Spinocerebellar ataxia types 1, 2, 3, and 6

Disease severity and nonataxia symptoms

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Supplemental data at www.neurology.org

ABSTRACT

Objective: To identify factors that determine disease severity and clinical phenotype of the most common spinocerebellar ataxias (SCAs), we studied 526 patients with SCA1, SCA2, SCA3. or SCA6.

Methods: To measure the severity of ataxia we used the Scale for the Assessment and Rating of Ataxia (SARA). In addition, nonataxia symptoms were assessed with the Inventory of Non-Ataxia Symptoms (INAS). The INAS count denotes the number of nonataxia symptoms in each patient.

Results: An analysis of covariance with SARA score as dependent variable and repeat lengths of the expanded and normal allele, age at onset, and disease duration as independent variables led to multivariate models that explained 60.4% of the SARA score variance in SCA1, 45.4% in SCA2, 46.8% in SCA3, and 33.7% in SCA6. In SCA1, SCA2, and SCA3, SARA was mainly determined by repeat length of the expanded allele, age at onset, and disease duration. The only factors determining the SARA score in SCA6 were age at onset and disease duration. The INAS count was 5.0 ± 2.3 in SCA1, 4.6 ± 2.2 in SCA2, 5.2 ± 2.5 in SCA3, and 2.0 ± 1.7 in SCA6. In SCA1, SCA2, and SCA3, SARA score and disease duration were the strongest predictors of the INAS count. In SCA6, only age at onset and disease duration had an effect on the INAS count.

Conclusions: Our study suggests that spinocerebellar ataxia (SCA) 1, SCA2, and SCA3 share a number of common biologic properties, whereas SCA6 is distinct in that its phenotype is more determined by age than by disease-related factors. *Neurology*® 2008;71:982–989

GLOSSARY

INAS = Inventory of Non-Ataxia Symptoms; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCA** = spinocerebellar ataxia.

The spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of autosomal dominantly inherited progressive ataxia disorders. Up to now, more than 25 different gene loci have been found. In more than 10 SCAs, the affected genes and causative mutations have been identified. The most common SCAs, which together account for more than half of all affected families, are SCA1, SCA2, SCA3, and SCA6. Each of these disorders is caused by a translated CAG repeat expansion mutation.[1-6] Expanded CAG repeats are dynamic mutations with variable length that may change during transmission. Patients with longer repeats have an earlier disease onset, a more severe phenotype, and faster disease progression than patients with shorter repeats.[7-9]

In all SCAs, ataxia is the predominant clinical manifestation. Nevertheless, patients may present with additional nonataxia symptoms. SCA1, SCA2, and SCA3 are characterized by the appearance of such additional symptoms.[10-16] SCA6, on the other hand, is considered an almost purely cerebellar disorder. SCA6 is also different in that it begins between the age of 50 to 60

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years while most other SCAs including SCA1, SCA2, and SCA3 have an onset between 30 and 40 years.[17,18]

Although there are numerous studies that describe clinical manifestations of SCA1, SCA2, SCA3, and SCA6, knowledge of the factors that determine disease severity and clinical phenotype of SCAs is limited. This is because large comparative studies using validated clinical outcome measures are lacking. We therefore performed a multicenter study that included 526 patients with SCA1, SCA2, SCA3, or SCA6. All patients underwent a standardized clinical evaluation using scales that measure severity of ataxia and presence of nonataxia symptoms. We were particularly interested to learn how repeat length, age at onset, and disease duration affect severity of ataxia and appearance of nonataxia symptoms.

METHODS 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 that contains data of all SCA patients that have been in contact with one of the study centers. Patients were consecutively recruited within a predetermined period between July 2005 and August 2006. The study population consisted of 526 patients (SCA1: 117, SCA2: 163, SCA3: 139, SCA6: 107).

Assessments were done according to a written study protocol. There were maximally three investigators at each center. All investigators were experienced in the use of the applied scales.

To measure the severity of ataxia we used the Scale for the Assessment and Rating of Ataxia (SARA) that has been recently developed and validated.[19] The SARA sum score ranges from 0 to 40 with 0 indicating absence of ataxia and 40 the most severe degree of ataxia.

