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Peripheral Neuropathy in Spinocerebellar Ataxia Type 1, 2, 3, and 6

Christoph Linnemann[1,2] · Sophie Tezenas du Montcel[3,4,5] · Maryla Rakowicz[6] ·
Tanja Schmitz-Hübsch[7] · Sandra Szymanski[8] · Jose Berciano[9,10] ·
Bart P. van de Warrenburg[11] · Karine Pedersen[12] · Chantal Depondt[12] · Rafal Rola[6] ·
Thomas Klockgether[7,13] · Antonio García[9,10] · Gurkan Mutlu[3] · Ludger Schöls[1,14]

Abstract Spinocerebellar ataxias (SCAs) are characterized by autosomal dominantly inherited progressive ataxia but are clinically heterogeneous due to variable involvement of non-cerebellar parts of the nervous system. Non-cerebellar symptoms contribute significantly to the burden of SCAs, may guide the clinician to the underlying genetic subtype, and might be useful markers to monitor disease. Peripheral neuropathy is frequently observed in SCA, but subtype-specific features and subclinical manifestations have rarely been evaluated. We performed a multicenter nerve conduction study with 162 patients with genetically confirmed SCA1, SCA2, SCA3, and SCA6. The study proved peripheral nerves to be involved in the neurodegenerative process in 82 % of SCA1, 63 % of SCA2, 55 % of SCA3, and 22 % of SCA6 patients. Most patients of all subtypes revealed affection of both sensory and motor fibers. Neuropathy was most frequently of mixed type with axonal and demyelinating characteristics in all SCA subtypes. However, nerve conduction velocities of SCA1 patients were slower compared to other genotypes. SCA6 patients revealed less axonal damage than patients with other subtypes. No influence of CAG repeat length or biometric determinants on peripheral neuropathy could be identified in SCA1, SCA3, and SCA6. In SCA2, earlier onset and more severe ataxia were associated with peripheral neuropathy. We proved peripheral neuropathy to be a frequent site of the neurodegenerative process in all common SCA subtypes. Since damage to peripheral nerves is readily assessable by electrophysiological means, nerve conduction studies should be performed in a longitudinal approach to assess these parameters as potential progression markers.

Keywords Spinocerebellar ataxia · Peripheral neuropathy · Nerve conduction · Electrophysiology · Progression marker

✉ Ludger Schöls
Ludger.Schoels@uni-tuebingen.de

1 Department of Neurology and Hertie-Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany

2 Center of Old Age Psychiatry, Psychiatric University Hospital, Basel, Switzerland

3 AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles-Foix, Biostatistics Unit, Paris, France

4 Sorbonne Universités, Université Pierre et Marie Curie (UPMC) Univ Paris 06, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France

5 INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France

6 Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland

7 Department of Neurology, University of Bonn, Bonn, Germany

8 Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany

9 Department of Neurology, University Hospital Marqués de Valldecilla, IDIVAL, CIBERNED and UC, Santander, Spain

10 Department of Clinical Neurophysiology, University Hospital Marqués de Valldecilla, IDIVAL, CIBERNED and UC, Santander, Spain

11 Department of Neurology, Radboud University Medical Center, Nijmegen, Netherlands

12 Department of Neurology, University of Brussels, Brussels, Belgium

13 German Research Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

14 German Research Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

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Introduction

Spinocerebellar ataxias (SCAs) comprise a group of hereditary neurodegenerative disorders with progressive ataxia as key symptom (for review see [1]). Beside this hallmark of the disease, SCA presents with variable phenotypes due to differential involvement of non-cerebellar parts of the nervous system. Hereby, phenotypic differences have been observed between as well as within specific genotypes.

Spinocerebellar ataxias type 1, 2, 3, and 6 are the worldwide most prevalent subtypes and share CAG repeat expansions in coding regions of the respective genes as a common disease mechanism [1, 2]. Although the genetic basis is known for more than a decade, no cure is available for these slowly progressive and severely disabling diseases. Substantial progress has been made to assess the severity of ataxia, non-cerebellar involvement, and progression rate of SCAs using semi-quantitative clinical rating scales, yet quantitative measures and progression markers are widely missing [3–7].

