BRAIN
A JOURNAL OF NEUROLOGY

Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults

Eleni Panagiotakaki,[1] Giuseppe Gobbi,[2] Brian Neville,[3] Friedrich Ebinger,[4] Jaume Campistol,[5] Soňa Nevšímalová,[6] Laura Laan,[7] Paul Casaer,[8] Georg Spiel,[9] Melania Giannotta,[2] Carmen Fons,[5] Miriam Ninan,[3] Guenter Sange,[9] Tsveta Schyns,[10] Rosaria Vavassori,[10] Dominique Poncelin,[10] The ENRAH Consortium[10],* and Alexis Arzimanoglou[1,11]

1 Institute for Children and Adolescents with Epilepsy (IDEE), Hôpital Femme Mère Enfant, University Hospitals of Lyon (HCL), France
2 Child Neurology Unit, Department of Neuroscience, Maggiore Hospital, Bologna, Italy
3 Institute of Child Health, UCL, London, UK
4 Department of Child Neurology, Heidelberg University Hospital, Germany
5 Department of Neurology, Sant Joan de Deu Hospital, Barcelona, Spain
6 Department of Neurology, Charles University, 1st Faculty of Medicine and Teaching Hospital, Prague, Czech Republic
7 Department of Neurology, K5Q, Leiden University Medical Centre, Leiden, The Netherlands
8 Department of Paediatrics University Hospital Gasthuisberg, Leuven, Belgium
9 Department of Neurology and Psychiatry of Children and Adolescents, General Hospital, Klagenfurt, Austria
10 The ENRAH Consortium
11 Inserm U821 and TIGER Research Group, Lyon, France

*The members of the The ENRAH Consortium are listed in the Appendix 1.

Correspondence to: Pr. Alexis Arzimanoglou,
Head of the Institute for Children and Adolescents with Epilepsy (IDEE),
Hôpital Femme Mère Enfant,
Hospices Civils de Lyon,
59 Boulevard Pinel, 69677,
LYON, France
E-mail: aarzimanoglou@orange.fr

Alternating hemiplegia of childhood is a neurological disorder characterized by episodes of hemiplegia, various non-epileptic paroxysmal events and global neurological impairment. Characterization of the evolution and outcome into adulthood has not been sufficiently investigated. The goal of this study was to elucidate the natural history of alternating hemiplegia within a large cohort of 157 patients, as part of the European Network for Research on Alternating Hemiplegia project. A questionnaire was formulated to determine the severity of both paroxysmal and global neurological impairment and address progression of the disorder by allocating data to specific age epochs up to and over 24 years of age. Patients in early age groups were consistently present in subsequent later age groups and for each patient, data were collected for each corresponding age epoch. The study was based on predominantly retrospective and, for a period of 2 years, prospective data. At inclusion, patients were aged from 9 months to 52 years. The median age at diagnosis was 20 months. All patients experienced hemiplegic attacks; 86.5% reported episodes of bilateral weakness, 88% dystonic attacks, 53% epileptic seizures, 72% developed chorea and/or dystonia and 92% mental retardation. When data over the course of the illness were examined for the whole cohort, the severity of symptoms did not appear to change, with the exception of abnormal ocular movements and hypotonia that regressed, but did

not disappear into adulthood (from 86 to 36% and 76 to 36%, respectively). No statistically significant correlation between a history of severe paroxysmal hemiplegic/dystonic episodes and a worse neurological outcome was identified. Seven patients died, some of whom experienced severe plegic attacks or epileptic seizures at the time of death. History of severe plegic/dystonic attacks was not found to be an aggravating factor for deceased patients. Our results provide evidence that the natural history of alternating hemiplegia is highly variable and unpredictable for individual patients. However, we did not find evidence to support a steadily progressive and degenerative course of the disorder when patients were analysed as a group. For a minority of patients, a risk of sudden death was associated with more severe neurological impairment. The European Network for Research on Alternating Hemiplegia Registry, validated by our study, includes all major neurological signs and symptoms of alternating hemiplegia and may thus be used as a precedent for the progressive inclusion and follow-up of patients as well as a reference for genetic studies and treatment trials.

Introduction

Alternating hemiplegia of childhood (AHC) is a disorder characterized by transient episodes of alternating hemiplegia/hemiparesis and often tetraplegia as well as other paroxysmal manifestations (dystonic attacks, paroxysmal nystagmus, episodes of autonomic disturbances and epileptic seizures) starting in the first 18 months of life (Verret and Steele, 1971; Aicardi, 1987). Between attacks, patients have an abnormal neurological examination with signs of ataxia, involuntary abnormal movements (such as athetosis or chorea) and the majority develop mental retardation (Bourgeois *et al.*, 1993). The condition was initially described in 1971 (Verret and Steele, 1971) and other authors have since added to the description (Dittrich *et al.,* 1979; Krägeloh and Aicardi, 1980). The disappearance of paroxysmal symptoms with, and immediately following sleep was reported for the first time in 1987 (Aicardi, 1987). Several authors suggested that similar pathophysiological mechanisms with hemiplegic migraine could be implicated in AHC (Golden and French, 1975; Hosking *et al.*, 1978; Hockaday, 1979). However, fixed neurological deficits are unusual in hemiplegic migraine and the overall clinical picture and evolution are very different (Verret and Steele, 1971; Hockaday, 1979). Approximately half of patients present with epilepsy and seizures may sometimes occur simultaneously with plegic/dystonic attacks (Neville and Ninan, 2007). The seizures are predominantly partial but may manifest as status epilepticus requiring urgent medical attention (Aicardi *et al.*, 1995b).

Onset of the disease usually occurs before the age of 6 months (sometimes in the neonatal period) with repeated tonic/dystonic attacks and paroxysmal (often monocular) nystagmus, with hemiplegic and bilateral events appearing later (Aicardi *et al*., 1995a; Sweney *et al.*, 2009). During hemiplegic events a varying intensity of paralysis may occur from one moment to another and can sometimes alternate between sides during the same episode, often mixed with dystonia. Consciousness is preserved during episodes that can last from a few minutes to several days. Bilateral plegic attacks, monocular nystagmus and other abnormal ocular movements like paroxysmal strabismus (Bursztyn *et al.*, 2000) are considered to be highly characteristic of the disease (Aicardi, 1987).

Due to the rare nature of the disorder, estimated at about one in a million, previous reports have not sufficiently investigated outcome of AHC in adulthood. The present study describes the data obtained from the largest cohort of AHC patients to date; a European web-based registry that was created within the ENRAH project (European Network for Research on Alternating Hemiplegia; http://www.enrah.net). The aim was to collect, review and evaluate the clinical aspects of almost all known cases of the disease in the participating countries, with emphasis on the natural history and long-term outcome of the disease.

Materials and methods

The ENRAH project

The ENRAH is a non-profit European organization, initiated through a project funded by the European Commission within the sixth Framework Programme (scheduled between April 2005 and June 2007). The ENRAH was established by patient organizations and health workers with the goal to promote knowledge, communication and research concerning AHC.

To assess the clinical presentation of AHC with age, a questionnaire was designed to gather information on the clinical presentation of AHC at specific ages from a total of 157 patients. The questionnaire was structured as a multiple choice to include specific questions that were repeated for each age group (Appendix 1 in online Supplementary material). Any further information was written on space provided, as required. The questionnaire was developed through comprehensive discussions within the ENRAH group and validated by the treating child neurologists (E.P., G.G., B.N., F.E., J.C., S.N., L.L., P.C., G.S. and A.A.).

Data collection

Data were collected retrospectively for the period preceding the onset of the project and prospectively between April 2005 and June 2007 from paediatric neurology university centres from nine European countries (see below). Data collection was undertaken by 12 delegated participating clinicians (one or two per reference centre) with the informed consent of the patient and/or his/her legal representative, after approval from independent national ethics committees, in

accordance with European and national legislation and regulations. The delegated clinicians completed the questionnaire either after direct contact with patients and/or after medical records revision and using additional information provided by the treating physician (paediatrician, paediatric neurologist, neurologist or other practitioner) or family. For each of the patients, data were collected for every corresponding age epoch. The final visit (prospective) corresponded to the age of the patient at inclusion in this study. An average evaluation over a period of years was obtained after reviewing subsequent clinical visits and completing information by interviewing family and physicians. National parent associations assisted in the collection of data and guided physicians to contact patients. To ensure a consistent standard of collected information throughout the study, regular meetings were held between the participating clinicians.

