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Episodic ataxia type 1: clinical characterization, quality of life and genotype–phenotype correlation

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*See Appendix 1 for details of the Consortium for Clinical Investigation of Neurologic Channelopathies

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Episodic ataxia type 1 is considered a rare neuronal ion channel disorder characterized by brief attacks of unsteadiness and dizziness with persistent myokymia. To characterize the natural history, develop outcome measures for future clinical trials, and correlate genotype with phenotype, we undertook an international, prospective, cross-sectional study. Thirty-nine individuals (51% male) were enrolled: median age 37 years (range 15–65 years). We identified 10 different pathogenic point mutations in *KCNA1* that accounted for the genetic basis of 85% of the cohort. Participants with *KCNA1* mutations were more likely to have a positive family history. Analysis of the total cohort showed that the first episode of ataxia occurred before age 20 in all but one patient, with an average age of onset of 7.9 years. Physical exertion, emotional stress and environmental temperature were the most common triggers for attacks. Attack frequency ranged from daily to monthly, even with the same *KCNA1* genotype. Average attack duration was in the order of minutes. Ten participants (26%) developed permanent cerebellar signs, which were related to disease duration. The average Scale for the Assessment and Rating of Ataxia score (SARA, a standardized measure of cerebellar dysfunction on clinical examination, scores range from 0–40) was an average of 3.15 for all participants (range 0–14), but was only 2 in those with isolated episodic ataxia compared with 7.7 in those with progressive cerebellar ataxia in addition to episodic ataxia. Thirty-seven participants completed the SF-36, a quality of life survey; all eight domain norm-based average scores (mean = 50) were below normal with mental health being the lowest (41.3) in those with mutation positive episodic ataxia type 1. Scores on SF-36 correlated negatively with attack frequency. Of the 39 participants in the study, 33 harboured mutations in *KCNA1* whereas the remaining six had no mutation identified. Episodic ataxia type 1 phenocopies have not been described previously and we report their clinical features, which appear to be different to those with a *KCNA1* mutation. This large prospective study of both genetically confirmed episodic ataxia type 1 and episodic ataxia type 1 phenocopies provides

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detailed baseline characteristics of these disorders and their impact on participants. We found that attacks had a significant effect on quality of life. Unlike previous studies, we found that a significant number of individuals with genetically confirmed episodic ataxia type 1 (21%) had accumulated persistent cerebellar symptoms and signs. These data will enable the development of outcome measures for clinical trials of treatment.

Keywords: episodic ataxia type 1 (EA1); *KCNA1*; quality of life

Abbreviations: EA1 = episodic ataxia type 1; SARA = Scale for the Assessment and Rating of Ataxia

Introduction

Episodic ataxia type 1 (EA1) is an autosomal dominant ion channel disorder affecting the cerebellum and peripheral nerves. Patients have intermittent symptoms, with little or no difficulties in between attacks, are not thought to develop progressive deficits (Jen *et al*., 2007). Attacks can abate in adulthood (VanDyke *et al*., 1975; Brunt and van Weerden, 1990). Episodes of ataxia are frequent and short-lasting and may be associated with a feeling of 'dizziness' which patients often find hard to precisely characterize. Patients experience a profound sense of imbalance or dysequilibrium during an attack. Interictal myokymia, a fine rippling muscle movement, may be exacerbated during an attack and patients may describe this as a tremor (Jen *et al*., 2007). An unresolved issue is whether the attacks are isolated to ataxia (wide-based stance, unsteady, uncoordinated gait, dysarthia and incoordination) or also include symptoms of muscle weakness and stiffness. Attacks can be precipitated by sudden movement, emotion or intercurrent infection. Patients may have sensory warning symptoms before an attack (VanDyke *et al*., 1975; Brunt and van Weerden 1990). The age of onset of EA1 attacks is usually in early childhood or adolescence (<20 years) and patients often experience multiple attacks in a day, some of which may cluster (Rajakulendran *et al*., 2007). Linkage analysis in EA1 families implicated chromosome 12p13 (Litt *et al*., 1994) and the responsible gene was found to be *KCNA1* (Browne *et al*., 1994). This is a single exon gene that encodes the delayed-rectifier potassium channel, $K_v1.1$ responsible for repolarizing nerves after depolarization. Multiple point mutations have now been identified (Jen *et al*., 2007).

To quantify the clinical characteristics of EA1, its effect on quality of life, and to determine whether there are any genotype–phenotype correlations, we set up an international multi-centre study on a large number of patients with EA1. We report the clinical characteristics and quality of life findings in both EA1 and EA1 phenocopies and genotype–phenotype correlation in EA1.

