The natural history of spinocerebellar ataxia type 1, 2, 3, and 6

A 2-year follow-up study

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ABSTRACT

Objective: To obtain quantitative data on the progression of the most common spinocerebellar ataxias (SCAs) and identify factors that influence their progression, we initiated the EUROSCA natural history study, a multicentric longitudinal cohort study of 526 patients with SCA1, SCA2, SCA3, or SCA6. We report the results of the 1- and 2-year follow-up visits.

Methods: As the primary outcome measure we used the Scale for the Assessment and Rating of Ataxia (SARA, 0–40), and as a secondary measure the Inventory of Non-Ataxia Symptoms (INAS, 0–16) count.

Results: The annual increase of the SARA score was greatest in SCA1 (2.18 ± 0.17, mean ± SE) followed by SCA3 (1.61 ± 0.12) and SCA2 (1.40 ± 0.11). SARA progression in SCA6 was slowest and nonlinear (first year: 0.35 ± 0.34, second year: 1.44 ± 0.34). Analysis of the INAS count yielded similar results. Larger expanded repeats and earlier age at onset were associated with faster SARA progression in SCA1 and SCA2. In SCA1, repeat length of the expanded allele had a similar effect on INAS progression. In SCA3, SARA progression was influenced by the disease duration at inclusion, and INAS progression was faster in females.

Conclusions: Our study gives a comprehensive quantitative account of disease progression in SCA1, SCA2, SCA3, and SCA6 and identifies factors that specifically affect disease progression. *Neurology*® 2011;77:1035–1041

GLOSSARY

ADCA = autosomal dominant cerebellar ataxia; **ICARS** = International Cooperative Ataxia Rating Scale; **INAS** = Inventory of Non-Ataxia Symptoms; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCA** = spinocerebellar ataxia.

The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of dominantly inherited ataxia disorders. By now, almost 30 different gene loci have been found. The most common SCAs, which together account for more than half of all affected families, are SCA1, SCA2, SCA3, and SCA6.[1–3] Each of these disorders is caused by a translated CAG repeat expansion mutation.[4–8]

The clinical phenotypes of SCA1, SCA2, SCA3, and SCA6 have been firmly established. In all of them, progressive ataxia is the predominant clinical manifestation. However, patients

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Supplemental data at www.neurology.org

Supplemental Data

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with SCA1, SCA2, and SCA3 frequently present with additional nonataxia symptoms,[9–16] whereas SCA6 is considered an almost purely cerebellar disorder. SCA6 is also different as it usually begins between the age of 50 to 60 years, whereas SCA1, SCA2, and SCA3 have an onset between 30 and 40 years.[17,18] Much less is known about the natural history of these disorders. In particular, quantitative information on the rate of disease progression is almost completely lacking.[19–21]

To obtain quantitative data on disease progression in the common SCA disorders, we initiated the EUROSCA natural history study, a multicentric longitudinal cohort study of 526 patients with SCA1, SCA2, SCA3, or SCA6.[16] We report the results of the 1- and 2-year follow-up visits. Apart from determining and comparing the rate of disease progression in SCA1, SCA2, SCA3, and SCA6, we analyzed how gender, repeat length of the expanded and normal allele, age at onset, and disease duration affect the progression rate.

METHODS

Study design. The study was performed at 17 European centers which together form the EUROSCA clinical group. Patients were eligible when they had progressive, otherwise unexplained ataxia and a positive molecular genetic test for SCA1, SCA2, SCA3, or SCA6. Cases were ascertained with the help of an electronic patient registry. Patients were consecutively recruited within a predetermined period between July 2005 and August 2006.[16] Assessments were done according to a written study protocol. Patients were first seen at a baseline visit (visit 1), followed by visits after 1 year (visit 2) and after 2 years (visit 3). There were maximally 3 investigators at each center. In 9 of 17 centers, patients were seen by the same investigator at all visits. In the remaining centers, investigators changed in a subset of patients. All investigators were experienced in the use of the applied scales.