Following initial data collection, one member of the ENRAH Validation Committee (A.A., B.N. or G.G.) reviewed data from a particular centre (data were not reviewed from a centre by a residing member). Any queries raised by a Committee member were discussed with the delegated clinician, who provided any further information sometimes through discussion with the previously treating physician or family members. Patient data were ultimately scrutinized again by the Validation Committee who together reviewed the final 157 included cases. Information of these 157 patients was subsequently transferred in an electronic form to the European Registry. This electronic database is available on a secure Internet site (HC Forum® Internet platform) and access to the registry is secured by the use of a smart card (an integrated circuit card requiring a password and card reader). These data are accessible only to project participants or other persons with a research interest, following approval by the Steering Committee of ENRAH.

The participating paediatric neurology university centres included: (i) Department of Neurology and Psychiatry of Children and Adolescents, General Hospital, Klagenfurt, Austria; (ii) Department of Paediatrics University Hospital Gasthuisberg, Leuven, Belgium; (iii) Department of Neurology, Charles University, First Faculty of Medicine and Teaching Hospital, Prague, Czech Republic; (iv) Department of Paediatric Neurology, Robert Debré Hospital, APHP, Paris, France; (v) Institute for Children and Adolescents with Epilepsy (IDEE), Women and Children's Hospital, University Hospitals of Lyon (HCL), France; (vi) Department of Child Neurology, University Hospital of Heidelberg, Germany; (vii) Child Neurology Unit, Department of Neuroscience, Maggiore Hospital Bologna, Italy; (viii) Department of Neurology, K5Q, Leiden University Medical Centre, Leiden, The Netherlands; (ix) Department of Neurology, Hospital Sant Joan de Deu, Barcelona, Spain; and (x) the Neurosciences Unit, the UCL Institute of Child Health, London, UK.

Patient inclusion

A total of 157 patients with AHC (87 females and 70 males) were included in this study. At inclusion patients were aged between 9 months and 52 years; and included two pairs of siblings, of which one were monozygotic female twins.

Some of the subjects may have been included in previously published studies, particularly 20 out of 54 patients of French origin who were included in the series of Sweney *et al.* (2009). However, all of the information regarding patients included in our study was collected and reviewed independently of all prior studies. Particularly for the 20 patients of French origin, data on last visit(s) was collected prospectively by the same investigator (E.P.) in collaboration with the treating paediatric neurologist and the family. Seven diagnostic criteria for AHC were used for inclusion (Table 1).

Table 1 Diagnostic criteria used for patient inclusion

1 Onset of paroxysmal events before 18 months of age.
2 Repeated bouts of hemiplegia involving right and left side of the body in some attacks.
3 Episodes of bilateral hemiplegia or quadriplegia starting either as generalization of a hemiplegic episode or bilateral from the start.
4 Other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnoea and other autonomic phenomena occurring during hemiplegic bouts or in isolation.
5 Immediate disappearance of all symptoms upon sleep, with probable recurrence of long-lasting bouts 10–20 min after awakening.
6 Evidence of developmental delay, mental retardation, neurologic abnormalities, choreoathetosis and dystonia or ataxia.
7 Not attributable to other disorders.

The ENRAH validation Committee agreed that, given the lack of an AHC biological marker, the criteria 1 (onset <18 months), 2 (bouts of alternating hemiplegia), 3 (bilateral hemiplegia) and 7 (the fact that the symptoms present could not be attributable to another disorder) are mandatory for considering a patient as having a 'typical' AHC form. However, for the few patients that evolution allowed confirmation of AHC diagnosis at inclusion into our study, the diagnosis of a typical form was accepted even if the exact age at onset (criterion 1) or the presence of episodes of bilateral hemiplegia could not be retraced with certainty from the patient file (especially because of the retrospective nature of a majority of data with information sometimes going back decades). Cases with abnormal laboratory findings were included (e.g. an abnormal cerebral imaging), if clinical presentation was typical of AHC and such a finding, when taken alone, could not explain the clinical picture (criterion 7).

On their own, none of the AHC diagnostic criteria can be considered as pathognomonic. In clinical practice, it is the co-existence of some of the signs and symptoms, and for some cases later evolution, that allow diagnosis. Consequently, for our study, we considered that the presence of highly suggestive symptoms, such as abnormal eye movements in very young patients, and/or the inhibitory effect of sleep, reinforced the diagnosis of 'typical' AHC.

Information collected

The questionnaire is given in Appendix 1 in online Supplementary material. General information included a detailed family history to investigate the presence of neurological disease, migraine, epilepsy and other paroxysmal disorders in the family. Medical history was subsequently collated to include pregnancy and delivery details, growth and other somatic complaints, as well as the presence of any comorbidities. Characteristics of paroxysmal events were detailed, as were the presence of premonitory signs or aura and any beneficial effects of sleep (disappearance of paroxysmal symptoms). During the course of the disease, epileptic episodes were distinguished from usual paroxysmal events (plegic, dystonic attacks) on the basis of clearly different clinical presentation and by the presence of an ictal electroencephalogram or abnormal interictal electroencephalographic tracings, which contrasted with previous normal or non-specific tracings.

We searched for the presence of neurological signs between paroxysmal events, such as abnormal movements (chorea, dystonia, myoclonus and tremor), abnormalities associated with independent walking

and gross and fine motor skills, mental retardation and behavioural and communication problems. The questionnaire also addressed school attendance and social integration in adulthood.

To assess disease severity with age, detailed information concerning paroxysmal and non-paroxysmal features was collected for different age epochs: 0–2, 2–6, 6–12, 12–18, 18–24 and >24 years. Laboratory tests, imaging, neurophysiological and other investigations were also included and classified according to age group, together with information of different treatments (relative efficacy) and trigger events and alleviating factors of the paroxysmal events.

Data analysis

To assess the severity of paroxysmal hemiplegic/dystonic events and other more general disabling effects a 'paroxysmal disability index' and a 'non-paroxysmal disability index' were developed, respectively, on the basis of the most characteristic signs and symptoms of the disorder.

To determine if the severity of attacks was related to a poor prognosis, we firstly searched for a correlation between the values of paroxysmal and non-paroxysmal disability indices for each age group using the Pearson correlation coefficient (Microsoft Office Excel 2003). Secondly, in order to identify a cumulative effect of severe attacks with time, and for patients with a sufficiently long follow-up period (12–18 years), we compared the mean value of paroxysmal disability indices from all age epochs investigated for each patient with their final non-paroxysmal disability index at the end of the follow-up.

For the purpose of statistical evaluation, the effect of age on paroxysmal and non-paroxysmal indices was calculated initially using data from all patients and subsequently excluding atypical cases and also two cases with chromosomal abnormalities and one case with a cerebral structural abnormality (polymicrogyria).

To determine if the severity of attacks or if the severity of global disability was related to sudden death, the non-parametric Mann–Whitney test (Wilcoxon test) was used to compare the values of paroxysmal disability indices, non-paroxysmal disability indices and the final non-paroxysmal indices between the groups of deceased and non-deceased patients.

Determination of 'paroxysmal disability index'

The 'paroxysmal disability index' was based on the three major variables that determine the extent of plegic and dystonic attacks: (i) severity; (ii) frequency and (iii) duration. It is defined as the sum of scores allocated to the three variables, divided by the total number of available variables.

The three variables were determined for both plegic and tonic/dystonic attacks (maximum of six variables/patient) and were scored as follows: (i) severity, number of extremities involved (one limb = 1 point, more than one limb = 2 points, both sides or 4 limbs = 3 points); (ii) frequency (<1 attack/year = 1 point, monthly attacks = 2 points, weekly = 3 points, daily = 4 points); and (iii) duration (<1 h = 1 point, 1–6 h = 2 points, 6–12 h = 3 points, 12–24 h = 4 points, >24 h = 5 points).

