component 5 (Spearman $r = 0.49$, $p = 0.001$, $q$ value = 0.01).

### Logistic Regression Model

We built a multiple logistic regression model using a global PSQI score ≥ 5 or <5 as the dependent variable (Figure 5). Predictors were age, epileptic seizure frequency, plegic spells, dystonic spells, and plegic spells during sleep. Our predictors were able to classify individuals with a PSQI score ≥5, with an AUC of 0.77 ($p = 0.04$).

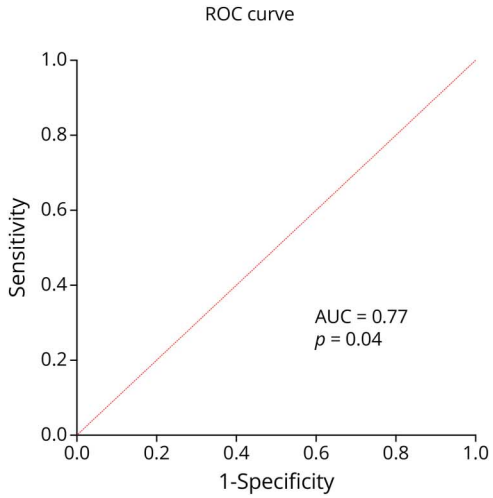
## Discussion

This is a comprehensive survey of self-reported or family-reported AHC-related sleep issues including pediatric and adult individuals. Sleep disruption has been discussed among the AHC community for years. Anecdotally, many with lived experience of AHC have reported that sleep can be challenging. Our survey has demonstrated sleep disturbances in a relatively large AHC international cohort across different age groups.

Children up to 12 years old are recommended to sleep at least 7–9 hours per day.[21] Modern lifestyles, living environments, and climate change are affecting time, duration, and quality of sleep for many people.[21-24] Recently, a UK survey on 2000 adults revealed a high burden of sleep problems, calling for the Government to develop a National Sleep Strategy to tackle the problem.[25] These effects might be worse in difficult-to-treat, complex, and rare neurodevelopmental disorders with or without epilepsy.[26]

Approximately one-half of our cases reported sleep disruption, which most described as persistent and highly disabling. We also attempted to further dissect the clinical features of AHC-related sleep disruption, by collecting data regarding number and duration of arousals per night, impact of "bad nights" on the next day, effect of jetlag, seasonality, and disruption of their regular routine. Our findings suggest that these factors all contribute to AHC-related sleep disruption. Moreover, several individuals from this cohort reported

**Figure 5** Multiple Logistic Regression Model




| Variable | Odds ratio | 95% CI (profile likelihood) |
|---|---|---|
| Intercept | 0.1978 | 0.01634 to 1.660 |
| Age | 0.9786 | 0.9260 to 1.029 |
| AHC paroxysmal spells burden | 1.238 | 0.9542 to 1.673 |
| sq24[§] | 2.266 | 1.021 to 6.313 |

Multiple logistic regression model using global PSQI score ≥ 5 or <5 as the dependent variable. Predictors were age, epileptic seizure frequency, plegic spells, dystonic spells, and plegic spells during sleep. PSQI = Pittsburgh sleep quality index.

regularly taking medications to address their sleep issues. Notably, we cannot rule out that AHC itself might influence individuals' subjective experiences with crossing time zones because 30 of 44 respondents (68.2%) had never traveled to a different time zone.

Our study also highlighted that typical paroxysmal spells, such as plegic or dystonic spells, do not always resolve upon sleep in individuals with AHC. In fact, plegic spells can occur from sleep in a subset of individuals, as reported by caregivers. This empirical information challenges the conventional understanding outlined in the Aicardi criteria[7] (i.e., immediate disappearance of all symptoms on sleep). A "benign nocturnal AHC" form with recurrent plegic attacks arising exclusively out of sleep has been described, with a more favorable outcome compared with the classic AHC.[27-30] Our study showed that individuals with classic AHC may experience paroxysmal attacks from both wakefulness and sleep. However, we cannot rule out the possibility that spells reported from sleep may have actually occurred after an arousal.