Outcome measures. As the primary outcome measure to assess disease progression, we used the Scale for the Assessment and Rating of Ataxia (SARA).[22] The SARA sumscore ranges from 0 to 40 with 0 indicating absence of ataxia and 40 the most severe degree of ataxia.

The Inventory of Non-Ataxia Symptoms (INAS) was used as a secondary outcome measure. INAS was devised to assess nonataxia symptoms in SCAs.[16] It consists of 30 items which are grouped into the following 16 symptoms or syndromes: areflexia, hyperreflexia, extensor plantar response, spasticity, paresis, amyotrophy, fasciculations, myoclonus, rigidity, chorea, dystonia, resting tremor, sensory symptoms, brainstem oculomotor signs, urinary dysfunction, and cognitive impairment. In this study, only the presence or absence of one of these symptoms was considered. When several INAS items were related to one symptom, the symptom was recorded as present if at least one item was positive. The number of nonataxia symptoms was counted in each patient yielding the INAS count with a range from 0 to 16.

Genetic analysis. Repeat lengths of the expanded and normal alleles were determined at the Department of Human Genetics of the University of Tübingen. At baseline, DNA samples were available in 450 of the 526 study participants. In 53 participants, information about repeat lengths was taken from medical records.[16] From those in whom DNA samples and repeat length information was lacking, DNA samples were taken at follow-up visits so that repeat length information was available in all but 3 patients who were seen for any follow-up.

Statistical analysis. Patient characteristics are given as mean ± SD. To analyze disease progression, a linear mixed model was used. Center, family, and pseudonym nested in the family were considered as random effect. First, linearity of the progression rate was tested via nested models (likelihood ratio test). Second, an analysis of covariance was performed with SARA or INAS count as dependent variables and gender, age at onset, disease duration, repeat length of the expanded allele, and repeat length of the normal allele as independent variables. Influence of these variables on the progression rate was tested via interactions between the given factor and the time variable. The model was also adjusted on family and center effect. Independent factors that were significant in the univariate analysis were included in a multivariate model, including the interactions with backward selection. Estimates derived from the model are given as mean ± SE. To identify a possible effect of disease severity at baseline on disease progression, we correlated the SARA increase with the baseline SARA score. Statistical analyses were performed with SAS 9.1 software (SAS Institute, Cary, NC). All tests were 2-sided. Test results were considered significant at the 0.05 level.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committees of the contributing centers. Informed and written consent was obtained from all study participants.

RESULTS

Patients. At baseline (visit 1), the study population consisted of 526 patients (SCA1: 117, SCA2: 163, SCA3: 139, SCA6: 107). Demographic and clinical data are given in table 1. After 1 year (visit 2), 479 patients (SCA1: 113, SCA2: 155, SCA3: 125, SCA6: 86), and after 2 years (visit 3), 415 patients (SCA1: 88, SCA2: 132, SCA3: 111, SCA6: 84) were seen (figure e-1 on the *Neurology*® Web site at www.neurology.org). Eleven patients were seen at visit 3, but not at visit 2. Of the 111 patients who were not seen at visit 3, 51 were lost to follow-up, 26 had died (SCA1: 11, SCA2: 7, SCA3: 8), 20 had withdrawn consent, and 14 were not seen for other reasons. Baseline characteristics of patients with SCA1, SCA2, and SCA6 with at least one follow-up and those without any follow-up were not different. Patients with SCA3 without follow-up had an earlier age at onset (28 ± 10 vs 38 ± 11, $p = 0.0106$) and a higher SARA score (24 ± 10 vs 14 ± 8, $p = 0.0029$) (table e-1).