Determination of 'non-paroxysmal disability index'

The severity of global neurological impairment is described as the 'non-paroxysmal disability index', calculated for every patient in different age groups and at the end of the follow-up period. The non-paroxysmal disability index was defined as the sum of scores allocated to a possible seven variables, divided by the number of available variables: (i) the ability to walk independently (independent walking = 0 points, walking with help = 1 point, not possible = 2 points); (ii) behavioural disorder (no = 0 points, yes = 1 point); (iii) communication disorder (no = 0 points, yes = 1 point); (iv) gross motor abnormalities; (v) fine motor abnormalities; (vi) movement disorders (chorea, dystonia, myoclonus, tremor and complex movement disorders); and (vii) mental retardation [variables (iv–vii) were quantified as follows: none = 0 points, mild = 1 point, moderate = 2 points, severe = 3 points].

Results

Data on 157 patients (87 females and 70 males), aged between 9 months and 52 years were collected. Most were of Caucasian origin, and as a group were of short stature and low weight, in comparison to mean values according to age (Table 2). The median age at diagnosis of the disease was 20 months. Two specific family histories were reported: one female patient with a sister with autism and one male patient with a sister suffering from velocardiofacial syndrome.

Sixteen patients were considered as 'atypical' when mandatory clinical symptoms were lacking and overall evaluation could not provide sufficient evidence (13/157) or when additional features (3/157) were present (polymicrogyria in one patient and karyotypic abnormalities in two); however, the clinical phenomenology of those three patients was highly evocative of AHC and could not be attributed to the above co-morbidities.

Concerning disease evolution, no major difference was found in statistical analyses when the 16 'atypical' cases were included.

Table 2 Demographics

Number of patients within specific age groups[a]		Height centiles (at the end of follow-up)		Weight centiles (at the end of follow-up)	
0–2 years	157	<2nd percentile	6 patients	<2nd percentile	14 patients
2–6 years	144	2–10th percentile	20 patients	2–10th percentile	19 patients
6–12 years	107	10–25th percentile	23 patients	10–25th percentile	24 patients
12–18 years	70	25–50th percentile	27 patients	25–50th percentile	27 patients
18–24 years	37	50–75th percentile	23 patients	50–75th percentile	14 patients
>24 years	14	75–90th percentile	3 patients	75–90th percentile	7 patients
		90–98th percentile	1 patient	90–98th percentile	4 patients

a Patients in early age groups were consistently present in subsequent later age groups.

Overall clinical presentation of alternating hemiplegia of childhood

Semiology of paroxysmal events

The median age at first attack was 3.5 months (between the first day of life and four years) and the first hemiplegic events occurred at a median age of 7 months (between the first month and eight years). Attacks of hemiplegia were the first sign of the disease in only 30% of patients (n = 47), for the remainder, hemiplegia followed other paroxysms with a median delay of 5 months. Neurological episodes during the neonatal period were noted in 12.5% of patients (n = 20) and varied from unusual behaviour and presumed seizures to clearly identified early onset dystonic, autonomic or ocular attacks. Five children experienced their first episode on the first day of life, manifested mainly by ocular movements and dystonic attacks (usually limbs stiffening with a vibratory tremor, but sometimes torticollis or opisthotonus) or an episode of marked hypotonia.

All patients experienced hemiplegic attacks (criterion 2). The majority of patients (152/157) also presented with other paroxysmal phenomena (criterion 4). Hemiplegic attacks usually involved one upper and an ipsilateral lower limb, but could involve either only one limb, or limbs on contralateral sides. The paralysis was usually characterized by a flaccid weakness without pyramidal signs. During attacks the face was usually spared, however, facial hemiparesis did occur with mouth deviation and slurred speech. Two children described an inability to speak only when hemiparesis was on the right side and continued to speak normally when paralyzed on the left. Eighty-eight percent (138/157) of patients also experienced tonic/dystonic attacks involving one limb or two or more limbs on ipsilateral or contralateral sides of the body and occurring alone or mixed with hemiplegic episodes. Dystonic attacks could also involve the tongue causing difficulties in breathing and swallowing. Some children appeared cyanotic and experienced a feeling of suffocation during dystonic attacks; these episodes were reported to be particularly stressful.

During bilateral plegic attacks (86.5% of patients), children were unable to swallow and experienced excessive salivation and drooling. Those with language already acquired were unable to speak during these episodes and most patients were unable to eat and at best could only accept crushed foods. During most of these attacks, patients were conscious, but some were somnolent and appeared lethargic. During bilateral attacks, autonomic disturbances including cardiorespiratory problems were very pronounced and comprised bradycardia, stridor, bronchospasm, hyperventilation, noisy breathing, gasping for breath or apnoeic spells. In some cases, intestinal motility was accelerated.

Autonomic phenomena (during bilateral, other attacks or alone) were present in 65% of patients (102/157) and also included a reddening or pallor of the face, fever, tachycardia or bradycardia and mydriasis. Apnoeic spells sometimes required a monitoring device at home, and in very severe cases, intubation and mechanical ventilation were performed.

Paroxysmal abnormal ocular movements were present in 91% of patients (143/157) and included unilateral or bilateral and horizontal, vertical or rotatory nystagmus, as well as tonic upgaze or tonic lateral deviation of the eyes. Ocular movements sometimes involved convergent strabismus or loss of convergence. In one child, one eye was directed upwards and the other downwards during a paroxysmal episode. Eye movements were predominantly homolateral to the side of paralysis (if they presented concomitantly with attacks of hemiplegia).

Headaches were reported by 58% (53/91) of patients, in whom the presence or absence of headache could be ascertained; exclusion was made of patients younger than 6 years old (50 patients) and of those with mental retardation or communication problems who were unable to answer definitively (16 patients). Headache was either in the form of classic isolated migraine (16%; 15/91) or in the form of migraine or headache with hemiplegia. Localized pain in affected limbs during attacks was sometimes severe to the point that, in one child, regular morphine administration was required.

Epileptic seizures were experienced by 53% of patients (83/157), at least once in their lifetime. Epileptic seizures tended to be mostly focal or focal with secondary generalization (in 45–67%, according to age), although three out of the four patients over 24 years of age who had epilepsy, presented with generalized seizures. Overall, seizures were not very frequent and occurred one to six times a year for 52–75% of patients taking antiepileptic medication (percentages varied according to age group). Epilepsy of patients with AHC in our study was therefore relatively well controlled with medication. Five children presented unexplained episodes of explosive, violent laughter accompanied by limb movements, terror and ocular movements or mydriasis. In most of these children these episodes were interpreted as epileptic seizures and in one patient they decreased after vagus nerve stimulation implantation.

Premonitory signs or aura before paroxysmal episodes were reported by 41% of patients (64/157). Some of these patients exhibited a different behavioural pattern and appeared irritable. Others reported a sensation of pinpricks or discomfort of the hands or feet that later spread to adjacent parts of the body in an ascending or descending manner, with a progression of paralysis. One child described a sore throat before attacks, concomitant with a strange sensation in the hand.

The inhibitory effect of sleep on attacks was reported for the majority of patients (83%; 130/157). For 28 patients this information could not be confirmed with certainty. This was defined as loss of abnormal posture, the ability to move within the limit of what could be observed and uniquely normal motor function for a short period of 10–20 min on awakening. Relaxation in a calm environment (reassurance, music, massage and averting attention) was reported to have a beneficial effect on attacks. The number of attacks increased in adolescent/adult female patients during menstruation.

Long-term neurological impairment

At walking age (150/157 patients older than 2 years), gait was considered to be unsteady in 84% (126/150) of patients. Of the total number of 157 patients, 113 (72%) had long-term chorea and/or dystonia, 117 (75%) hypotonia and 144 (92%) developmental delay or mental retardation: 29 (18%) mild, 78 (50%)

moderate, 37 (23.5%) severe. Nine (6%) exhibited no retardation and for four (2.5%) there was insufficient information. The impact of paroxysmal events on school attendance and out-of-home activities was severe with only 34 patients attending for more than 90% of the expected time, 56 patients for 50–90% of time and 13 patients for <50% of time. For the remaining, 13 patients were of preschool age, eight were not following school due to very severe handicap, and no information was available for 33 patients. During adulthood, from a total of 37 adult patients, only one patient was working independently in employment, 13 patients were working in an assisted environment, 20 patients had never worked and for three patients there was no available information.