Materials and methods

Study design

This study was an international, prospective, observational study of the clinical characteristics and genotype–phenotype correlation of EA1. Data were held centrally on a secure server at the Data and Technology Coordinating Centre (DTCC, Tampa, Florida, USA). Initially, participants who fulfilled two of the following three criteria or were related to someone who fulfilled two of the following three criteria were included: (i) clear cut episodes of recurrent, transient ataxia; (ii) symptoms triggered by stress/exertion; and (iii) progressive interictal ataxia. The criteria were later modified, to require one of the following three criteria: (i) clear cut episodes of recurrent, transient ataxia; (ii) mutation confirmed in *KCNA1*; and (iii) ataxic features with a first degree relative with episodic ataxia. If the patient did not have a known mutation in *KCNA1*, a clinical diagnosis was assigned to the patient as EA1 if they had short attack duration, interictal myokymia and no interictal eye movement abnormalities. Participants aged 5 years and older were enrolled. If participants were unable to travel to participating centres, they could be seen in their homes by the investigators. Participants were recruited between September 2006 and May 2010, from four sites in the USA, one in Canada, and one in the UK. The evaluators were trained to perform all evaluations in a standardized manner at an investigator meeting.

Outcome measures

As the primary outcome measure to assess disease progression, we used the Scale for the Assessment and Rating of Ataxia (SARA). The SARA score ranges from 0 to 40, with 0 indicating no ataxia and 40 the most severe degree of ataxia. Quality of life was assessed using the SF-36, a self-administered questionnaire that measures eight quality of life domains. This provides psychometrically-based physical and mental health summary measure scores that can be compared to normalized control data, with an average of 50 and a standard deviation of 10 (Ware and Sherbourne, 1992). An activities of daily living assessment tested nine domains with a maximum score of 36 (0 being no impairment).

Interactive voice response system

At the baseline visit, participants were given a brief orientation to an automated interactive voice response system and were expected to call in every attack for eight consecutive weeks after recruitment. As part of the system orientation, participants were given the freephone telephone number, a unique identification number, and an instruction sheet for use of the telephone-based interactive voice response data collection system. They were given practice user identification numbers for training purposes. This system assessed symptom presence (yes/no) during attacks. The symptoms were: ataxia, headache, slurred speech, stiffness, tremors, vertigo, visual disturbance, weakness and stiffness of muscles. Further questions asked if there was a trigger for the attack, the date and the duration of the attack. Individuals were asked to estimate the attack severity (on an ordinal scale 0–9, where 0 is none and 9 is very severe) and the effect on daily functioning on a three-point scale (mild, moderate and severe). Any further episodes on that day could also be entered. Before moving on to each element of the interactive voice response, the automated system asked participants if the information they had entered was correct. As the interest here was in creating a real time voice response diary of symptom frequency and severity, once the data were entered there was no

mechanism to edit an interactive voice response entry. This approach was taken to reduce 'editing' of entries after the fact, introducing 'back-filling' bias seen in traditional paper diaries (Palmblad and Tiplady, 2004; Gwaltney *et al*., 2008). The subject response data were immediately stored on an Oracle database.

Genetic analysis

Those in whom a molecular diagnosis was not determined before enrolment underwent DNA sequencing of *KCNA1* using standard conditions (Eunson *et al*., 2000).

Statistical analysis

Data are presented as means and standard deviations unless otherwise stated. *P*-values are reported as two-tailed with a cut-off of 0.05 for significance. Continuous variables that follow a parametric distribution were analysed by Student's *t*-test. Non-parametric variables were analysed by Wilcoxon Rank Sum test.

Standard protocol approval, registration and patient consent

The study was approved by the ethics committees of the contributing centres. Written informed consent was obtained from all study participants. Oversight for protocol consistency was provided by the DTCC, which also performed periodic audits of each contributing centre.

Results

Baseline data

Thirty-nine individuals with EA1-like features were enrolled. Baseline data on their clinical history were obtained by a structured interview. Fifty-one per cent were male with a median age of 37 years (range 15–65). All but one developed episodic ataxia before the age of 20 years, with an average onset of 7.8 years. Physical exertion, emotional stress and environmental temperature were the most commonly reported triggers for attacks. Attack frequency ranged from daily to monthly. Average attack duration was reported by participants to be the order of minutes. All participants were screened for mutations in *KCNA1*, which were identified in 33 (85%). Participants with *KCNA1* mutations were analysed separately from those without mutations. Those with a demonstrable *KCNA1* mutation usually had an affected first degree relative, although two apparently had no affected relatives (6%). It is not known whether these represent *de novo* mutations as parental DNA was unavailable. Detailed results are provided below that distinguish between genetically confirmed and mutation negative participants.

Genetically confirmed episodic ataxia type 1

Clinical characterization

Thirty-three individuals had genetically confirmed EA1; 58% were female. Their median age at enrolment was 36 (range 16–65 years). The average age of onset of symptoms was 7.8 years (range 0–20 years). On average, each genetically confirmed patient had three affected first-degree relatives (range 0–5).

Most participants reported attacks lasting minutes ($n = 31$, 94%), whereas two experienced attacks lasting hours (6%). Current attack frequency varied because of the use of preventative medications. Attacks occurred daily in 11 participants (33.3%), weekly in nine (27.3%) and monthly in 13 (39.4%). Twenty-six participants only experienced episodes of ataxia (78.8%) whereas seven experienced both episodic and progressive ataxia (21.2%). Table 1 lists the most frequently reported triggers for attacks in genetically confirmed EA1 participants. Attacks could also occur without an identifiable trigger.