A total of 780 of 894 (87.2%) of all follow-up visits were done in a time window of ± 3 months around the scheduled time. Eleven patients with deviations of more than 6 months were reclassified to the earlier or later visit. Eleven patients in whom visit

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Table 1 Demographic, genetic, and clinical characteristics of the study population[a]

	SCA1	SCA2	SCA3	SCA6
No.	117	163	139	107
No. of families	90	103	107	81
M/F	71/46	75/88	73/66	58/49
Repeat length expanded allele	47.4 ± 5.2 (39-66)	39.3 ± 3.2 (33-52)	68.8 ± 4.6 (56-91)	22.4 ± 0.9 (21-28)
Repeat length normal allele	28.9 ± 1.7 (22-36)	22.2 ± 1.4 (14-33)	21.7 ± 5.0 (14-35)	12.6 ± 1.1 (8-16)
Age, y	46.3 ± 12.2 (18-76)	46.3 ± 13.3 (18-84)	48.8 ± 11.8 (14-81)	64.9 ± 11.0 (37-85)
Age at onset, y	37.0 ± 10.6 (15-65)	34.9 ± 12.7 (7-66)	37.1 ± 11.4 (5-66)	54.5 ± 10.2 (31-77)
Disease duration, y	9.5 ± 5.5 (1-28)	11.3 ± 6.5 (0-40)	11.6 ± 5.9 (1-28)	10.4 ± 6.4 (1-33)
SARA score	15.6 ± 9.1 (2-40)	15.8 ± 8.0 (2-39)	15.1 ± 8.6 (1-40)	15.0 ± 6.7 (1-33)

Abbreviations: SARA = Scale for the Assessment and Rating of Ataxia; SCA = spinocerebellar ataxia.
[a] If applicable, values are given as mean ± SD (range).

3 was performed more than 2.5 years after inclusion were discarded from this analysis.

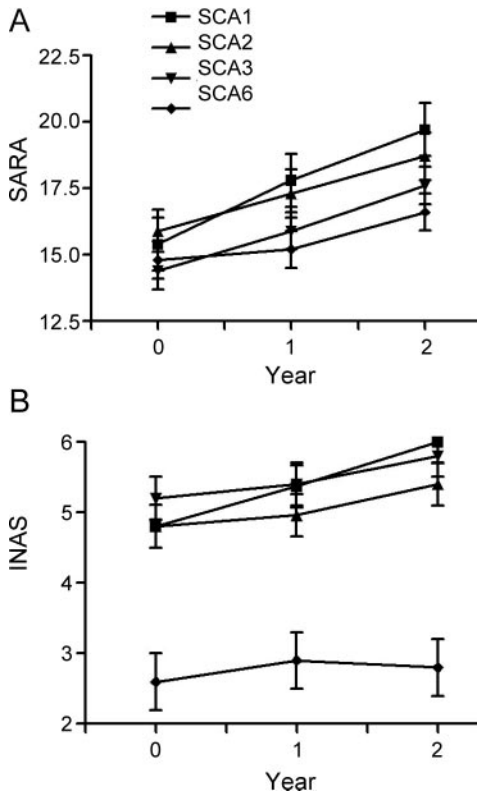
Disease progression. To assess disease progression, we used the SARA score. SARA scores at baseline did not differ between SCA1 (15.4 ± 1.0, mean ± SE), SCA2 (15.9 ± 0.8), SCA3 (14.4 ± 0.7), and SCA6 (14.8 ± 0.7). The annual increase of the SARA score was 2.18 ± 0.17 in SCA1 ($p < 0.0001$), 1.40 ± 0.11 in SCA2 ($p < 0.0001$), and 1.61 ± 0.12 in SCA3 ($p < 0.0001$). Progression was faster in SCA1 than in SCA2 ($p < 0.0001$) and SCA3 ($p = 0.0033$), whereas progression rate did not differ between SCA2 and SCA3. In SCA6, progression was nonlinear. SARA increased by 0.35 ± 0.34 in the first year ($p = 0.29$) and by 1.44 ± 0.34 in the second year ($p < 0.0001$) (figure 1A).