Evolution of clinical presentation of alternating hemiplegia of childhood in patients

Data during the first 2 years was available for all 157 patients. Further data corresponding to 2–6 years were available for 144 patients, 6–12 years for 107 patients, 12–18 years for 70 patients, 18–24 years for 37 patients and >24 years for 14 patients (Table 2). Clinical presentation at different age groups was analysed for all 157 patients and was similar to that of the subset of 14 patients, each with a follow-up period of >24 years (Figs 1 and 2).

Paroxysmal events

During the initial report (0–2 years) attacks of hemiplegia occurred in at least 93% (146/157) of patients. Prevalence of plegic attacks moderately decreased with age and by adulthood. Tonic attacks occurred initially in 74% (116/157) of patients and their prevalence remained relatively stable. During adulthood all patients continued to experience either plegic and tonic or only plegic attacks and only one patient experienced only tonic attacks. Episodes of abnormal ocular movements, characteristic of the disease in infancy and early childhood were present in 86% (135/157) of patients at 0–2 years, but were decreased to about a third of patients in the older age groups (18–24 and >24 years). Events of autonomic dysfunction were present in 49% (77/157) of patients at 0–2 years and their prevalence remained constant. The prevalence of epilepsy was relatively stable and varied between approximately one-third to less than half of patients in different age groups, with a peak frequency in adolescence.

Global neurological impairment

In this cohort all 157 patients presented neurological abnormalities in addition to paroxysmal events (they all fulfilled criterion 6). At 0–2 years, 84% (132/157) of patients experienced gross motor delay and gross motor skill abnormalities that remained constant with time and present in at least three-quarters of adult patients.
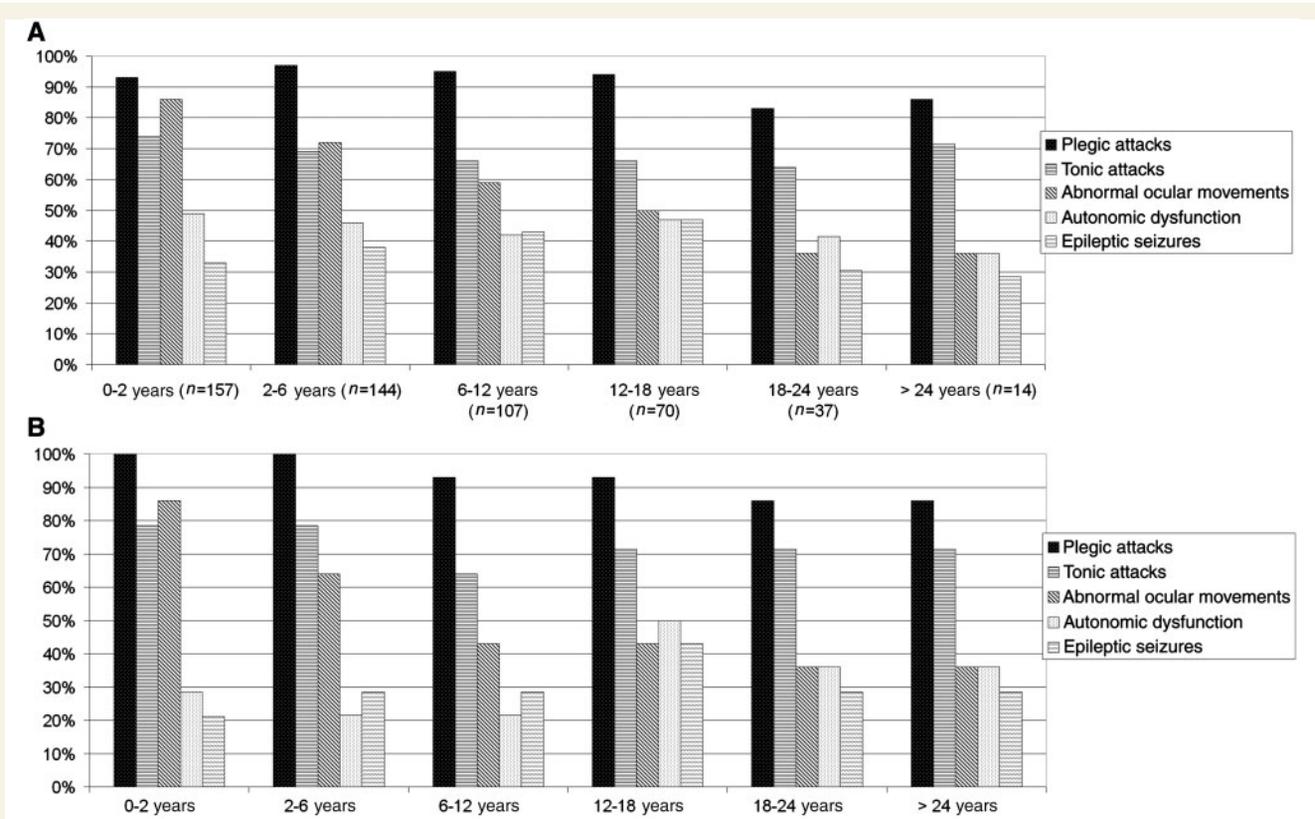

Figure 1 Paroxysmal features of AHC at different ages in (**A**) all patients and (**B**) a subset of 14 patients each with at least 24 years follow-up period.
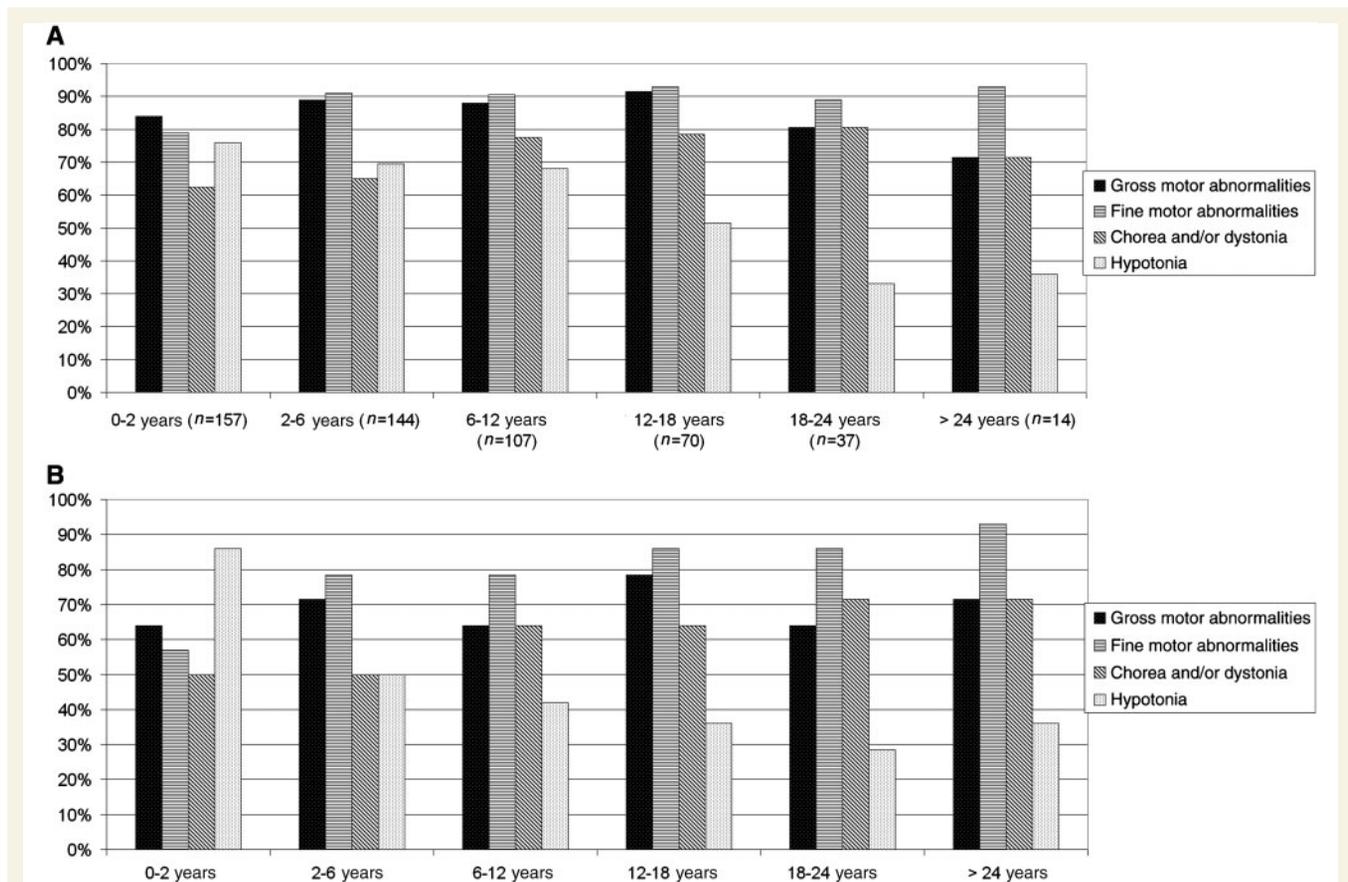
Figure 2 Non-paroxysmal features of AHC at different ages in (**A**) all patients and (**B**) a subset of 14 patients each with at least 24 years follow-up period.