The clinical features of the attacks could be variable, but the core features were of imbalance, incoordination and slurred speech (Table 2). Most participants also reported feeling weak during an attack. Tremors and muscle twitching represented episodic exacerbation of baseline myokymia.

Some people reported additional symptoms during attacks that were not on the list provided. Three members of Family 2 reported a rising sensation from the legs up through the body; one patient reported short-lived paraesthesias and another had recurrent dystonic episodes. In the literature, one pedigree was reported to experience paroxysmal dyspnoea (Shook *et al*., 2008); one of our participants described this, along with hot flushes and palpitations.

During the attacks, approximately one-quarter of the participants were able to walk independently, one-quarter were able to walk with a stick (3%) or frame (21%), a quarter required the help of one assistant and 15% need the help of two people to walk. The remaining 12% were unable to walk at all during an attack (Fig. 1).

Medication use

Fourteen individuals reported having tried preventative medications. Acetazolamide was tried by eight participants, of which two found it to be helpful in reducing their attacks. It had to be discontinued in two participants because of side effects and therefore was not used at an effective dose. Carbamazepine was used in seven participants, three of whom derived benefit. One worsened on carbamazepine and a further participant was unable to tolerate it. Lamotrigine was used as a second line agent in two participants with attacks only, both of whom improved on it.

There was a higher attack frequency in those on medications (average 21.4 attacks per month) compared to those not on medications (5.7 per month, $P < 0.05$), which is perhaps related to greater motivation to take medication when attack frequency is high. Those currently on medication had a shorter disease duration than those who were not (16.9 versus 31.0 years, $P < 0.05$), which supports the observation that participants tend to have fewer attacks as they get older.

Other symptoms

Cases in the literature reveal that additional symptoms may occur in EA1, either during attacks or in between them. The most commonly reported symptom is interictal neuromyotonia or myokymia (Eunson *et al*., 2000; Kinali *et al*., 2004; Poujois *et al*., 2006; Chen

Table 1 Triggers of attacks in genetically confirmed participants with EA1

Trigger	Number ($n = 33$)	%
Exertion/exercise	29	87.9
Stress/emotional upset	28	84.8
Environmental temperature	18	54.5
Fever	10	30.3
Caffeine	9	27.3
Alcohol	9	27.3
Sudden movement	9	27.3
Diet	9	27.3
Rest after exertion/exercise	9	27.3
Startle	8	24.2
Prolonged rest	7	21.2
Pregnancy	6 (of 19 females)	31.6
Menstruation	5 (of 19 females)	26.3
Tiredness	2	6.1
Strong smells	1	3.0
Anxiety	1	3.0
Bending over/looking down	1	3.0

During the structured interview, participants were asked which triggers might lead to their attacks of ataxia.

Table 2 Symptoms during attacks in genetically confirmed participants with EA1

Symptom	Number ($n = 33$)	%
Imbalance	31	93.9
Slurred speech	31	93.9
Incoordination of hands	28	84.8
Weakness	28	84.8
Tremors	27	81.8
Muscle twitching	26	78.8
Muscle stiffness	21	63.6
Spinning sensation	14	42.4
Visual disturbance	13	39.4
Nausea	6	18.2
Headache	4	12.1
Vomiting	1	3.0

During the structured interview, participants were asked what symptoms they experience during their attacks of ataxia.

et al., 2007; Imbrici *et al.*, 2008). Some have persistent distal weakness (Klein *et al.*, 2004). Consistent with the literature, the most commonly associated additional symptoms were those affecting the PNS, usually myokymia. This was reported in seven individuals (21.2%). Five participants reported vestibular symptoms (15.2%) whereas four had additional psychiatric symptoms (12.2%). The nature of these symptoms was not further specified and may be unrelated to their condition. Three participants had seizures in addition to their episodes of ataxia, which has also been reported in the literature (Zuberi *et al.*, 1999; Eunson *et al.*, 2000).

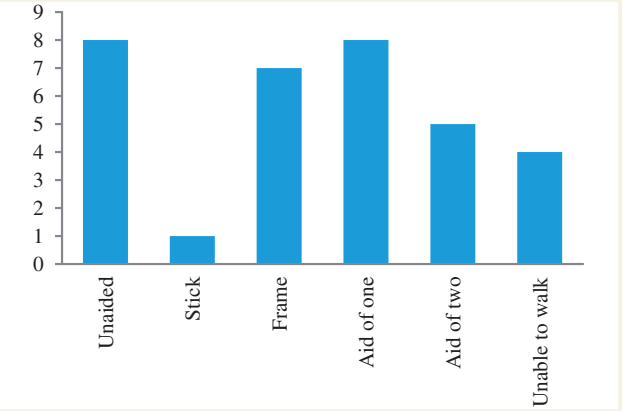

Figure 1 Ability of genetically proven EA1 participants to walk during an attack ($n = 33$). Participants were asked to rate how difficult it would be for them to walk during an average attack and were given the following options: unaided, with one stick, with a frame, with the aid of one person, with the aid of two people or not at all.