Nonataxia symptoms were assessed with the Inventory of Non-Ataxia Symptoms (INAS). INAS consists of 30 items, each of which is related to one of 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 (horizontal and vertical ophthalmoparesis, slowing of saccades), 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, a dimensionless value with a range from 0 to 16. Reliability of INAS ratings was previously tested in two clinical trials that served to validate SARA. For most INAS items, it was found to be acceptable.

In 450 of the 526 study participants, DNA samples were available. In these samples, repeat lengths of the expanded and normal alleles were determined at the Department of Human Genetics of the University of Tübingen. In 53 participants, information about repeat lengths was taken from medical records. In the remaining 23 participants, information on repeat length was lacking.

Statistical analyses were performed with SAS 8 software (SAS Institute, Cary, NC). Test results were considered significant at the 0.05 level. Patient clinical characteristics were compared among SCA groups with an analysis of variance for continuous variables and with a χ^2 test for categorical variables. Associations between the SARA score and covariates were tested using Pearson correlation test for continuous variables and univariate analysis of variance for categorical variables. For each SCA group, an analysis of covariance was performed with SARA score as dependent variable and gender, repeat lengths of the expanded and normal allele, age at onset, and disease duration as independent variables. The model was adjusted on family and center effect, and simple interactions were included. Effects were removed in descending significance, until all remaining effects were significant at the 0.05 level (backward selection). Relationships between nonataxia symptoms and clinical characteristics were studied using univariate logistic regressions with Bonferroni correction. For each SCA type, modeling of INAS count was performed with an analysis of covariance. As for SARA modeling, independent effects were backward selected.

The study was approved by the ethics committees of the contributing centers. Informed and written consent was obtained from all study participants.

RESULTS **Patients.** Demographic and clinical data of the study population are given in table 1. The patients with SCA1 (n = 117) came from 90 families, the SCA2 (n = 163) from 103, the SCA3 (n = 139) from 107, and the SCA6 (n = 107) from 81. Age and age at onset were similar in SCA1 (age: 46.3 ± 12.2 years; age at onset: 37.0 ± 10.6 years), SCA2 (age: 46.3 ± 13.3 years; age at onset: 34.9 ± 12.7 years), and SCA3 (age: 48.8 ± 11.8 years; age at onset: 37.1 ± 11.4 years), but considerably higher in SCA6 (age: 64.9 ± 11.0 years; age at onset: 54.5 ± 10.2 years). In contrast, disease duration was in the same range in all groups (SCA1: 9.5 ± 5.5 years; SCA2: 11.3 ± 6.5 years; SCA3: 11.6 ± 5.9 years; SCA6: 10.4 ± 6.4 years).

Ataxia. Disease severity, as indicated by the SARA score, was similar in all groups (SCA1: 15.6 ± 9.1; SCA2: 15.8 ± 8.0; SCA3: 15.1 ± 8.6; SCA6: 15.0 ± 6.7) (table 1). The SARA score increased with repeat length of the expanded allele in SCA2 and SCA3, but not in SCA1 and SCA6. There was no correlation between SARA and repeat length of the normal allele in any of the groups. In SCA1 and SCA6, but not in SCA2 and SCA3, SARA increased with age. In SCA2, but not in the other SCA disorders, SARA was greater in patients with earlier disease onset. In all groups, the SARA score increased with disease duration (table 2). Inspection of the correlation curves showed that the increase of the SARA score over time was faster in SCA1 than in the other groups. This was confirmed by an analysis of covariance that re-

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

	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	15.6 ± 9.1 (2-40)	15.8 ± 8.0 (2-39)	15.1 ± 8.6 (1-40)	15.0 ± 6.7 (1-33)
INAS count	5.0 ± 2.3 (0-11)	4.6 ± 2.2 (0-13)	5.2 ± 2.5 (0-12)	2.0 ± 1.7 (0-9)

If applicable, values are given as mean ± SD (range).
SCA = spinocerebellar ataxia; SARA = Scale for the Assessment and Rating of Ataxia; INAS = Inventory of Non-Ataxia Symptoms.

vealed an interaction between SCA type and disease duration ($p < 0.001$).