Only 27% (41/157) of patients were able to walk without help at the age of 2 years. Likewise, 79% (124/157) of patients experienced fine motor delay at an early age. Fine motor skill abnormalities increased with age and were present in the vast majority of adult patients. This was also the case with chorea and dystonia. Hypotonia was present early in 76% (119/157) of patients, appeared to decrease with time and was present in only one-third of adult patients.

Effect of time on the paroxysmal and non-paroxysmal disability indices

The paroxysmal disability index was calculated for all patients at all time periods and the median values and standard deviations are presented in Fig. 3A. The results demonstrate that there was no significant difference in paroxysmal events with time, and the extent of plegic and tonic attacks remained fairly constant throughout the different age groups. There was no difference when analysis was performed after exclusion of the 16 atypical patients.

When the paroxysmal disability index was plotted against time for each patient individually, with a follow-up period of at least 18 years, significant variability of severity of paroxysmal attacks was observed between patients (Fig. 4A).

The effect of the non-paroxysmal disability index with time was analysed for all patients at all time periods (Fig. 3B). Similar to that of the paroxysmal disability index, it was not possible to identify a pattern of improvement or regression with time, although a high degree of individual variability was noted when the data of individual patients with a follow-up period of at least 18 years were plotted with time (Fig. 4B). There was no difference when analysis was performed after exclusion of the 16 atypical patients. Among the 37 older patients with a follow-up period of at least 18 years, three could be considered to follow a consistently progressive course.

Individually, a fluctuating course, characterized by alternating periods of more and less severe attacks and global disability was therefore a frequent feature, making any specific patterns of progression difficult to identify. Furthermore, no correlation was identified between the values of paroxysmal and non-paroxysmal disability indices for the different age groups ($r = -0.07$, -0.18, 0.01, 0.01, -0.15 and -0.42 for each age group in ascending order and after exclusion of the 16 aforementioned cases, $r = -0.09$, -0.2, -0.06, -0.006, -0.17 and -0.4). Also, no correlation was identified when the mean value of paroxysmal disability indices throughout lifetime (for older patients with a follow-up of at least 12–18 years), was compared with the final non-paroxysmal disability index at the end of the follow-up period
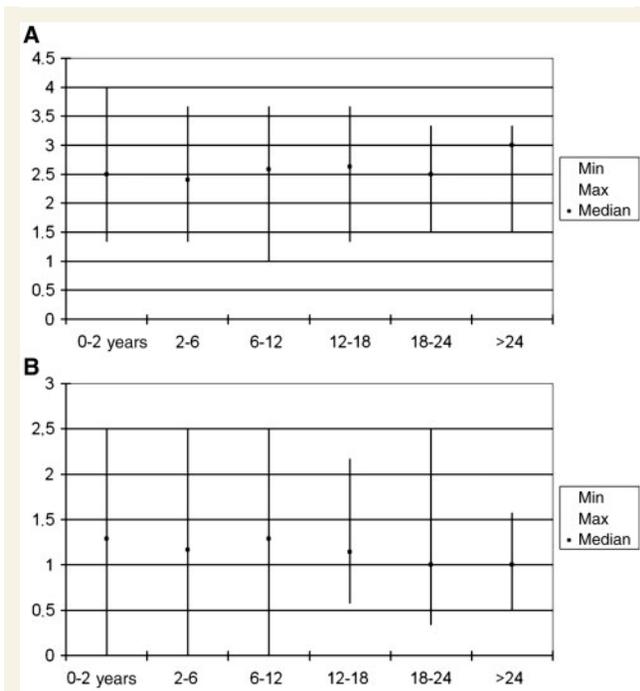
Figure 3 Median disability indices of all patients as a function of time. (**A**) Median values of paroxysmal disability index. (**B**) Median values of non-paroxysmal disability index. Bars depict standard deviation (1 or 2 SD).

($r = -0.06$, and after exclusion of the 16 atypical cases $r = -0.014$).

Patient deaths

Seven patients in this cohort died, one of whom died during the prospective period. One female patient died at the age of 25 years from cardiorespiratory failure. A 12-year-old male patient died after a very severe and prolonged state of quadriplegia and a second 12-year-old male died during an epileptic seizure complicated by cardiorespiratory arrest (the latter child was previously hospitalized in an intensive care unit for severe respiratory problems during bilateral attacks). Two female patients died at the age of 2 years following a very severe attack characterized as status epilepticus, although some months before frequent plegic attacks, with or without epileptic seizures, were experienced. The 28-year-old patient who died during the prospective part of the study did so during a very prolonged plegic attack. During the few months that preceded his death he was experiencing predominantly bilateral and prolonged (>24 h) attacks. The last patient died at the age of 3.5 years. No information was available about the circumstances of her death. Her principle paroxysmal events were bilateral plegic attacks which occurred weekly, lasting from 12–24 h, and were associated with autonomic dysfunction and were unresponsive to treatment. She had no epileptic seizures.

To identify disease characteristics associated with a risk of death, we compared the mean paroxysmal disability index between the groups of deceased and non-deceased patients. No significant difference was observed ($P = 0.6$). However, when either the mean non-paroxysmal disability index or final non-paroxysmal disability index was compared between the groups of deceased and non-deceased patients, both were significantly higher in the group of deceased patients ($P = 0.05$, 0.01, respectively; Fig. 5).

Laboratory investigations

The registry included the results of extensive investigations performed at various stages of the disorder, however, none were characteristic or informative and as such, are not reported in detail.

Magnetic resonance imaging abnormalities such as non-specific cerebral atrophy, discrete vermian atrophy, hippocampal sclerosis, cortical dysplasia and syringomyelia were reported in isolated cases. One patient presented extensive bilateral polymicrogyria with typical AHC clinical presentation. Characteristic hemiplegic events, provoked by excitement during clinical examination with no electroencephalographic modification, were reported (E.P., A.A.). The patient was included in the cohort on the basis that the clinical picture was not explained by cerebral imaging.

Two patients presented chromosomal abnormalities; one female demonstrated a 47, XXX karyotype and one male a translocation (t11,22) (q23;11.2), thus far unreported in patients with AHC (the mother and grandmother of the boy had the same translocation and were in good health). Both patients had a clinically typical presentation of AHC and were also included in the cohort.

Screening of the *ATP1A2* gene was performed in 20 patients, the *CACNA1A* gene in nine patients and the *SCN1A* gene in three patients, however no mutations were identified for any of the genes. Furthermore, no mutations associated with myoclonic epilepsy associated with ragged red fibres (MERRF) in three patients, or mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS) in six patients, were identified.

