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Early Symptoms in Spinocerebellar Ataxia Type 1, 2, 3, and 6

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Abstract: Onset of genetically determined neurodegenerative diseases is difficult to specify because of their insidious and slowly progressive nature. This is especially true for spinocerebellar ataxia (SCA) because of varying affection of many parts of the nervous system and huge variability of symptoms. We investigated early symptoms in 287 patients with SCA1, SCA2, SCA3, or SCA6 and calculated the influence of CAG repeat length on age of onset depending on (1) the definition of disease onset, (2) people defining onset, and (3) duration of symptoms. Gait difficulty was the initial symptom in two-thirds of patients. Double vision, dysarthria, impaired hand writing, and episodic vertigo preceded ataxia in 4% of patients, respectively. Frequency of other early symptoms did not differ from controls and was regarded unspecific. Data about disease onset varied between patients and relatives for 1 year or more in 44% of cases. Influence of repeat length on age of onset was maximum when onset was defined as beginning of permanent gait disturbance and cases with symptoms for more than 10 years were excluded. Under these conditions, CAG repeat length determined 64% of onset variability in SCA1, 67% in SCA2, 46% in SCA3, and 41% in SCA6 demonstrating substantial influence of nonrepeat factors on disease onset in all SCA subtypes. Identification of these factors is of interest as potential targets for disease modifying compounds. In this respect, recognition of early symptoms that develop before onset of ataxia is mandatory to determine the shift from presymptomatic to affected status in SCA. © 2008 Movement Disorder Society

Key words: spinocerebellar ataxia; early symptoms; determinants of age at onset; CAG repeat expansion

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Spinocerebellar ataxia (SCA) comprises a group of neurodegenerative multisystem disorders, which present with progressive ataxia as their key feature. It is caused by mutations in more than 25 genes of which 14 have been cloned so far.[1–3] The expansion of a CAG trinucleotide repeat in the coding region of the respective gene causes the disease in seven subtypes including the most prevalent genotypes in Europe (SCA1, SCA2, SCA3, and SCA6). SCA is a phenotypically heterogeneous insidious disease characterized by slowly progressive gait ataxia and variable additional symptoms including visual problems, dysarthria, dysphagia, limb ataxia, spasticity, Parkinsonism, dystonia, peripheral neuropathy, restless legs syndrome, and urge incontinence. Because of its hereditary nature, the pathogenic process is likely to start early in life or even prior to birth, but early development is generally normal and often patients remain clinically healthy far beyond the second, third, or even seventh decade of their life. The exact disease onset, however, often remains unclear and has only rarely been well defined in previous studies. Determination of disease onset might differ whether patients are asked for onset of gait ataxia or, alternatively, for onset of any other kind of behavioral or neurological problem. Moreover, it might vary depending on the person that is asked—either the patient or his/her relatives. Despite lack of standardization in the assessment of age at onset, significant correlations have been found between the age of onset and the number of the CAG motifs in the expanded allele in all of the more common SCA subtypes (SCA1, SCA2, SCA3, and SCA6) and repeat length can account for 50 to 80% of variability in age of onset,[4–10] it still remains unknown to what extend differences in the ascertainment of disease onset contribute to the unexplained portions of variability. Apart from CAG repeat expansions, alternative genetic or environmental factors influencing age of onset in SCA have rarely been identified[11–13]—although they are of major interest due to their likely function as modifiers of disease progression.

We assessed early symptoms other than gait ataxia in the most frequent subtypes of SCA. To optimize accuracy of specifications, we combined information from both patients and close relatives in the assessment of onset of gait ataxia. Correlations of repeat length and disease onset were calculated for (1) occurrence of the first disease related symptom and (2) the onset of gait disturbance.