Investigations

Additional investigations were not formally part of the study, but were available by review of medical records. Twelve participants had EMG/nerve conduction studies and neuromyotonia was seen in 10. Brain MRI was performed in 12 individuals. This was normal in 11 (91.7%), with one person having cerebellar atrophy (8.3%). This participant reported persistent cerebellar ataxia in addition to attacks of ataxia.

Cumulative disability

Most participants classified themselves as having only episodic ataxia. However, seven individuals (21.2%) reported both episodic and progressive ataxia. Persistent cerebellar ataxia in EA1 has only been reported once before in the literature (Demos *et al.*, 2009). However, in these two cases it was also associated with cognitive impairment, which was not present in our cases.

Scale for the Assessment and Rating of Ataxia

The average SARA score (a standardized measure of cerebellar dysfunction on examination) was 3.4 for all participants. Those who reported both attacks of ataxia and persistent cerebellar ataxia had higher SARA scores (9.4) whereas in those with attacks only this was 1.8 ($P < 0.001$, Wilcoxon Rank sum test). Those with persistent cerebellar ataxia and high SARA scores had an average disease duration of 39.8 years compared to those with attacks only of 25.4 years ($P < 0.05$, Wilcoxon Rank sum test). This was also highly correlated with current age ($P < 0.05$, Wilcoxon Rank sum test). In those with persistent cerebellar ataxia, gait, speech, heel-shin test and the finger-nose test were the highest scoring elements on the SARA, suggesting both appendicular and midline ataxia. In contrast, no cerebellar eye signs were elicited and sitting balance was normal.

Activities of daily living

Most participants were not affected on a day-to-day basis in between their attacks and were able to live independently. However, those with persistent cerebellar ataxia had difficulties in activities of daily living, particularly with falling, walking and speech. Across the cohort, the average activities of daily living score was 1.4 (maximum possible score 36). In those with persistent cerebellar ataxia this was 5.1 compared with 0.38 in those with attacks only ($P < 0.001$, Wilcoxon Rank sum test).

Quality of life

Most participants had obtained a high school diploma or equivalent and were currently or had previously been employed. None were disabled as a result of their condition. All participants except one completed a baseline SF-36 questionnaire. All eight domain norm-based average scores (mean = 50, standard deviation = 10) were below normal with mental health being the lowest (41.3) (Fig. 2). However, all scores were within one standard deviation of normal (for all scores see Supplementary Table 1). Scores for bodily pain were significantly worse in those with persistent cerebellar ataxia (33.8 versus 47.8, $P < 0.05$, *t*-test). Mental health scores were equivalent across the two groups. Other domains scores were lower than both normal controls and EA1 with attacks only, but did not reach statistical significance (physical functioning, role emotional, vitality and role physical) or were similar in score (social functioning, general health and mental health). However, the physical component score, derived from the four physical domains was significantly lower in those with persistent cerebellar ataxia (46.9 versus 39.3, $P < 0.05$, *t*-test), consistent with their level of disability.

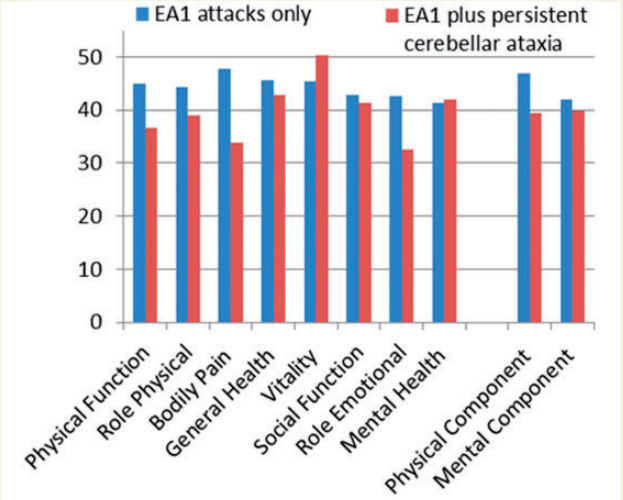

Figure 2 SF-36 domain scores in genetically proven EA1 participants, with and without persistent cerebellar ataxia. *$P < 0.05$. We compared scores on the SF-36 between those with genetically confirmed EA1 with attacks only ($n = 26$) and those with attacks and persistent cerebellar ataxia ($n = 7$). We hypothesized that persistent rather than intermittent symptoms would lead to a worse quality of life.