Treatment

The study was not specifically designed to evaluate treatment strategies and outcome. Patients received a number of different treatments simultaneously, furthermore, the natural progression of the disease is such that periods of 'ups' and 'downs', even without changes due to treatment, are common. We can therefore only report on the general impressions of treatment, as expressed by the patients themselves, their families or the physician.

Nearly all patients were given flunarizine as a prophylactic agent of non-epileptic attacks. Flunarizine was considered to be partially effective in 76% (108/141) of patients. Antiepileptic drugs, alone or in combination, were administered in nearly all patients for prophylaxis of paroxysmal non-epileptic (hemiplegic, dystonic attacks, etc.) as well as epileptic episodes. None of the drugs used had a prominent effect on non-paroxysmal events. Occasionally some reduction in frequency or severity of the paroxysmal events was reported. Benzodiazepines (and particularly diazepam) or some antiepileptic drugs were often used to reduce the duration of dystonic events, occasionally with success. Agents that induce sleep, such as melatonin, chloral hydrate and niaprazine, were also used during acute episodes. A minority of patients also tried other agents like neuroleptics, beta-blockers, L-dopa, antihistamines,
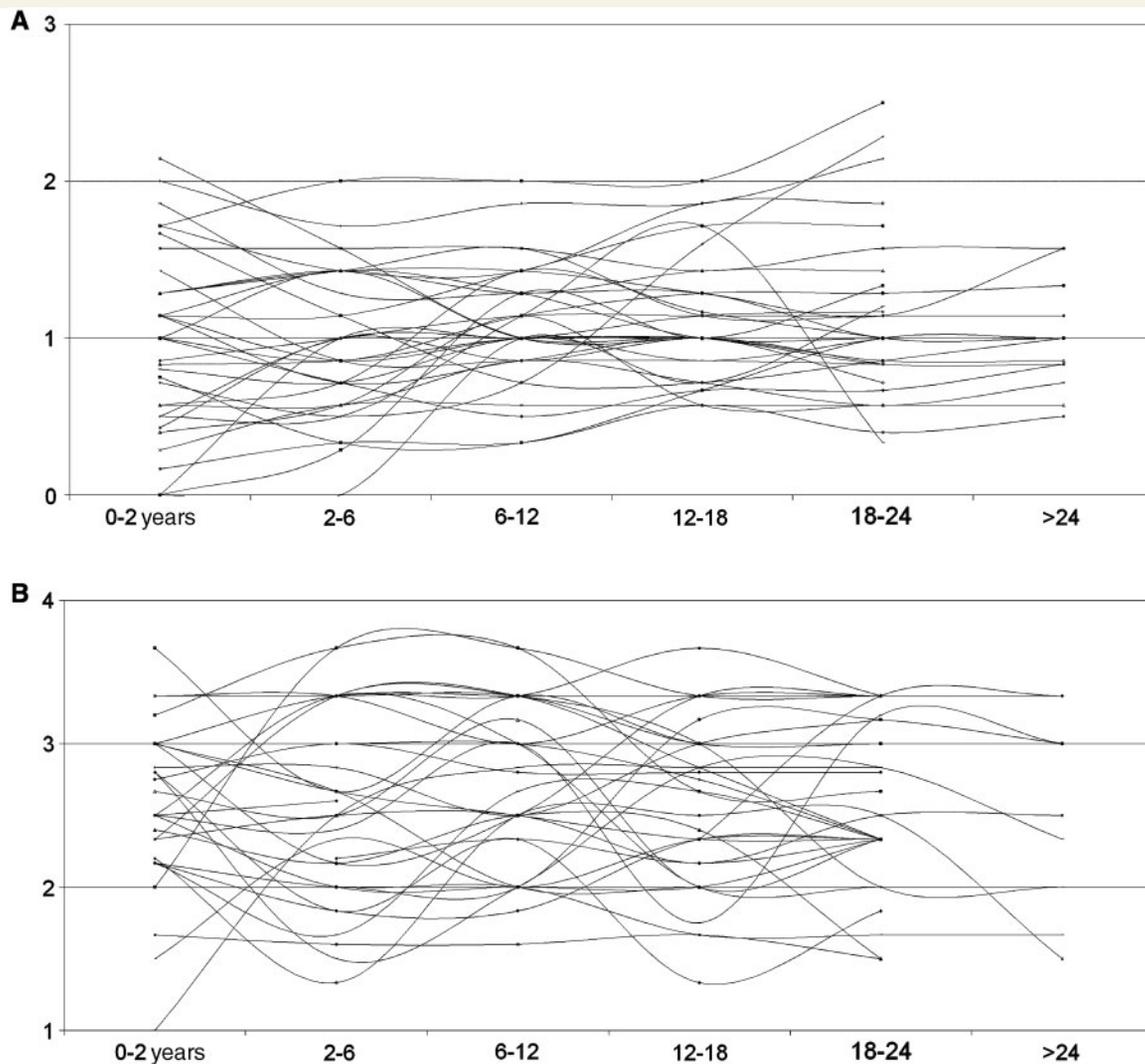
Figure 4 Paroxysmal (**A**) and non-paroxysmal (**B**) disability index values as a function of time for individual patients with available clinical information up to adulthood (at least 18 years of age, n = 37).

selective serotonin reuptake inhibitors and others, without clinically meaningful effect.

Two children were misdiagnosed with opsoclonus-myoclonus syndrome at an early stage and were treated with corticosteroids and immunoglobulins. For one child there was no improvement, however a marked improvement was observed for the other child, especially with steroid treatment.

Discussion

In this predominantly retrospective study, we investigated the clinical features of AHC in a cohort of 157 patients, which included 37 adults. Patients were from nine different European countries, within the ENRAH project, and to our knowledge this is the most extensive cohort of patients with AHC reported. Our results firstly emphasize the significant variability of the disease course between individuals, and secondly, indicate no general pattern of

progression, supporting the notion that AHC is a non-progressive or non-degenerative disorder.

General description of the disease is consistent with former studies. We identified an age of onset of between 0 and 50 months (median 3.5 months) in agreement with previous reports (Bourgeois *et al.*, 1995; Sakuragawa, 1995; Mikati *et al.*, 2000). Hemiplegic attacks were the first sign in only 30% of cases (similar to the series of Mikati *et al.*, 2000). Plegic attacks (hemiplegic or bilateral plegic events) occurred in all patients and were the main paroxysmal event of the disease. The second most common phenomena were abnormal ocular movements (91%) and tonic attacks (88%). Some authors (Bourgeois *et al.*, 1993; Sweney *et al.*, 2009) observed a similar high incidence for both the latter phenomena, although lower incidences of 65 and 60%, respectively, have also been observed (Mikati *et al.*, 2000). The prevalence of epileptic seizures varied between 28 and 47% depending on the age group (Fig. 1) and 53% of patients experienced epileptic seizures at least once in their lives,
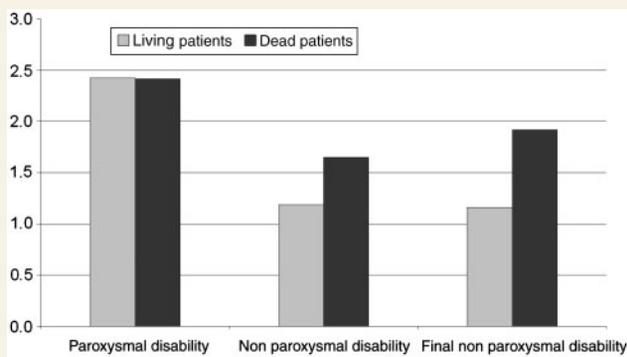
Figure 5 Comparisons of mean paroxysmal and non-paroxysmal index values and final non-paroxysmal index values between deceased and non-deceased patients.

in agreement with previous studies (Sakuragawa, 1995), although other authors have described a lower prevalence of epilepsy (Mikati *et al.*, 2000; Sweney *et al.*, 2009). Mental retardation was present in at least 92% of patients (of which 50% were moderately retarded) confirming previous reports (Bourgeois *et al.*, 1995; Sakuragawa, 1995; Mikati *et al.*, 2000; Sweney *et al.*, 2009).