PATIENTS AND METHODS

Patients were recruited in the clinical network of EUROSCA, an international consortium funded by the European Union for clinical and basic research in SCA (http://www.eurosca.org). Two hundred and eighty-seven patients were recruited in specialized ataxia clinics in Bochum (Germany), Bonn (Germany), Brussels (Belgium), Essen (Germany), Innsbruck (Austria), Milan (Italy), Naples (Italy), Nijmegen (The Netherlands), Paris (France), Pec (Hungary), Tübingen (Germany), and Warsaw (Poland) including 78 patients with SCA1, 97 patients with SCA2, 62 with SCA3, and 50 with SCA6. Data on age, disease severity as assessed by the scale for the assessment and rating of ataxia (SARA[14]), and CAG repeat length are given in Table 1. Additionally, 122 age- and sex-matched control subjects without a history of neurological disease were interviewed for symptoms that may occur early in SCA. All patients and controls gave their written informed consent prior to inclusion. The study was approved by the Ethics Committees of the participating centers.

Structured interviews were performed with patients and their close relatives concerning the year of onset of permanent gait disturbance, double vision, reduced visual acuity, dysarthria, frequent throat clearing reflecting early dysphagia, problems with hand writing, episodic vertigo, neuropathic symptoms like weakness or sensory complaints, cramps, restless legs syndrome, sleep disturbances, or urinary urgency (Appendix).

TABLE 1. *Biographic, genetic, and clinical data of patients included in this study*

	Whole cohort N = 287	SCA1 N = 78	SCA2 N = 97	SCA3 N = 62	SCA6 N = 50
Age at examination (yr)	50.0 ± 14.0 (18–84)	45.6 ± 12.4 (25–76)	47.2 ± 13.7 (18–84)	48.8 ± 12.5 (24–72)	63.6 ± 10.2 (38–83)
Age at onset of gait ataxia (yr)	39 ± 13 (7–77)	37 ± 11 (16–66)	35 ± 12 (7–66)	38 ± 11 (18–60)	54 ± 11 (34–77)
Disease duration (yr)	10.1 ± 6.1 (1–33)	8.8 ± 5.2 (1–22)	11.1 ± 6.4 (1–30)	10.4 ± 6.0 (1–25)	9.9 ± 6.5 (1–33)
Sex (male/female)	150/137	49/29	42/55	32/30	27/23
SARA	14.9 ± 7.9 (0–40)	15.8 ± 9.4 (2–40)	15.6 ± 7.5 (2–36)	13.9 ± 8.1 (0–35.5)	13.6 ± 5.8 (1–31)
CAG expanded	NA	47 ± 5 (39–62)	39 ± 3 (33–47)	68 ± 4 (56–75)	22 ± 1 (22–28)
CAG normal	NA	30 ± 2 (27–36)	22 ± 2 (20–33)	21 ± 5 (14–34)	13 ± 1 (8–14)

Disease duration is given as years with gait disturbance as fixed by the patients after discussion with their relatives. Higher SARA sum scores indicate more severe disease.[14] Data are presented as mean ± standard deviation and range (in parenthesis).

NA, not applicable.

Additionally, we asked for other early symptoms that may be related to SCA from the patient's point of view. In case of incongruent information, we asked patients to discuss these differences with their relatives. Ultimately, the year of onset of symptoms was fixed by the patients.

CAG repeat length was analyzed in DNA extracted from EDTA blood samples. DNA was available from 259 patients (SCA1: 73, SCA2: 87, SCA3: 53, SCA6: 46). To optimize comparability of repeat lengths, all analyses were performed in the same lab (Human Genetics, Tübingen). A multiplex PCR assay (described in Ref. 15) was further optimized for robust amplification of all SCA mutations in one PCR assay: Genomic DNA of 250 to 500 ng was used per PCR reaction. Primer sequences, PCR conditions, and details of fragment analysis are provided on request. As CAG repeats do not perfectly result in a 3-bp spacing, expected fragment lengths were compared with known (sequenced) genotype standards and the allele calling was adapted accordingly.