Patient self-reported episodes

Participants were asked to telephone our freephone number every day that they experienced episodes of ataxia in the 8-week period after recruitment to the study. This time frame was chosen to ascertain at least some attacks in those with infrequent episodes whilst not being too onerous on those with frequent attacks. Data were obtained from 17 participants, 11 with EA1 attacks only and six with EA1 and persistent cerebellar ataxia. This represents 44% and 86% of the EA1 attack only and EA1 with persistent cerebellar ataxia populations, respectively. Any participants who did not respond were contacted weekly to remind them of this part of the study to maximize compliance. Some individuals experienced infrequent attacks, so may have been attack-free during their 8-week period. The data from the interactive voice response are summarized in Table 3 (Supplementary Table 3 shows medians). There are too few data to perform meaningful statistical comparisons between the three groups. However, it is notable how some symptoms are frequent, such as ataxia, whereas others are rarer, such as vertigo. No participants reported identical symptoms during different attacks (see Supplementary Table 4 for individual averages). One member of Family 7 reported two attacks, neither of which included any of the eight recorded symptoms of ataxia, headache, slurred speech, muscle stiffness, tremors, vertigo, visual disturbance or weakness. Another member of Family 7 reported weakness during one attack, with none of the other symptoms during eight other reports. This suggests that these individuals have attacks which are different to their relatives and the interactive voice response system failed to capture adequate data on their attacks as the symptoms from which they were suffering were not in the automated menu.

KCNA1 mutation negative episodic ataxia type 1-like disease

Six participants fulfilled the inclusion criteria by experiencing short episodes of ataxia without interictal nystagmus, but were found not to carry a mutation in *KCNA1*. These cannot therefore be called EA1. The clinical features of EA1-like disease are compared with genetically proven EA1 in Table 4.

Half of the participants experienced only attacks whereas the remainder had associated persistent cerebellar ataxia, considerably more than was seen in genetically confirmed EA1 cases (50% versus 21%). Attacks were precipitated by exertion/exercise and stress or emotional upset in all, by alcohol in two and by caffeine or environmental temperature in one. Two participants tried acetazolamide; it was effective in one. The other four participants had not tried any medications. During the attacks, four individuals (66%) were able to walk, whereas the remaining two (33%) required the assistance of one person. The average SARA score was 0 in those with attacks only and 3.7 in those with persistent cerebellar ataxia. The activities of daily living score was paradoxically higher in those with attacks only (0.7) compared with 0.3 in those with persistent cerebellar ataxia and attacks (range 0–1 in both groups). Three individuals (50%) reported vestibular symptoms, two (33%) had bulbar

Table 3 Symptoms reported during attacks on interactive voice response system over 8 weeks

Average (range)	EA1 attacks only $n = 11$	EA1 attacks and persistent cerebellar ataxia $n = 6$	EA1-like $n = 3$
Total number of attacks reported	5.5 (2–18)	6.3 (2–15)	10.3 (9–12)
Triggers (%)	45 (0–100)	53.9 (0–100)	61.6 (40–100)
Severity (0–9)	4.0 (0–9)	4.1 (0–9)	3.8 (0–8)
Median attack duration (h)*	0.058 (0–1.58)	0.23 (0.0011–4)	0.96 (0.75–1)
Effect on daily function (1: mild, 2: moderate, 3: severe)	1.4 (1–3)	1.9 (1–3)	2.1 (1–3)
Number of additional attacks that day	0.9 (0–6)	2.9 (0–20)	0.4 (0–3)
Symptoms during attack (%):			
Ataxia	63.6	56.2	100
Headache	20.3	38.1	6.1
Slurred speech	38.2	55.1	63.9
Stiffness of muscles	32.6	50.4	50.6
Tremors	49.3	41.2	13.9
Vertigo	12.4	49.9	73.9
Visual disturbance	45.5	37.9	37.0
Weakness	57.1	80.6	97.2

*Median not mean.
Analysis of data collected on the interactive voice response system. Participants were requested to call in all attacks during the 8-week period following their recruitment.

Table 4 Comparison between genetically confirmed EA1 and EA1-like cases

	KCNA1 mutation positive ($n = 33$)	%	*KCNA1* mutation negative ($n = 6$)	%	*P*-value
Age at enrolment	35.7 years (16–65)		36.2 years (14–45)		0.95
Sex M:F	14:19	42.4	6:0	100	0.02*
Age of onset	7.8 (0–20)		9.8 (0–19)		0.25
Ataxia:					
Attacks only	26	78.8	3	50	0.16
Persistent cerebellar ataxia and attacks	7	21.2	3	50	
Disease duration (years):					
Attacks only	25.0		30.0		0.58
Persistent cerebellar ataxia and attacks	38.9		36.0		0.17
Attack duration:					
Minutes	31	93.9	3	50	0.02*
Hours	2	6.1	3	50	
Frequency:					
Daily	11	33.3	4	66.7	0.08
Weekly	9	27.3	1	16.7	
Monthly	13	39.4	1	16.7	
Positive family history	31	93.9	4	66.7	0.09
SARA score:					
Attacks only	1.8 (0–6)		0		0.1
Persistent cerebellar ataxia and attacks	9.4 (2–14)		3.7 (0–7)		0.07
Activities of daily living score:					
Attacks only	0.3 (0–2)		0.7 (0–1)		0.50
Persistent cerebellar ataxia and attacks	5.1 (0–10)		0.3 (0–1)		0.07

Ranges in brackets, *statistically significant.
Demographic data of those with genetically confirmed EA1 compared to those where no *KCNA1* mutation was identified.

symptoms and another two (33%) had psychiatric symptoms. Four participants had a normal MRI brain and none underwent an EMG/nerve conduction study examination.