Evolution of paroxysmal events

It has been reported that paroxysmal nystagmus disappears in all cases before the age of 10 years (Bourgeois *et al.*, 1995) and earlier reports indicated that tonic attacks tend to decrease in frequency and severity or even disappear with time after 5–7 years (Bourgeois *et al.*, 1993). Other authors have reported similar results (Aicardi, 1987; Siemes and Cordes, 1993; Silver and Andermann, 1993; Mikati *et al.*, 2000). The data of patients reported here indicate that the occurrence of abnormal ocular movements diminished in adulthood, but that these movements did not completely disappear in all patients. Occurrence of tonic attacks seemed to remain constant when analysis was performed for the whole patient group, however, there was significant individual variability. The same was true for hemiplegic phenomena.

Evolution of global neurological impairment

Neurological disability is present in all patients with AHC and a normal neurological examination should make one reconsider the diagnosis of AHC. For patients described here, gross motor abnormalities were reported early (Fig. 2) and were constantly present when the different age epochs were examined. Early in life, motor milestones were achieved with a variable delay. The majority of patients had an ataxic gait and they rarely acquired independent walking before 2 years of age. The prevalence of gross motor skill abnormalities was constant and was still present in at least three-quarters of patients in adult life.

Abnormalities of fine motor skills were present in the vast majority of patients and increased (or became more evident) with age, as previously reported (Bourgeois *et al.*, 1993). Abnormal movements like chorea and dystonia were present with frequencies similar to those in previous reports (Bourgeois

et al., 1993, 1995; Sakuragawa, 1995; Mikati *et al.*, 2000). The majority of patients (91.5%) presented some kind of abnormal movements (chorea, dystonia, myoclonus or tremor) in various combinations and degrees. Hypotonia generally improved with time and was present in only a third of adult patients.

Patients often had difficulties in acquiring speech and presented with attention deficit disorder or other behavioural problems as well as neuropsychological deficits that have previously been reported (Shafer *et al.*, 2005).

When the non-paroxysmal index was calculated on the basis of behavioural and communicative disability and mental retardation alone, in the absence of all motor disabilities; i.e. the 'cognitive severity index', no significant difference was identified with this index with time. However, an increase in behavioural troubles was observed for a subset of patients.

Patient deaths

Previous studies have reported unexplained sudden death of patients with AHC, however, due to the rarity of such cases, events have not been described in any detail. In our study, 4% (7/157) of patients died suddenly, usually associated with very severe attacks or seizures. For at least two cases, sudden death was associated with a severe and prolonged plegic episode and three other patients died during very prolonged episodes combining plegic phenomena with what was characterized as status epilepticus. During these episodes, patients presented a cardiorespiratory failure and died as a result of a cardiac arrest.

Whereas the severity of plegic/dystonic attacks was not increased in the group of deceased patients, the mean and final non-paroxysmal disability indices were significantly greater in this group. Moreover, the association of particularly severe plegic attacks or seizures at the moment of death suggests that autonomic disturbances are a precipitating factor of sudden death, reminiscent of sudden death associated with epilepsy. Accordingly, this would suggest the presence of factors, as yet unknown, that may influence susceptibility of sudden death; acquired or genetic factors that determine a worse neurological outcome and a shorter life span in some patients, independent of the burden of paroxysmal events.

Overall outcome

Our results suggest, in agreement with previous reports (Bourgeois *et al.*, 1993; Aicardi *et al.*, 1995*b*; Mikati *et al.*, 2000), that neurological signs of the disease become more apparent after the first years of life and overall, remain more or less fixed. This is in contrast to other reports (Nevšímalová *et al.*, 1994; Nishiki *et al.*, 1994; Gordon, 1995) that suggest a progressive neurological deficit. As shown in Figs 3 and 4, for the majority of patients there were no identifiable groups that differ in the severity of attacks or progression of general disability (improvement or regression). A decrease in variation was observed into adulthood (patients tended to be more 'similar' with age), although this difference may merely reflect the lower patient numbers. However, a significant degree of individual variability was observed and each patient exhibited his/her own disease course (Fig. 4).

Our results confirm that paroxysmal phenomena persist into adulthood. However, it remained unclear as to whether there was an eventual correlation between the severity of paroxysmal events and the evolution of neurological disability. Amelioration by different drugs can offer symptomatic improvement without necessarily altering the evolution in terms of final disability score, supporting the concept that the severity of paroxysmal events may not be directly related to an eventual severe outcome. In this study, we were unable to identify a correlation between paroxysmal and non-paroxysmal disability indices, further supporting the lack of evidence for a cause-and-effect relationship between the paroxysmal attacks and eventual overall neurological disability. The existence of more severe attacks and greater disability in some patients could simply be the expression of a more severe form of the disease due to differences in genetic and/or environmental factors.

In previous studies (Aicardi *et al.*, 1995*a*), as is the case for some patients in the present study, parents reported a loss of skills following very severe and prolonged, particularly bilateral, plegic episodes. In general, this loss of skills (in our study and previous studies) is not permanent, but recovery can last many months. However, patients usually lack a proper evaluation of skills, before and after recovery, and information is mainly based on the family's estimation of a child's neurological state. Moreover, in the present cohort some families paradoxically also reported the opposite situation, that is, an overall improvement and acquisition of new skills after a severe episode.

As is the case with other reports, recognition of early disease progression (in the first 2 years) was not possible since early time periods were based purely on a retrospective description, which were, furthermore, pooled from patients of different ages. A longitudinal study would be required to further overcome the limitations encountered in this study.

Aetiological factors

At present there is no biological marker specific for the disease. As a result patients generally undergo extensive investigations such as imaging, neurophysiological studies, biochemical and genetic tests, which are usually inconclusive. Some of the patients reported here had non-specific structural abnormalities based on magnetic resonance imaging scanning and an extensive bilateral polymicrogyria was identified in only one case. Previous reports (Sakuragawa, 1992; Saito *et al.*, 1998) have also mentioned structural abnormalities of unknown significance, such as cerebellar atrophy in four of 23 Japanese patients. Genetic screening for mutations in genes that encode for ion channel transporters (*ATP1A2, CACNA1A, SCN1A*) was negative, inconsistent with previous reports that identified one mutation in the *ATP1A2* gene (Kanavakis *et al.*, 2003; Bassi *et al.*, 2004; Swoboda *et al.*, 2004), but in agreement with other studies that did not identify mutations in the genes *ATP1A2, CACNA1A* and *SLC1A3* associated with familial hemiplegic migraine and episodic ataxia (Haan *et al.*, 2000; Kors *et al.*, 2004; De Vries *et al.*, 2006).

Treatment

A number of different drug treatments for AHC have been shown to be relatively unsuccessful in the past, with the exception of flunarizine (Casaer and Azou, 1984; Casaer, 1987; Silver and Andermann, 1993) with which open trials indicated a positive response for at least 75% of patients studied (Sakuragawa, 1995; Mikati *et al.*, 2000). We have obtained similar results with flunarizine, demonstrating at least partial efficacy in ~76% of patients. Topiramate has recently been proposed as an alternative to flunarizine (Di Rosa *et al.*, 2006; Jiang *et al.*, 2006). In this cohort, the drug was reported to be only moderately efficacious in six out of 20 patients. Drug efficacy is difficult to evaluate as the disease often exhibits a 'roller-coaster' course, with periods of aggravation and improvement. Moreover, the majority of patients often receive multiple drugs and it is difficult to attribute a positive result to any particular medication. There is a need for prospective double-blinded studies, although this may be limited by small patient numbers.

Conclusion

When all patients were examined collectively, the reported severity of clinical presentation and neurological disability remained constant with age, with the exception of abnormal ocular movements and hypotonia that appeared to regress, but not disappear, into adulthood. When analysed individually, however, the reported clinical presentation was sometimes highly variable with age.