Statistics

To test whether the reported onset of permanent gait disturbance varies between patients and relatives, a paired Student's *t*-test was performed. Correlations between quantitative variables were assessed using Pearson's correlation coefficient. Differences for quantitative variables between genotypes were compared using ANOVA with pairwise comparisons after a significant global ANOVA (Tukey-Kramer correction of *P*-value) except for the delay between early symptom and gait ataxia that were compared using a Kruskal–Wallis test. Frequency of symptoms in patients and controls are compared using a Fisher's Exact Test with adjustment for age (year of birth) and sex (logistic regression). Correlations between repeat length and other variables were performed after exclusion of patients with extreme numbers of CAG repeats defined as follows: expanded alleles SCA6 $\geq$ 28 CAG (1 patient); normal alleles SCA1 $\geq$ 33 CAG (3 patients), SCA2 $\geq$ 27 CAG (2 patients), SCA3 $\geq$ 33 CAG (2 patients), and SCA6 $\leq$ 8 CAG (1 patient). All tests were performed two-sided. $P < 0.05$ was considered significant. Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Data about onset of permanent gait disturbance varied frequently (44%) between SCA patients and their relatives for 1 year or more. In 8.5% of patient-relative pairs these differences exceeded 5 years. SCA2 patients gave a later year of onset compared to their relatives (1.3 years $\pm$ 4.8), whereas SCA3 patients recalled earlier onset than relatives (-1.1 years $\pm$ 2.7; SCA2 and SCA3: ANOVA with Tukey Kramer adjustment for pairwise comparisons, $P < 0.002$). In their final decision, 17.4% of patients changed their appraisal about onset of permanent gait difficulties in favor of their relatives' estimation. Differences between patients and care givers increased with longstanding disease ($r = 0.33$, $P < 0.0001$; Pearson's correlation coefficient) but not with disease severity as assessed by SARA ($r = 0.05$, $P = 0.46$).

Gait difficulty was reported as the initial symptom in two-thirds (66%) of all SCA patients. Symptoms preceding gait ataxia were in the order of frequency cramps (9%), dysarthria (5%), sleep disturbance (5%), double vision (4%), problems with hand writing (4%), episodic vertigo (4%), neuropathic symptoms like weakness or sensory complaints (3%), restless legs syndrome (3%), urinary urgency (3%), reduced visual acuity (2%), frequent throat clearing suggesting beginning dysphagia (1%), and other symptoms preceding gait disturbance (1%). In comparison to the control group, only double vision, dysarthria, problems with hand writing, and episodic vertigo occurred more frequently in SCA patients (Table 2). Restricted to these items, 12% of SCA1, 13% of SCA2, 15% of SCA3, and 24% of SCA6 patients started the disease with other symptoms but gait ataxia. Episodic vertigo was especially frequent as initial symptom in SCA6 patients when compared with other SCA subtypes (12.2% vs. 1.6–2.6%; $P < 0.03$; Fisher's Exact Test). Frequency of other early signs did not differ between SCA genotypes.

Double vision occurred up to 8 years before gait disturbance in SCA1, up to 23 years in SCA2, 16 years in SCA3, and 35 years in SCA6 (median 6 years). Episodic vertigo preceded gait ataxia by up to 10 years in SCA1, 1 year in SCA2, 2 years in SCA3, and 15 years in SCA6 (median 4 years). Four percent of SCA patients experienced these symptoms more than 5 years before onset of gait ataxia (5% in SCA1, 3% in SCA2, 2% in SCA3, and 8% in SCA6). Dysarthria and problems with hand writing were reported not more than 5 years before onset of gait ataxia.