An analysis of covariance with SARA score as dependent variable and gender, repeat lengths of the expanded and normal allele, age at onset, and disease duration as independent variables led to multivariate models of SARA that explained 60.4% of the variance in SCA1, 45.4% in SCA2, 46.8% in SCA3, and 33.7% in SCA6. The estimates and p values of the respective values are given in table e-1 on the *Neurology*® Web site at www.neurology.org. In none of the groups did gender have an effect on the SARA score. Age was not included in the model, as it is the sum of age at onset and disease duration.

The multivariate models predicting the SARA score in SCA1, SCA2, and SCA3 were quite similar. SARA was mainly determined by disease duration, age at onset, and repeat length of the expanded allele. In all three disorders, there were positive interactions between disease duration and age at onset as well as disease duration and repeat length of the expanded allele indicating an increase of the SARA score with each of these factors. Repeat length of the normal allele was included only in the SCA1 model. The negative estimate of the interaction between the repeat length of the expanded and normal allele indicates that the disease is most severe with long expanded and short normal alleles (table e-1). The effect of the repeat lengths on the SARA score in SCA1 is illustrated in the figure. In this example, age at onset (37 years) and disease duration (9 years) were set at the median values of the SCA1 group.

The only factors determining the SARA score in SCA6 were age at onset and disease duration. Higher age at onset and longer disease duration predicted more severe ataxia (table e-1).

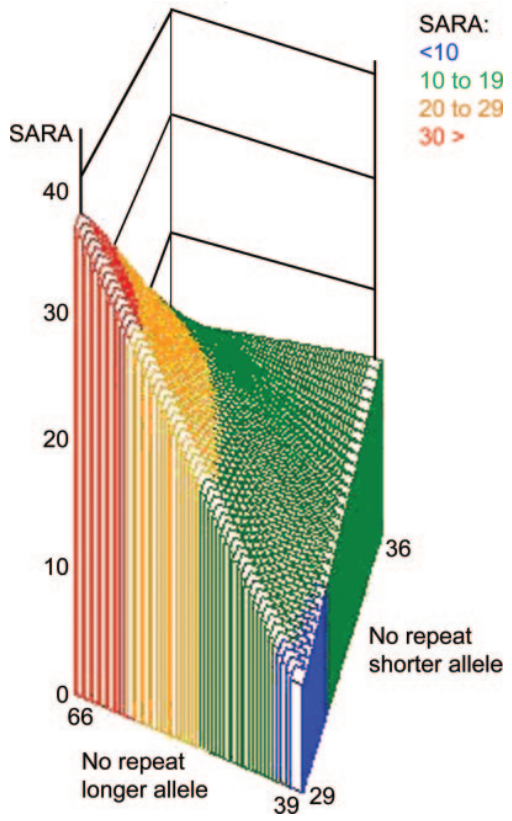
Nonataxia symptoms. The distribution of nonataxia symptoms among the groups was uneven (table 3). Pyramidal tract signs were most frequent in SCA1,

Table 2 Correlation of the SARA score and the INAS count with repeat lengths of expanded and normal allele, age, age at onset, disease duration, and among SARA and INAS

	SCA1		SCA2		SCA3		SCA6	
	SARA	INAS	SARA	INAS	SARA	INAS	SARA	INAS
Repeat length expanded allele	NS	NS	0.38	0.38	0.35	0.31	NS	NS
Repeat length normal allele	NS	NS	NS	NS	NS	NS	NS	NS
Age, y	0.28*	NS	NS	−0.23*	NS	NS	0.38	0.31
Age at onset, y	NS	NS	−0.28	−0.31	NS	−0.29	NS	NS
Disease duration, y	0.65	0.39	0.39	0.16†	0.49	0.40	0.53	0.38
SARA	—	0.62	—	0.61	—	0.61	—	NS

Correlation coefficients are given. All p values were <0.001, unless otherwise stated.
*$p < 0.01$, †$p < 0.05$.
SARA = Scale for the Assessment and Rating of Ataxia; INAS = Inventory of Non-Ataxia Symptoms; SCA = spinocerebellar ataxia; NS = not significant.