As a secondary measure of disease progression, we used the INAS count. INAS count at baseline did not differ among SCA1 (4.8 ± 0.3), SCA2 (4.7 ± 0.3), and SCA3 (5.3 ± 0.3), but was smaller in SCA6 (2.6 ± 0.3, $p < 0.0001$). The annual increase of the INAS score was 0.56 ± 0.11 in SCA1 ($p < 0.0001$), 0.30 ± 0.08 in SCA2 ($p = 0.0002$), and 0.30 ± 0.08 in SCA3 ($p = 0.0005$). Progression in SCA1 was faster than in SCA2 and SCA3 ($p < 0.0001$). The INAS count did not increase in patients with SCA6 (0.10 ± 0.08, $p = 0.22$) (figure 1B).

Determinants of disease progression. In SCA1, earlier age at onset and larger expanded alleles were associated with faster SARA progression. An earlier onset of 1 year accelerated the annual SARA increase by 0.04 ± 0.02 ($p = 0.0054$) and one additional repeat by 0.11 ± 0.03 ($p = 0.0007$) (figure 2A). Multivariate analysis indicated that repeat length of the expanded allele was an independent factor in SCA1, whereas the effect of age at onset lost significance when adjusted for repeat length. Repeat length of the expanded allele had a similar effect on INAS progression in SCA1. One additional unit accelerated INAS increase by 0.05 ± 0.02 ($p = 0.0133$) (figure 2B).

In SCA2, earlier age at onset and larger expanded alleles were associated with faster SARA progression.

Figure 1 Time course of disease progression in spinocerebellar ataxia (SCA)1, SCA2, SCA3, and SCA6 with Scale for the Assessment and Rating of Ataxia (SARA) (A) and Inventory of Non-Ataxia Symptoms (INAS) (B) as outcome measure



Data are given as mean ± SE.

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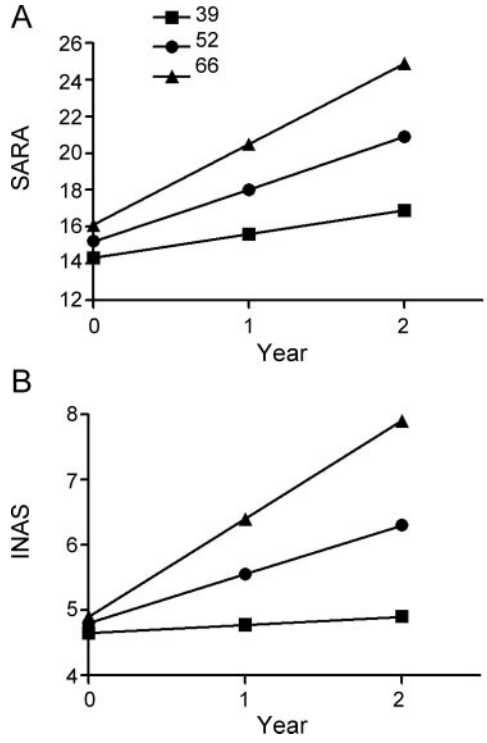
Figure 2 **Effect of the repeat length of the expanded allele on evolution of Scale for the Assessment and Rating of Ataxia (SARA) (A) and Inventory of Non-Ataxia Symptoms (INAS) (B) in spinocerebellar ataxia (SCA) 1**



An earlier onset of 1 year accelerated the annual SARA increase by 0.03 ± 0.01 ($p = 0.0013$) and one additional repeat by 0.10 ± 0.03 ($p = 0.0047$). In the multivariate analysis, age at onset was the only independent factor. We did not identify factors that had an influence on INAS progression in SCA2.

In SCA3, SARA progression increased by 0.05 ± 0.02 ($p = 0.02$) with each additional year of disease duration. The rate of INAS increase depended on gender. Female patients had a faster progression (0.56 ± 0.11) than male patients (0.08 ± 0.12, $p = 0.0041$). Baseline characteristics of male and female patients with SCA3 were not different (table e-2).