CAG repeat length in the expanded allele was responsible for about 60% of variability in age at onset of gait ataxia in SCA1 and SCA2, for about 25% in SCA3, and about 20% in SCA6. No major differences in correlation with repeat length were observed when

TABLE 2. *Symptoms preceding gait abnormalities in SCA*

	Co	All SCA	SCA1	SCA2	SCA3	SCA6
Double vision	–	4.3	1.3	3.2	10.0**,[a]	4.2
Reduced visual acuity	4.1	2.1	5.1	1	–	2
Dysarthria	–	4.7	2.6	5.6*	3.3	8.2*
Frequent throat clearing	–	1.4	2.6	1.1	1.6	–
Problems with hand writing	–	4	5.3	5.6*	1.7	2.1
Episodic vertigo	1.6	3.9	2.6	2.1	1.6	12.2*
Neuropathic symptoms	4.1	2.9	4	–	4.8	4.1
Cramps	8.2	8.9	11.5	9.9	4.9	8
Restless legs syndrome	6.3	2.8	5.3	2.1	1.6	2
Sleep disturbances	9.0	4.7	2.6	2.2*	5	12.5
Urinary urgency	1.6	2.8	3.9	3.2	1.6	2
Other preceding symptoms		0.7	1.3	–	1.7	–

Proportion of patients (%) who reported onset of the respective symptom prior to gait ataxia.
*$P < 0.05$; **$P < 0.01$ (comparison of SCA vs. control group; Fisher's Exact Test after adjustment for age and sex).
[a]$P < 0.05$ (comparison to SCA1, 2, and 3).

information about age of onset was provided by patients or by their relatives or after discussion of both (Table 3). Under the hypothesis that long disease duration may hamper accuracy of memory concerning onset of the disease, we repeated correlations after exclusion of patients with the disease for more than 10 years. This improved correlations especially in SCA3 and SCA6 (Table 3, Fig. 1A–D). Exclusion of patients with more severe disease (SARA sum score above 20 points[14]) had a similar effect. Consideration of nongait symptoms did not further improve the predictive value of CAG repeat for age of onset (Table 3). No effect of normal alleles on age at onset was found.

We tested the hypothesis that initial symptoms of SCA may be determined by repeat length. No group differences in number of CAG repeats were found concerning first symptoms in any SCA genotype (Wilcoxon two-sample test).

TABLE 3. *Correlation of CAG repeat length and age of onset*

Age of onset defined by	SCA1 (%)	SCA2 (%)	SCA3 (%)	SCA6 (%)
Patients only[a]	57***	59***	27***	19**
Relatives only[a]	51***	61***	24***	17*
Patients + relatives[a]	57***	60***	26***	20**
Patients + relatives + duration < 10 yr[a]	64***	67***	46***	41***
Patients + relatives + SARA < 20[a]	53***	67***	47***	21**
Occurrence of diplopia, dysarthria, clumsiness, episodic vertigo, or gait disturbance	55***	54***	25**	2

Percentages to which repeat length determined age of onset are given for different definitions of disease onset.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a]Onset of progressive gait ataxia.

DISCUSSION

This systematic study on disease onset in SCA demonstrated that gait ataxia is the initial complaint in only two-thirds of patients. When rather unspecific symptoms like cramps, restless legs, and sleep disturbance were excluded still 16% of SCA patients report other problems than gait as the earliest symptom. Especially, diplopia and episodic vertigo but also dysrthria and clumsiness occurred prior to onset of gait ataxia. None of the early clinical signs had specificity for a certain SCA subtype but episodic vertigo was more common in SCA6. This reflects the close relationship of SCA6 and episodic ataxia type 2 (EA2), both of which are caused by mutations in the α_{1A}-subunit of the voltage-gated neuronal calcium channel.[16] Although patients with EA2 frequently develop cerebellar atrophy on MRI and permanent gait ataxia after longstanding disease, episodic ataxia has rarely been reported in patients with SCA6.[17–21]

Detection of early signs is of major importance for consecutive treatment management. If disease modulating compounds become available, they may be most efficient when introduced to patients in early stages of the disease. On the other hand, treatment before disease onset may not be advisable in drugs with potential side effects. Thus, reliable diagnosis of disease onset is a major challenge and recognition of nonataxia symptoms might be a promising approach.