Five participants with the EA1-like phenotype completed the SF-36 questionnaire (Fig. 3). Scores across all eight domains were lower than normal controls, but by less than one standard deviation (for all figures see Supplementary Table 2). The lowest score was in social functioning. Participants had a higher score than controls and EA1 cases in bodily pain, indicating that they suffer less bodily pain, but again, this was less than one standard deviation higher and did not achieve statistical significance. Self-rated quality of life data were compared between those

with genetically proven EA1 ($n = 33$) and those with EA1-like disease ($n = 6$).

Patient self-reported episodes

Data were obtained from three participants, which represents 50% of the study population (Table 3). All participants reported ataxia during their attacks, compared with only 63.6% in those with genetically-proven EA1 attacks alone. In addition, 97.2% reported weakness compared with 57.1% of the genetically-proven EA1 attacks cohort; however, the data were too small to make statistical comparisons.

Genotype–phenotype correlation

Participants were recruited from seven families and three singleton cases. Mutations in *KCNA1* were located throughout the gene. The mutations in families were: R307C (Graves *et al*., 2010), F414S (Graves *et al*., 2010), F184C (Browne *et al*., 1995), A242P (Eunson *et al*., 2000), C185W (Tomlinson *et al*., 2010), V404I (Scheffer *et al*., 1998) and delF250 (Shook *et al*., 2008). Mutations were unique to each family and the triggers of attacks were not always the same in affected individuals of the same pedigree (Table 5). However, both members of Family 4 had identical triggers, whereas members of Family 3 only had exertion and temperature in common, with most other triggers only occurring in one of five affected members. The largest pedigree (Family 2) has two distantly related branches (Graves *et al*., 2010). Seven members enrolled: five from one branch, two from the other. Symptoms during attacks also varied across pedigrees (Table 6). All five members of Family 3 had eight core symptoms in common during attacks (imbalance, slurred speech, incoordination of hands, weakness, tremors, muscle twitching and muscle stiffness), but the six members of Family 7 only shared one symptom (muscle stiffness), with other symptoms present only in two to five members, depending upon the symptom. However, when this is compared with real time data recorded by the interactive voice response system, symptoms during attacks seemed to be less uniform (Supplementary Table 4). This is likely because of the composite nature of history taking. Participants report all symptoms that they may have during an attack, when recalling their history (creating the impression of an 'average attack'), compared with the precise data capture method of the interactive voice response providing information for that specific attack only. *KCNA1* mutations in singleton cases were T226R (Zuberi *et al*., 1999), I407M (Tomlinson *et al*., 2013) and G311S (Zerr *et al*.,1998).

Family 2 also showed variability in the ability to walk during an attack. One person was able to walk during an attack; one needed the aid of a stick; one required the help of one assistant; two required the help of two assistants to walk while two were unable to walk at all.

Persistent cerebellar ataxia was associated with five different *KCNA1* mutations and was also variable when seen in pedigrees, occurring in one of four members of Family 1, one of six members of Family 7, but three of five members of Family 3 (see Table 5 for mutations). It was also seen in association with the G311S and T226R mutations in individuals.

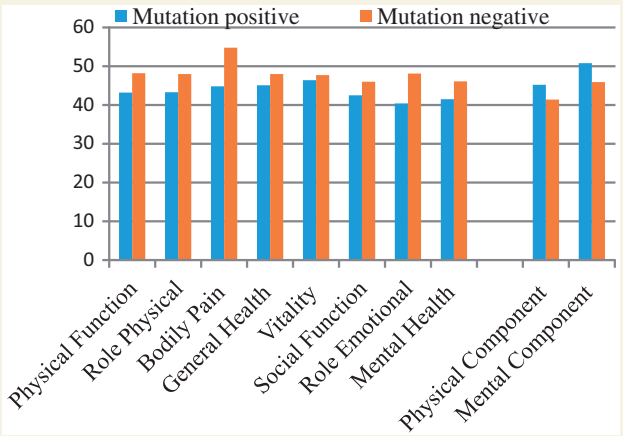

Figure 3 Comparison between SF-36 scores in those with genetically proven EA1 and those with EA1-like disease.

Discussion

This large prospective study of patients with EA1 provides baseline qualitative and quantitative clinical data including the effect of this disorder on patient quality of life. This is the first prospective large cohort study of EA1. Previous reports dealt mainly with small case series or single case descriptions. We showed that EA1 is a childhood onset disorder characterized by recurrent brief attacks of imbalance, incoordination and dysarthria but in addition, was often accompanied by muscle stiffness and weakness, reflecting the central and peripheral location of the affected potassium channels in the human nervous system (Wang *et al*., 1993, 1994). These attacks can be triggered by many different stressors or can be paroxysmal. Many participants reported impaired quality of life and there was a trend towards worse scores in mental health domains on the SF-36. Furthermore those who developed persistent cerebellar ataxia reported more bodily pain, cumulative disability and poor quality of life.