Figure **Graphical display of the effects of the repeat lengths of the expanded and normal alleles on the SARA score in SCA1**



Family and center were entered in the model as random effect. The SARA values predicted by the multivariate model are depicted by the colored bars. For this example, age at onset (37 years) and disease duration (9 years) were set at the median values of the SCA1 group. SARA = Scale for the Assessment and Rating of Ataxia; SCA = spinocerebellar ataxia.

whereas motor symptoms indicating peripheral nerve involvement were most frequent in SCA2. Myoclonus, rigidity, chorea/dyskinesia, dystonia, and resting tremor were rare in all groups with the exception of dystonia, which was found in 23.9% of all patients with SCA3.

To identify factors that determine the occurrence of specific nonataxia symptoms we performed a logistic regression for each symptom with repeat length of the expanded allele, age at onset, age, disease duration, and SARA score as independent variables. For SCA1, this analysis showed that higher age was associated with urinary dysfunction and cognitive impairment. In SCA2, longer repeats and earlier age at onset increased the likelihood of muscle atrophy and brainstem oculomotor signs. Longer repeats were further associated with chorea/dyskinesia and dystonia. In SCA3, larger repeats and earlier age at onset were associated with spasticity and hyperreflexia. In contrast, motor symptoms indicating peripheral nerve involvement in SCA3 were more likely with higher age at onset, higher age, and longer disease duration. In SCA6, the likelihood of a number of symptoms increased with age at onset, disease duration, and age. Higher SARA score increased the risks of various nonataxia symptoms in all four diseases. A list of those symptoms that were significantly affected by repeat length, age at onset, age, or disease duration is given in table 4.

The INAS count, which is a measure of noncerebellar involvement, was similar in SCA1 (5.0 ± 2.3), SCA2 (4.6 ± 2.2), and SCA3 (5.2 ± 2.5) and considerably lower in SCA6 (2.0 ± 1.7) (table 1). The INAS count increased with disease duration in all groups, and with SARA in SCA1, SCA2, and SCA3. In SCA2 and SCA3, the INAS count increased with repeat length of the expanded allele and decreased with age at onset (table 2).

An analysis of covariance with the INAS score as dependent variable and repeat length of the expanded allele, age at onset, and disease duration as independent variables led to multivariate models of INAS that explained only 15.2% (SCA1) to 41.2% (SCA6) of the variance. When SARA was included, this value increased to 43.1% in SCA1, 48.3% in SCA2, and 57.5% in SCA3, whereas SARA was no significant predictor for the INAS count in SCA6. The strongest predictors of the INAS count in SCA1, SCA2, and SCA3 were SARA score and disease duration. In SCA6, only age at onset and disease duration had an effect on INAS count (table e-2).

DISCUSSION This study provides a comprehensive and quantitative account of the clinical phenotypes and their determining factors of the four most common SCAs: SCA1, SCA2, SCA3, and SCA6. The analysis is based on a cross-sectional examination of 526 patients with SCA using standardized and validated clinical assessment instruments.

To assess disease severity we used the newly developed SARA scale that is based on a semiquantitative assessment of cerebellar ataxia on an impairment level. SARA underwent a rigorous validation procedure involving three clinical trials in large groups of patients with SCA and non-SCA ataxia, and controls. Although the cerebellum is directly involved in the coordination of eye movements, oculomotor functions are not considered in SARA as the validation trials indicated that they are determined by other factors than appendicular and midline ataxia.[19,20]

The present data allowed calculating genotype-specific multivariate models that predicted the SARA score with considerable accuracy. The part of the variance that was explained ranged from 33.7% in SCA6 to 60.4% in SCA1. In accordance with the