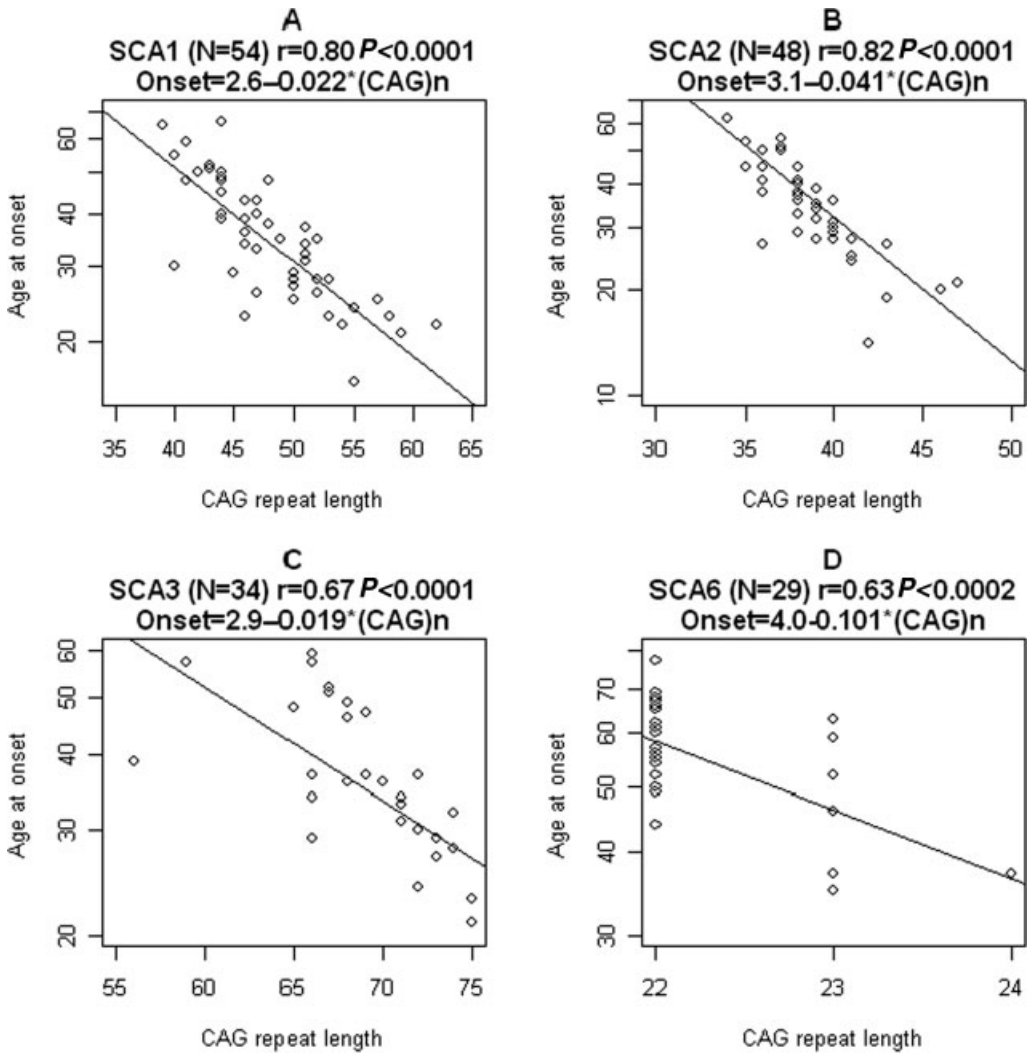

FIG. 1. Linear regression analysis of age at onset and length of expanded CAG repeat. Onset has been defined as beginning of progressive gait ataxia. Patients with disease durations of more than 10 years have been excluded.