We observed that attacks can be diminished by the use of preventative medications, although the retrospective views of participants shown here suggest that these are successful only in a minority of cases tested (36%). This apparent lack of effectiveness of prophylactic medications is contrary to our clinical experience, which is that most patients will improve on a modest dose of carbamazepine. It is striking, however, that the majority of participants had never tried medications. There may also be an element of underdiagnosis, in that a lot of individuals view their symptoms as a familial trait and have therefore not sought medical attention. There was a higher attack frequency in those on medications (average 21.4 attacks per month) compared to those not on medications (5.65 per month, $P < 0.05$). However, this is likely to be an underestimate, given that they would have an even higher attack frequency if they were not on effective preventative medications. Those currently on medication had shorter disease duration than those who were not (16.9 versus 31 years, $P < 0.05$). Only half of the participants remained on medication, which were those who found the medication useful. Whether this represents symptoms being more tolerable than the idea of taking medications or that the individuals had grown used to their attacks remains unclear.

Table 5 Triggers of attacks compared within pedigrees

Trigger	Family 1 *n* = 4 R307C	Family 2 *n* = 7 F414S	Family 3 *n* = 5 F184C	Family 4 *n* = 2 A242P	Family 5 *n* = 3 C185W	Family 6 *n* = 3 V404I	Family 7 *n* = 6 delF250
Exertion or exercise	4 (100)	6 (85.7)	5 (100)	2 (100)	3 (100)	1 (33.3)	6 (100)
Stress or emotional upset	4 (100)	6 (85.7)	5 (100)	2 (100)	0	2 (66.7)	6 (100)
Environmental temperature	1 (25)	5 (71.4)	4 (80)	2 (100)	0	0	6 (100)
Fever	4 (100)	6 (85.7)	0	2 (100)	3 (100)	3 (100)	0
Caffeine	4 (100)	0	1 (20)	0	0	0	3 (50)
Alcohol	3 (75)	3 (42.7)	1 (20)	0	0	1 (33)	1 (16.7)
Sudden movement	4 (100)	6 (85.7)	0	2 (100)	0	3 (100)	0
Diet	3 (75)	1 (14.3)	1 (20)	0	0	0	3 (50)
Rest after exertion or exercise	1 (25)	5 (71.4)	2 (40)	0	0	0	0
Startle	4 (100)	5 (71.4)	1 (20)	2 (100)	0	3 (100)	0
Prolonged rest	2 (50)	1 (14.3)	1 (20)	0	0	0	2 (33.3)
Pregnancy	1 of 2 (50)	1 of 4 (25)	0 of 2	2 (100)	0 of 2	0 of 2	1 of 4 (25)
Menstruation	2 of 2 (100)	1 of 4 (25)	0	0	0	0	2 of 4 (50)
Tiredness	4 (100)	0	0	0	0	3 (100)	0
Strong smells	1 (25)	0	0	0	0	0	0
Anxiety	0	1 (14.3)	0	0	0	0	0
Bending over or looking down	0	0	0	0	0	1 (33.3)	0

Values in brackets are percentages.
Analysis of attack triggers in members of the families recruited. This shows interfamilial and intrafamilial variability.

Table 6 Symptoms of attacks compared within pedigrees

Symptom Mutation	Family 1 *n* = 4 R307C	Family 2 *n* = 7 F414S	Family 3 *n* = 5 F184C	Family 4 *n* = 2 A242P	Family 5 *n* = 3 C185W	Family 6 *n* = 3 V404I	Family 7 *n* = 6 delF250
Imbalance	4 (100)	7 (100)	5 (100)	2 (100)	3 (100)	3 (100)	4 (66.7)
Slurred speech	4 (100)	7 (100)	5 (100)	2 (100)	3 (100)	3 (100)	4 (66.7)
Incoordination of hands	4 (100)	5 (71.4)	5 (100)	2 (100)	2 (66)	3 (100)	4 (66.7)
Weakness	4 (100)	6 (85.7)	5 (100)	1 (50)	3 (100)	2 (66)	5 (83.3)
Tremors	2 (50)	7 (100)	5 (100)	2 (100)	1 (33.3)	3 (100)	5 (83.3)
Muscle twitching	2 (50)	5 (71.4)	5 (100)	2 (100)	2 (66.7)	2 (66.7)	5 (83.3)
Muscle stiffness	2 (50)	2 (28.6)	5 (100)	2 (100)	2 (66.7)	0	6 (100)
Spinning sensation	1 (25)	2 (28.6)	5 (100)	0	2 (66.7)	2 (66)	3 (50)
Visual disturbance	3 (75)	2 (28.6)	4 (80)	0	0	0	2 (33.3)
Nausea	2 (50)	3 (42.9)	0	0	1 (33.3)	0	0
Headache	2 (50)	1 (14.3)	0	0	0	1 (33.3)	0

Values in brackets are percentages.
Analysis of symptoms during an attack in members of the families recruited. This shows interfamilial and intrafamilial variability.