Peripheral nerves are readily assessable by nerve conduction studies in an objective and quantitative manner. Additionally, peripheral neuropathy is reported to be a frequent non-cerebellar affection in SCA, although large series are scarce. In a joint European project on spinocerebellar ataxias (EUROSCA), we set out to determine the frequency and neurophysiological characteristics of peripheral neuropathy in these four most common SCA subtypes and to analyze nerve conduction parameters as potential biomarkers in SCA.

Patients and Methods

A total of 162 patients with a mutation in the SCA1, 2, 3, or 6 genes (aged 48±14 years, range 18–81) and 79 healthy controls (aged 44±14 years, range 20–77) were recruited in seven centers (Departments of Neurology of University Clinics in Bochum, Bonn, Brussels, Nijmegen, Santander, Tuebingen, and Warsaw) participating in the EUROSCA project (http://www.eurosca.org). All patients and controls gave their written informed consent prior to inclusion. The study was approved by the Ethics Committees of the participating centers. Patients underwent a clinical and electrophysiological examination.

Clinical examination assessed disease severity by the Scale for the Assessment and Rating of Ataxia (SARA; [3]) and the Inventory of Non-Ataxia Symptoms (INAS; [6]). SARA is a semi-quantitative assessment of the impairment level including eight items (gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movement; and heel-shin slide). The semi-quantitative INAS consists of 30 items, related to 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. Detailed demographic and clinical characteristics of the SCA population are shown in Table 1.

Neuropathy by clinical means was assumed by the presence of areflexia, atrophy, fasciculation, and/or impaired vibration sense (≤5/8).

Nerve conduction studies included ulnar and tibial nerves for motor assessment and radial and sural nerves for sensory fibers. Nerve conduction studies were performed according to a standardized protocol throughout centers. As a measure of quality control, recordings of 10 healthy controls (2 per decade, age 20–70 years) were performed by each participant and compared between centers. To assure comparability of neurophysiological procedures further, centers with major discrepancies from the reference center in Tuebingen were visited by the coordinator to perform exemplary measurements together with the local neurophysiologist.

Stimulation and recording were performed by surface electrodes. In motor nerves, stimulus intensity was increased in 5-mA steps to maximum response starting with a standard stimulus duration of 0.2 ms. If supramaximal stimulation could not be reached by maximum current, stimulus duration was increased by steps of 0.1 ms. For the tibial nerve, recordings were performed from the abductor hallucis muscle with distal stimulation 7 cm proximal to recording electrodes and proximal stimulation at the hollow of the knee. Minimal F-wave latency was assessed from 20 recordings. The ulnar nerve was recorded from the abductor digiti minimi muscle. Distal stimulation was performed 5 cm proximal to recording electrodes at the wrist. Proximal stimulations were performed at the elbow (1) distal and (2) proximal of the sulcus ulnaris. Distal motor latency (DL), compound muscle action potential (CMAP), motor nerve conduction velocity (MNCV), and minimal F-wave latency (F) were assessed. CMAP amplitudes were measured peak to peak.

Sensory recordings from the sural and radial nerve were performed in antidromic technique. For the sural nerve, the active electrode was placed above the nerve at the external malleolus with the reference electrode 3 cm distally at the lateral side of the foot. Stimulation was performed with standard intensity of 20 mA at the mid-calf, 14 cm proximal to recording electrodes. Skin temperature was controlled and adjusted to 34 °C using heating. For recordings of the radial nerve, the active electrode was placed over the first dorsal spatium interosseum with the indifferent electrode 3 cm distally in direction to the index finger. Stimulation was performed at the radial forearm, 15 cm proximally to the recording electrode with a stimulus intensity of 20 mA. Sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV) were assessed. SNAP amplitudes were measured from baseline to peak. In general, right-sided nerves