Our results suggest that first symptoms may occur a decade or more before the onset of gait instability. The list of symptoms analyzed in this study is by no means complete but had to be restricted to problems that could be remembered with acceptable accuracy also after many years. In this respect, it is important to note that not only patients in late stages of the disease described early symptoms many years before onset of gait difficulties, but also patients with short disease duration and low SARA scores indicating less advanced disease reported problems such as diplopia to precede gait ataxia for up to 15 years.

Assessment of disease onset was poorly standardized in former studies.[4,5] In this study, the view of close relatives concerning the onset of gait ataxia differed from the patient's report in 17% of cases with a span of 5 to 20 years with mean differences between 1.2 and 4.5 years depending on the genotype. The largest differences between patients and relatives were observed when disease duration exceeded 10 years. These findings underline the importance of standardized assessment to yield most reliable results and stress the necessity of prospective studies of disease onset in SCA. Why SCA3 patients recognized onset of gait ataxia about 1 year earlier than their relatives, whereas SCA2 patients dated the beginning of gait difficulties 1 year later than their relatives remains unclear. It would be reasonable to expect that patients feel changes in gait stability before it becomes obvious from outside. Whether cognitive changes that are more pronounced in SCA2 than in other subtypes[22,23] contribute to the shift in recognition or memory in SCA2

has to be assessed in prospective studies including neuropsychological testing.

Our data confirm that CAG repeat length can only partially explain variability in age of onset of SCA. Our data revealed the closest correlation with CAG repeat length when (1) onset is defined by beginning of permanent gait disturbance and (2) patients with longstanding disease were excluded. Correlation did not improve further when nongait symptoms were taken into account. Interviews with caregivers did not improve correlation of onset age and CAG repeat length, although dates for onset varied substantially between patients and relatives. Under all conditions, CAG repeat length explained less than 50% of variability in age of onset in SCA3 and SCA6. In SCA6, the influence of repeat length may be masked by the rather uniform size of the expanded allele (22 CAG in 74% of SCA6 patients). However, our data show that onset variability in all SCA subtypes is driven by other genetic or environmental factors that remain to be identified. Given the enormous variability in onset data depending on the assessment strategy, prospective studies with standardized evaluation procedures of disease onset are necessary to identify disease modifiers that have minor effects than repeat length in expanded alleles.

Recent progress in the understanding of disease mechanisms in polyglutamine disorders and promising results in animal models[24–26] offer chances for clinical trials of potentially disease modifying compounds in the near future. If such compounds aim to delay disease, a precise prediction of onset age is warranted. This may not be possible for individual patients but is feasible for larger cohorts. To this end, recognition of early symptoms that may develop before the onset of gait ataxia is mandatory and will require prospective studies.

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APPENDIX

Instructions for the Structured Interview of Early Symptoms in SCA

Definition of Age at Onset

- Onset is defined as the beginning of permanent and progressive gait instability.
- Patients are asked for the onset of permanent and progressive gait instability. Orientation is provided from biography by asking for ataxia at major events in former years (e.g., 50th birthday party). Additionally, patient is confronted with onset data mentioned in former records if available.
- Close relatives are asked in the same manner. If no relatives accompany the patient call spouses or children.
- Then, ask the patient to settle potential discrepancies with the statement of his/her relatives for final determination of age at onset.
- Afterward, ask the patient for onset of gait ataxia in parents, sibs, and children. List these statements.

Early Symptoms of SCA

- After determination of onset of permanent gait instability ask the patient and his/her relatives for other symptoms of SCA that may have preceded the onset of gait ataxia. List spontaneous recall.
- Then, offer a list of potential early symptoms of SCA like
    - Double vision
    - Reduced visual acuity (If present, verify that this is due to retinopathy or optic atrophy)
    - Dysarthria
    - Problems with hand writing
    - Episodic vertigo
    - Weakness or sensory complaints related to peripheral neuropathy
    - Restless legs syndrome
    - Sleep disturbance (specify if possible)
    - Urinary urgency or incontinence.
- Ask for the year of first occurrence of symptoms that preceded gait ataxia.

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