In SCA6, gender had an effect on SARA progression. Male patients with SCA6 had a linear increase of 0.60 ± 0.17 ($p = 0.0007$), whereas the increase was nonlinear in female patients with SCA6 with an increase of 0.03 ± 0.60 ($p = 0.95$) in the first and 2.49 ± 0.61 ($p < 0.0001$) in the second year. In male patients with SCA6, longer disease duration at baseline decreased SARA progression (0.05 ± 0.02 per year, $p = 0.008$), whereas larger normal alleles increased it (0.38 ± 0.16 per unit, $p = 0.02$). Baseline characteristics of male and female patients with SCA6 were not different (table e-2). Multivariate analysis showed that disease duration and length of the normal allele were independent factors in male patients with SCA6. We did not identify factors that influenced SARA progression in female patients with SCA6.

In none of the subgroups did the baseline SARA score have an influence on SARA progression.

DISCUSSION This study provides a quantitative account of the natural history of the 4 most common SCAs. It is based on an analysis of the first 2 years of the ongoing EUROSCA natural history study, a multicentric longitudinal cohort study of 526 patients.

This is a prospective study that compares the natural history of SCA1, SCA2, SCA3, and SCA6. A previous natural history study of a large group of patients with ataxia that included 36 patients with SCA1, 56 patients with SCA2, and 110 patients with SCA3 measured disease progression by retrospective assessment of 4 disease stages.[19] The advantages of the present study are its prospective nature and the use of validated clinical scales. Conversely, the observation period of 2 years is comparably small given the median survival times of patients with SCA that range from 21 to 25 years. A continuation of the present study is therefore highly desirable. All patients were enrolled at tertiary referral centers and had moderate disease severity that still allowed most of them to travel to the respective center. The cohort is thus not fully representative for the entire SCA population which includes also patients in more advanced disease stages. Conversely, the target population for future interventional trials will probably closely resemble the present cohort.

Using SARA and the INAS count as outcome measures, we found that disease progression was fastest in SCA1 followed by SCA2 and SCA3, in which progression rate did not differ. Disease progression was slowest in SCA6. That both scales showed consistent differences of disease progression is not self-evident because SARA and INAS were devised to measure different and complementary aspects of the SCA disease phenotype. Whereas SARA is a measure of ataxia and thus reflects dysfunction of the cerebellum and its connections, INAS assesses nonataxia symptoms caused by dysfunction of parts of the nervous system other than the cerebellum and its connections.[22] The observation that the SARA score and INAS count change in a parallel manner suggests that the development of neurodegeneration in noncerebellar structures runs in parallel with that in the cerebellum itself.

The faster disease progression in SCA1 compared to the other SCA disorders is consistent with the results of the baseline analysis of the EUROSCA study.

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In this analysis, we found that SARA increased with disease duration in all genotypes, but that the correlation curve in SCA1 had a steeper increase than the curves in SCA2, SCA3, and SCA6.[16] Our results also agree with our earlier retrospective study.[19]

The progression rate of ataxia in SCA3 that we determined in the present study is in remarkable agreement with that reported in a recent prospective study of 34 Brazilian patients with SCA3 that used the International Cooperative Ataxia Rating Scale (ICARS) as an outcome measure.[20] The patients included in this study had almost the same baseline characteristics as our patients with SCA3. If one relates the annual score changes in both studies to the maximum SARA or ICARS score value, the annual increase was 4.0% in our study and 4.7% in the Brazilian study.

In the retrospective study mentioned above, a small group of patients with dominantly inherited ataxia and pure cerebellar phenotype classified as autosomal dominant cerebellar ataxia type III (ADCA-III) was included in whom molecular genetic testing had not been performed.[23] A part of these patients may have had SCA6. Disease progression of the ADCA-III group was indeed slower than that of the group with additional noncerebellar symptoms named ADCA-I that was mainly composed of patients with SCA1, SCA2, and SCA3.[19] We have currently no explanation for the nonlinear disease progression in female patients with SCA6. Continuation of this cohort will show whether progression remains nonlinear in this subgroup.