Table 3 Frequency of nonataxia symptoms

	SCA1	SCA2	SCA3	SCA6	*p*
Hyperreflexia	67.5	13.2	40.1	21.9	<0.001
Areflexia	17.9	64.4	57.8	23.8	<0.001
Extensor plantar	50.5	31.0	41.9	2.0	<0.001
Spasticity	59.3	8.9	44.4	13.6	<0.001
Paresis	22.4	14.4	24.8	5.7	<0.001
Muscle atrophy	29.1	22.5	39.0	10.7	<0.001
Fasciculations	39.1	38.3	37.0	2.8	<0.001
Myoclonus	4.3	13.7	4.4	0.0	<0.001
Rigidity	1.7	7.4	10.3	5.7	NS
Chorea/dyskinesia	6.8	6.8	10.1	1.9	NS
Dystonia	12.8	14.2	23.9	4.7	<0.001
Resting tremor	6.8	14.9	3.6	1.9	<0.001
Sensory symptoms	62.4	68.4	65.6	48.0	NS
Urinary dysfunction	35.0	40.4	45.6	31.1	NS
Cognitive impairment	21.5	25.9	19.3	10.5	NS
Brainstem oculomotor signs	74.1	87.0	67.9	25.2	<0.001

Values are percentages. After Bonferroni correction, only *p* values <0.0031 were considered significant.
SCA = spinocerebellar ataxia; NS = not significant.

progressive course of these diseases, disease duration was positively correlated with SARA score in the univariate analysis and a strong predictor of the SARA score in the multivariate models of all groups. A comparison of the regression curves revealed that progression was fastest in SCA1 and somewhat slower in SCA2, SCA3, and SCA6. This is in line with clinical observations suggesting that SCA1 often takes a more aggressive course than other SCAs. Moreover, a study using retrospective assessment of disease stages found a faster progression in SCA1 compared to SCA2, SCA3, and dominant ataxias with a purely cerebellar phenotype.[9] Nevertheless, results of prospective studies are required to obtain quantitative and reliable information on disease progression in the various SCAs.

In the SCA6 model, age at onset was the only factor other than disease duration that contributed to the SARA score. This is in line with the univariate analysis where the SARA score was positively correlated with age and disease duration. This suggests that disease severity in SCA6 is mainly age-dependent. However, compared to the models for SCA1, SCA2, and SCA3, the SCA6 model explained a much smaller part of the observed variance, suggesting that individual factors other than those included in the present model strongly contribute to disease severity in SCA6.

The models for SCA1, SCA2, and SCA3 were more complex than that for SCA6 and shared a number of common properties, the most important of which was the effect of the repeat length of the expanded allele. Although expected, this is a new finding as previous studies focused on the effect of repeat length on age at onset and rate of disease progression.[7,9] SCA1 had the unusual feature that the repeat length of the normal allele had an influence on the disease severity. According to the model, SCA1 is most severe with long expanded and short normal alleles. Interestingly, smaller normal alleles were previously found to be associated with earlier disease onset in SCA1.[7] The results of both studies thus point to the same "paradoxical" association of smaller normal alleles with a more severe phenotype in SCA.

Although ataxia is the prominent symptom of all SCAs, there are various neurologic symptoms that may accompany ataxia. Reliable and quantitative assessment of these symptoms is likewise important and difficult as the variable symptoms may contribute to disability but on the other hand require application of numerous different clinical scales. To escape this dilemma we devised INAS, a list of neurologic symptoms that allows determining the presence or absence of 16 nonataxia symptoms in a reliable and standardized way. By counting the number of nonataxia symptoms in each patient, INAS yields a simple quantitative measure of noncerebellar involvement.

The present data on the distribution and frequency of nonataxia symptoms in SCA1, SCA2, SCA3, and SCA6 confirm and extend the results of numerous previous studies.[10-18] Our data show that SCA6 is not a purely cerebellar disorder in a strict

Table 4 Logistic regression of each nonataxia symptom with repeat length of the expanded allele, age at onset, age, and disease duration as independent variables