The mean PSQI score was abnormal in our cohort. We demonstrated a clear relationship between several features of sleep and the burden of paroxysmal AHC spells, with a positive correlation between higher epileptic seizure frequency and greater variability of sleep in people with AHC. Of interest, a higher number of nocturnal arousals seem to be more associated with the occurrence of plegic spells while the duration of each arousal seems to be more related to the burden of dystonic spells. However, these findings are difficult to generalize, given the sample size and the highly heterogeneous clinical presentation.

An increased burden of both epileptic seizures and non-epileptic paroxysmal phenomena is significantly related to the PSQI score in our cohort. The analysis of PSQI components gave us the opportunity to further dissect the impact of AHC paroxysmal spells on sleep. Higher frequency of plegic spells was significantly correlated with the higher use of sleep medications (PSQI component 6). Higher frequency of dystonic spells was significantly correlated with higher sleep latency, lower sleep duration, worse sleep efficiency, and higher daytime dysfunction. We also found preliminary evidence that warm seasons might have a troublesome impact on people with AHC. We observed that the few people with AHC who filled the questionnaire during summer all had a PSQI score greater than 5. We previously discussed the complex relationship between climate change and neurologic diseases,[31] and we believe that it is essential to further investigate the impact of climate in rare neurologic conditions.[13] Our preliminary evidence may have biological plausibility, as demonstrated by the effect of temperature on the $Na^+/K^+$-ATPase channel.[32] Thus, people with AHC might be particularly vulnerable to elevated temperatures and climate change consequences.

Previous studies[9] failed to identify clinical factors associated with AHC-sleep disorders, possibly due to lack of adequate detailed lived experiences collected from individuals with AHC and their families. In this study, we observed that age and a higher frequency of seizures as well as dystonic or plegic spells, especially if occurring during sleep, might predict greater sleep disruption. Our model was able to predict a pathogenic PSQI score, with an AUC of 0.77.

Valuing "lived experience," we consider the open comment section a strength of our study, giving voice to people with AHC and/or their caregivers. "At night, even if he doesn't sleep during the day, waking up is a constant" (mentioned in the open comment section in Table 2)—many comments describe the difficulties eloquently.

Our study has several limitations, mainly due to the cross-sectional design of the survey, which may be influenced by biases such as ascertainment bias. In addition, not all individuals or families completed the survey, possibly because of the challenges in managing a life-threatening condition, which could mean that our data may underrepresent the most severe cases. Furthermore, all results and analyses are based solely on survey responses from AHC families, without polysomnographic confirmation. Another limitation is that we did not collect genetic data from our respondents—i.e., whether people with AHC had pathogenic variants in *ATP1A3* or other genes or had no genetic variants identified. Because the survey was anonymous, we could not collect individual-level genetic data. Although our findings suggest a possible effect of benzodiazepine and antiseizure medication polytherapy on sleep quality, we cannot draw causal inferences because of the limited sample size and cross-sectional design of the survey, and it remains challenging to disentangle the effects of epileptic seizures from those due to the burden of treatment.

The mechanisms underlying AHC-related sleep disruption are complex and multifactorial, and we do not claim to fully explain them. However, we believe that the relatively large international sample, the rigorous methodology with high internal consistency, and the detailed data collection make our results valuable.

We encourage the medical community to explore the unmet needs of rare neurodevelopmental disorders such as AHC. Our results clearly show the importance of conducting comprehensive and periodic assessments for sleep disruption in both children and adults with AHC, which may have significant repercussions on prognosis and treatment strategy, as well as on their caregivers and their quality of life.

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## Author Contributions

F. Fortunato: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. U. Vivekananda: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K.E. Behl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R. Vavassori: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R. Cordani: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Stagnaro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. E. De Grandis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S.M. Sisodiya: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Balestrini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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