Patients with SCA6 in our study had 2 to 3 nonataxia symptoms, an observation that challenges the view that SCA6 is a purely cerebellar disorder. However, we did not detect an increase of the INAS count within the 2-year follow-up period. This may suggest that a part of the nonataxia symptoms in SCA6 are owed to the higher age of patients with SCA6. Conversely, the 2-year observation period may have been too short to observe clinical signs of a disease-associated progression of extracerebellar neurodegeneration.

In inherited neurodegenerative diseases caused by CAG repeat expansions, the length of the expanded repeat is a major determinant of the clinical phenotype. In all CAG repeat disorders, larger repeats are associated with an earlier disease onset.[8,24] The baseline analysis of the present cohort showed that repeat length determined the severity of ataxia as measured by SARA in SCA1, SCA2, and SCA3, but not in SCA6. Further, repeat length was shown to have an influence on the number, type, and severity of accompanying nonataxia symptoms.[16] This effect is particularly strong in SCA3 in which the phenotypic variability can be at least partly explained by differences in repeat length of the expanded allele.[25] The effect of repeat length on disease progression is less clear. In the retrospective natural history study, larger repeats were associated with an increased risk to reach advanced disease stages in SCA2 and SCA3.[19] A similar effect of CAG repeat length was observed in a prospective study of 156 Brazilian patients with SCA3.

In SCA1, the length of the expanded allele had a strong effect on disease progression irrespective whether SARA or INAS was used as an outcome measure. A similar effect of the repeat length on disease progression was not reported in the previous retrospective study. However, in this study, earlier age at onset was associated with faster progression in SCA1.[19] As repeat length and age at onset are closely related in polyglutamine disorders, it is difficult to dissect effects of repeat length and age at onset. This argument likewise applies to our SCA2 results. Taken together, all available data prove an important and strong effect of the length of the expanded allele on disease progression in SCA1 and SCA2.

Consistent with one of the two published prospective SCA3 studies, we did not find an effect of the length of the expanded allele on disease progression in SCA3.[20] Similarly, there was no effect on the length of the expanded allele on disease progression in SCA6, which is not surprising given the small variation of length of the expanded allele in this disorder. Instead, male patients with SCA6 with larger normal alleles had a faster progression. Effects of the length of the normal alleles have been previously described in SCA1, SCA6, and Huntington disease. In SCA1, shorter normal alleles are associated with an earlier disease onset and more severe ataxia; in SCA6, larger normal alleles are associated with an earlier age at onset.[16,24] In Huntington disease, increasing sizes of the normal alleles were found to correlate with a more severe phenotype, whereas in patients with large expansions, the size of the normal allele had the opposite effect.[26] It is hypothesized that these associations are due to an interaction of the poyglutamine domains of the normal and expanded disease protein. The present observations in male patients with SCA6 together with previously published data on a relation between larger normal alleles and earlier disease onset in SCA6 suggest that longer normal alleles in SCA6 are associated with a more severe phenotype characterized by earlier disease onset and faster progression.[24]

In SCA3 and SCA6, effects of gender were observed. These effects were not related to different baseline characteristics of male and female patients. A faster progression to advanced disease stages of female patients with SCA2 and SCA3 was reported in the previous retrospective study.[19] Similarly, a trend toward a faster increase of ICARS score in female patients with SCA3 was found in a previous SCA3

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study.[20] The biological mechanism underlying the accelerating effect of female gender on disease progression in SCAs is presently unknown.

AUTHOR CONTRIBUTIONS

Dr. Jacobi: research project organization, research project execution, statistical analysis design, statistical analysis review and critique, manuscript review and critique. Dr. Bauer: research project conception, research project organization, research project execution, statistical analysis design, statistical analysis review and critique, manuscript review and critique. Dr. Giunti: research project conception, research project organization, research project execution, statistical analysis design, statistical analysis review and critique, manuscript review and critique. Dr. Labrum: research project organization, research project execution, statistical analysis review and critique, manuscript review and critique. Dr. Sweeny: research project organization, research project execution, statistical analysis review and critique, manuscript review and critique. 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