Genotype	Factor	Symptom	OR (95%)	p
SCA1	Age	Urinary dysfunction	1.046 (1.016–1.078)	0.0030
		Cognitive impairment	1.060 (1.024–1.096)	0.0010
SCA2	Repeat length expanded allele	Muscle atrophy	1.232 (1.105–1.374)	<0.001
		Chorea/dyskinesia	1.242 (1.075–1.434)	0.0030
		Dystonia	1.216 (1.093–1.353)	<0.001
		Brainstem oculomotor signs	1.764 (1.309–2.377)	<0.001
	Age at onset	Muscle atrophy	0.933 (0.902–0.966)	<0.0001
		Brainstem oculomotor signs	0.922 (0.892–0.954)	<0.0001
SCA3	Repeat length expanded allele	Hyperreflexia	1.210 (1.075–1.362)	0.0020
		Spasticity	1.333 (1.152–1.543)	<0.001
		Brainstem oculomotor signs	1.126 (1.034–1.226)	0.006
	Age at onset	Hyperreflexia	0.935 (0.901–0.971)	0.0005
		Areflexia	1.085 (1.033–1.139)	0.0011
		Spasticity	0.869 (0.827–0.914)	<0.0001
	Age	Hyperreflexia	0.930 (0.900–0.961)	<0.0001
		Areflexia	1.137 (1.067–1.212)	<0.0001
		Spasticity	0.886 (0.847–0.927)	<0.0001
		Muscle atrophy	1.045 (1.016–1.075)	0.0020
	Disease duration	Areflexia	1.118 (1.046–1.195)	0.0011
		Muscle atrophy	1.105 (1.035–1.179)	0.0026
		Urinary dysfunction	1.104 (1.037–1.175)	0.0020
		Brainstem oculomotor signs	1.126 (1.041–1.217)	0.0029
SCA6	Age at onset	Chorea/dyskinesia	1.129 (1.078–1.182)	<0.0001
	Age	Chorea/dyskinesia	1.170 (1.076–1.272)	0.0002
		Resting tremor	1.069 (1.023–1.117)	0.0029
	Disease duration	Areflexia	1.132 (1.051–1.219)	0.0011
		Extensor plantar	1.057 (1.020–1.096)	0.0024
		Urinary dysfunction	1.150 (1.072–1.234)	<0.0001

Only effects that were significant after Bonferroni correction ($p < 0.0031$) are shown.
OR = odds ratio; SCA = spinocerebellar ataxia.

neurologic sense. On average, each patient with SCA6 had two nonataxia symptoms.

To identify factors that determine the occurrence of nonataxia symptoms in SCA1, SCA2, SCA3, and SCA6, we performed univariate analyses that revealed patterns of symptoms and factors that were specific for each SCA. In SCA1, higher age was associated with urinary dysfunction and cognitive impairment. In SCA2, long expanded repeats and early age at onset increased the likelihood of brainstem oculomotor signs, muscle atrophy, and hyperkinetic movement disorders. The dependence of brainstem oculomotor signs on repeat length was expected as a previous oculographic study found that saccades were slower in patients with SCA2 with longer repeats.[21] The phenotypic variability in SCA3 has been attributed to differences in repeat length of the expanded allele. Large expanded alleles have been found in patients with early disease onset and marked pyramidal and extrapyramidal features, whereas those with prominent ataxia and ophthalmoplegia and patients with late disease onset and marked peripheral involvement had smaller expansions.[8] These results are partly confirmed by the present study. Indeed, larger repeats and earlier age at onset were associated with spasticity and hyperreflexia. On the other hand, our data suggest that the presence of peripheral motor signs is age-dependent and not influenced by repeat length. A previous nerve conduction study came to a similar conclusion. According to that study, the degree of peripheral damage in SCA3 did not depend on repeat length, but rather on age.[22]

In SCA1, SCA2, and SCA3, SARA score and disease duration were the strongest predictors of the

INAS count, i.e., the number of nonataxia symptoms in each patient. In SCA6, only age at onset and disease duration contributed to the INAS count. Exclusion of SARA—which is not a true independent variable—from the calculation resulted in an insufficient predictive power of the models. These observations characterize the INAS count as a disease and progression marker in SCA1, SCA2, and SCA3 that is strongly related but not equal to SARA. As it captures other aspects than SARA, it might be useful as an additional outcome measure in clinical studies. However, the sensitivity of the INAS count to change is currently unknown. The time- and age-dependence of the INAS count in SCA6 raises the question to which degree nonataxia symptoms in SCA6 are due to the disease itself or rather a consequence of aging.

Our data add further weight to the view that SCA1, SCA2, and SCA3 share a number of biologic properties whereas SCA6 is not only distinct in that it starts later and has less nonataxia symptoms, but also distinct in that its phenotype is more determined by age than by disease-related factors. Our results are of importance for the design of future interventional trials, in particular for the stratification of patients.

AUTHORS' AFFILIATIONS

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