For 7/157 patients, sudden death occurred, sometimes associated with severe plegic attacks and epileptic seizures. Patients who suffered sudden death, however, did not generally experience more severe plegic/dystonic attacks than other patients, but severity of global neurological impairment was significantly higher in the group of deceased patients. We speculate that increased autonomic dysfunction is a precipitating factor for sudden death.

In summary, on the basis of the largest cohort of patients with AHC to date, we present data suggesting that the natural history of the disorder is variable in severity and rather unpredictable. However, when patients were analysed as a group, we did not find strong evidence suggesting a steady progressive and degenerative course. Although much attention was given to accuracy of data collection, definitive conclusions are nonetheless subject to the partly retrospective nature of the study. A prospective European–US study, although very difficult to perform, may be needed to further explore the overall evolution of the disorder.

Acknowledgements

Funding

Supplementary material

Supplementary material is available at *Brain* online.

References

Aicardi J. Alternating hemiplegia of childhood. International Pediatrics 1987; 2: 115–9.

Aicardi J, Bourgeois M, Fusco L, Vigevano F, Silver K, Andermann F. Alternating hemiplegia of childhood: an overview. In: Andermann F, Aicardi J, Vigevano F, editors. Alternating hemiplegia of childhood. New York: Raven Press; 1995a. p. 207–12.

Aicardi J, Bourgeois M, Goutières F. Alternating hemiplegia of childhood: clinical findings and diagnostic criteria. In: Andermann F, Aicardi J, Vigevano F, editors. Alternating hemiplegia of childhood. New York: Raven Press; 1995b. p. 3–18.

Bassi MT, Bresolin N, Tonelli A, Nazos K, Crippa F, Baschirotto C, et al. A novel mutation in the *ATP1A2* gene causes alternating hemiplegia of childhood. J Med Genet 2004; 41: 621–8.

Bourgeois M, Aicardi J, Goutières F. Alternating hemiplegia of childhood. J Pediatr 1993; 122: 673–9.

Bourgeois M, Nevšímalová S, Aicardi J, Andermann F. Alternating hemiplegia of childhood: long-term outcome. In: Andermann F, Aicardi J,

Vigevano F, editors. Alternating hemiplegia of childhood. New York: Raven Press; 1995. p. 49–54.

Bursztyn J, Mikaeloff Y, Kaminska A, Plouin P, Soufflet C, Dulac O, et al. Alternating hemiplegia of childhood and oculomotor anomalies. J Fr Ophtalmol 2000; 23: 161–4.

Casaer P. Flunarizine in alternating hemiplegia in childhood: an international study in 12 children. Neuropediatrics 1987; 18: 191–5.

Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. Lancet 1984; 2: 579.

De Vries B, Haan J, Stam AH, Vanmolkot KR, Stroink H, Laan LA, et al. Alternating hemiplegia of childhood: no mutations in the glutamate transporter EAAT1. Neuropediatrics 2006; 37: 302–4.

Di Rosa G, Spanò M, Pustorino G, Ferrari MD, Stam AH, Sgrò DL, et al. Alternating hemiplegia of childhood successfully treated with topiramate: 18 months of follow-up. Neurology 2006; 66: 146.

Dittrich J, Havlová M, Nevšímalová S. Paroxysmal hemipareses in childhood. Dev Med Child Neurol 1979; 21: 800–7.

Golden GS, French JH. Basilar artery migraine in young children. Pediatrics 1975; 56: 722–6.

Gordon N. Alternating hemiplegia of childhood. Dev Med Child Neurol 1995; 37: 464–8.

Haan J, Kors EE, Terwindt GM, Vermeulen FL, Vergouwe MN, van den Maagdenberg AM, et al. Alternating hemiplegia of childhood: no mutations in the familial hemiplegic migraine CACNA1A gene. Cephalalgia 2000; 20: 696–700.

Hockaday JM. Basilar migraine in childhood. Dev Med Child Neurol 1979; 21: 455–63.

Hosking GP, Cavanagh NP, Wilson J. Alternating hemiplegia: complicated migraine of infancy. Arch Dis Child 1978; 53: 656–9.

Jiang W, Chi Z, Ma L, Du B, Shang W, Guo H, et al. Topiramate: a new agent for patients with alternating hemiplegia of childhood. Neuropediatrics 2006; 37: 229–33.

Kanavakis E, Xaidara A, Papathanasiou-Klontza D, Papadimitriou A, Velentza S, Youroukos S. Alternating hemiplegia of childhood: a syndrome inherited with an autosomal dominant trait. Dev Med Child Neurol 2003; 45: 833–6.

Kors EE, Vanmolkot KR, Haan J, Kheradmand Kia S, Stroink H, Laan LA, et al. Alternating hemiplegia of childhood: no mutations in the second familial hemiplegic migraine gene ATP1A2. Neuropediatrics 2004; 35: 293–6.

Krägeloh I, Aicardi J. Alternating hemiplegia in infants: report of five cases. Dev Med Child Neurol 1980; 22: 784–91.

Mikati MA, Kramer U, Zupanc ML, Shanahan RJ. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. Pediatr Neurol 2000; 23: 134–41.

Neville BG, Ninan M. The treatment and management of alternating hemiplegia of childhood. Dev Med Child Neurol 2007; 49: 777–80.

Nevšímalová S, Dittrich J, Havlová M, Tauberová A, Korsová B, Hájek M, et al. Alternating hemiplegia in childhood: a cross-sectional study. Brain Dev 1994; 16: 189–94.

Nishiki T, Takeuchi Y, Yamazoe I, Yoshioka H, Sawada T. Patient with unusual alternating hemiplegia. Pediatr Neurol 1994; 10: 153–6.

Saito Y, Sakuragawa N, Sasaki M, Sugai K, Hashimoto T. A case of alternating hemiplegia of childhood with cerebellar atrophy. Pediatr Neurol 1998; 19: 65–8.

Sakuragawa N. Alternating hemiplegia in childhood: 23 cases in Japan. Brain Dev 1992; 14: 283–8.

Sakuragawa N. Clinical findings in 23 Japanese patients with alternating hemiplegia of childhood. In: Andermann F, Aicardi J, Vigevano F, editors. Alternating hemiplegia of childhood. New York: Raven Press; 1995. p. 43–7.

Shafer ME, Mayfield JW, McDonald F. Alternating hemiplegia of childhood: a study of neuropsychological functioning. Appl Neuropsychol 2005; 12: 49–56.

Siemes H, Cordes M. Single-photon emission tomography investigations of alternating hemiplegia of childhood. Dev Med Child Neurol 1993; 35: 346–50.

Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology 1993; 43: 36–41.

Sweney MT, Silver K, Gerard-Blanluet M, Pedespan JM, Renault F, Arzimanoglou A, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. Pediatrics 2009; 123(3): e534–41.

Swoboda KJ, Kanavakis E, Xaidara A, Johnson JE, Leppert MF, Schlesinger-Massart MB, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine?: a novel *ATP1A2* mutation. Ann Neurol 2004; 55: 884–7.

Verret S, Steele JC. Alternating hemiplegia of childhood: a report of eight patients with complicated migraine beginning in infancy. Pediatrics 1971; 47: 675–80.

Appendix 1

The ENRAH Consortium Arzimanoglou Alexis (France), Campistol Jaume (Spain), Casaer Paul (Belgium), Ebinger Friedrich (Germany), Fons Carmen (Spain), Giannotta Melania (Italy), Gobbi Giuseppe (Italy), Kemlink David (Czech Republic), Laan Laura (The Netherlands), Neville Brian (UK), Nevšímalová Soňa (Czech Republic), Ninan Miriam (UK), Oechsler Claudia, Panagiotakaki Eleni (France), Spiel Georg (Austria), Bassi Maria Teresa (Italy), Casari Giorgio (Italy), Crawley Francis (Belgium), Martinelli Boneschi Filippo (Italy), Nicole Sophie (France), Poncelin Dominique (France), Sange Guenter (Austria), Schyns Tsveta (Austria), van den Maagdenberg Arn (The Netherlands), Vavassori Rosaria (Italy), Zucca Claudio (Italy).