The additional symptoms suffered during attacks were highly variable between individuals but remained constant within individuals, although not every attack was identical, as was seen by the data recorded from the interactive voice response system. Attack severity was variable, even within family members with the same mutation.

Most of those with EA1 exhibited myokymia and the characteristic signs of neuromyotonia on EMG and had a normal brain MRI. Neither of these tests are required in practice, however, as the genetic test is easily available, accessible and inexpensive.

Interestingly, at least one-fifth of our participants accumulated persistent cerebellar symptoms and signs, contrary to the perceived course of this condition. The accumulation of cerebellar dysfunction is more usually associated with episodic ataxia type 2 (EA2), which is associated with interictal nystagmus and longer attack duration. Indeed, interictal ataxia in association with episodic ataxia would usually lead to the diagnosis of EA2, although the attacks in this condition are much more severe and prolonged than that of EA1, usually lasting hours or days (Jen *et al*., 2007). There has only been one reported EA1 pedigree with persistent cerebellar ataxia, but this was in association with cognitive impairment and epilepsy, which was not seen in our cohort. The pedigree in the literature had the V408L *KCNA1* mutation (Demos *et al*., 2009). The individuals reported in this study with both episodic and progressive ataxia had signs of cerebellar dysfunction on examination, higher SARA and activities of daily living scores and a trend towards lower scores on the SF-36, suggesting that the factor associated with quality of life in this condition is the development of persistent cerebellar ataxia. In addition, individuals with

persistent cerebellar ataxia had more bodily pain than those with EA1 attacks only. It is difficult to account for this in terms of ataxia, as their SARA scores are relatively low. Patients with sporadic late-onset ataxia (Abele and Klockgether, 2007) and Friedreich's ataxia (Epstein *et al*., 2008), have been reported to have near-normal scores for bodily pain even though they were more disabled by their ataxia than our participants and in the late-onset ataxia group, had reported much lower scores across all SF-36 domains compared to our participants.

This is the first time patients with EA1 have been asked to document their attacks in real time. Through this process, we found that symptoms during attacks may be more variable than previously appreciated and that attacks can also be variable in their duration and severity. The interactive voice response system is a simple and quick method of capturing real time data that could be used in future treatment trials. However, compliance was a problem with some of the UK cohort. Freephone telephone numbers in the UK require a landline and if called from a mobile telephone, can cost a considerable amount of money. Two families with multiple members recruited were unable to participate as they only had mobile telephones. Therefore the difficulties using mobile telephones in the UK should be borne in mind in the design of future studies. Second, if the system were to be used in future trials, then the automated menu options for capturing symptoms during attacks could be expanded to cover more symptoms such as dyspnoea or dystonia.

By analysing members of the same pedigree, we could see the inter- and intrafamilial variability of this condition. No family had consistent triggers of symptoms across all members. Although imbalance, slurred speech and incoordination of the hands were core symptoms, two members of Family 7 did not complain of any of these symptoms during an attack. Vestibular symptoms in general are less common in EA1 compared to EA2 (Jen *et al*., 2007), however, all members of Family 3 described vertigo during attacks.

As EA1 is a highly characteristic clinical syndrome, we were surprised that six participants had no identifiable *KCNA1* mutation. To date there have been no publications of genetically negative EA1 cases or phenocopies of the condition, although this could represent publication bias. This group had certain characteristics in common; they were all male, were more likely to have progressive as well as episodic ataxia, and their attack duration tended to be longer that the average duration of the genetically defined cases of EA1. They did not fit into the phenotype of EA2, however, as they had overall short duration attacks and they did not have interictal nystagmus (Jen *et al*., 2007). No further genetic testing was carried out. As the phenotype was that of EA1 with brief attacks and no interictal nystagmus, only the *KCNA1* gene was studied. Sequencing of the calcium channel *CACNA1A* responsible for EA2 is not only time consuming and expensive, but also unlikely to be informative and therefore could not be justified on a phenotypic basis. Efforts are underway to search for defects in novel genes that could account for EA1-like symptoms and signs. It is possible that these cases harbour an unidentified new genetic cause of episodic ataxia or that they may represent non-genetic phenocopies.

In conclusion, we have prospectively characterized the clinical features and impact on quality of life of a large cohort of participants with EA1. We observed for the first time that this disorder has a significant impact on quality of life, a factor related to the development of progressive ataxia, newly described by this study. There was no clear correlation between genotype and attack frequency or disease severity, even within the same family. We also discovered variability of symptoms during episodes, both within an individual and between family members with the same mutation, not previously appreciated.

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Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

The Consortium of Clinical Investigation on Neurologic Channelopathies (CINCH)

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