Table 1 Demographic and disease characteristics in the SCA population

	SCA1	SCA2	SCA3	SCA6
N	44	39	47	32
Age (years)	41±10 (18; 58)	44±13 (20; 76)	47±12 (23; 72)	66±10 (47; 81)
Sex (male/female)	26/18	16/23	27/20	19/13
Duration of disease (years)	7.7±4.1 (0; 16)	12.3±6.9 (3; 29)	10.2±5.8 (0; 24)	10.6±5.3 (4; 20)
Age at onset (years)	33.1±9 (15; 49)	31.2±12.8 (11; 56)	35.7±11 (18; 57)	54.8±9.5 (34; 77)
Longer CAG repeat length	49.1±5.2 (42; 66)	39.6±3.7 (35; 52)	69.5±4.4 (56; 76)	22.4±1.1 (22; 28)
Shorter CAG repeat length	30±2 (27; 36)	22±0.2 (22; 23)	20.5±3.7 (14; 28)	12.7±1.1 (11; 14)
SARA total	13.4±5.4 (5.5; 31)	16.1±9 (3.5; 37)	14.4±7 (3; 35.5)	13±4.2 (1; 21.5)
INAS count	5.3±2.2 (1; 11)	5±2.3 (2; 13)	5.8±2.4 (1; 12)	3±1.7 (0; 6)

Data are shown as mean±standard deviation and range. An allele containing the larger repeat length was designated as the "longer repeat length"; the other was termed the shorter

SCA spinocerebellar ataxia, *SARA* Scale for the Assessment and Rating of Ataxia [3], *INAS* Inventory of Non-Ataxia Symptoms [6]

were recorded; in case of trauma, nerve biopsy, or pitting edema, the less affected side was chosen.

Each electrophysiological parameter was modeled in a group of healthy controls to determine thresholds from which abnormal values can be defined, taking into account center and physiological age effects. It is well known that nerve conduction parameters are dependent on age. Mixed effect models were used with "age" as fixed effect, "center" as fixed covariate, and random effects for all parameters. Z-scores were calculated for each parameter for every patient as the subtraction between the observed and the expected parameter divided by the standard error of the residuals of the models. In the control patient group, 95 % of the Z-scores were expected between −1.96 and +1.96, with a mean of 0 and a standard deviation of 1. Z-scores were considered abnormal if lower than −1.96 for CMAP amplitudes, SNAP amplitudes, MNCV, and SNCV and higher than 1.96 for DL and F. Tibial and ulnar nerves were considered abnormal if CMAP, MNCV, DL, or F was abnormal. Sural and radial nerves were considered abnormal if SNAP or SNCV was abnormal. A patient was diagnosed with neuropathy if parameters were abnormal for at least two nerves.

Neuropathy was defined as axonal if CMAP and SNAP were abnormal. Neuropathy was considered demyelinating if DML, MNCV, SNCV. or F was abnormal. Mixed neuropathy was diagnosed as a mixture of the preceding.

Electrophysiologically defined motor (respectively sensory) neuropathy was diagnosed if both motor nerves (respectively both sensory nerves) were abnormal but sensory (respectively motor) recordings presented normal results. Sensorimotor neuropathy was defined if at least one motor and one sensory nerve were abnormal.

Fisher exact test was used to compare differences of qualitative variables between SCA subtypes. Occurrence of electrophysiologically defined neuropathy was modeled using a logistic regression with gender, age, age at onset of the

disease, duration of the disease, INAS count, SARA score, disease stage, and shorter CAG repeat length or longer CAG repeat length as explanatory covariates. Complete data were extracted in each SCA group, and the covariates were first studied in univariate logistic regression models. When effect sizes were sufficient (SCA2 and 3), the covariates with a *p* value <0.30 (Wald test for associated parameter) were proposed in a multivariate logistic regression model forward selection procedure.

Group (SCA1, 2, 3, and 6) comparisons of Z-scores (differences of least squares means) were performed with analysis of variance and Tukey-Kramer adjustment of *p* values.

Results

Clinically defined neuropathy was most abundant in SCA2 patients (92 %) followed by SCA3 (84 %) and SCA1 (77 %) and less frequent in SCA6 patients (69 %). Differences between genotypes failed to reach significance (Fisher exact test, *p*=0.064).

Electrophysiologically defined neuropathy was most frequent in SCA1 patients (82 %) followed by SCA2 (63 %) and SCA3 (55 %). Only 22 % of the SCA6 patients fulfilled electrophysiological criteria of peripheral neuropathy (Fisher exact test, *p*<0.001, Fig. 1). The proportion of neuropathy was significantly lower in SCA6 patients than in SCA1 (*p*<0.001), SCA2 (*p*=0.0016), and SCA3 (*p*=0.005) patients and was significantly higher in SCA1 than in SCA3 patients (*p*= 0.0076). These comparisons lead to the same conclusion after Bonferroni correction. Agreement between clinically and electrophysiologically defined neuropathy was reached in 57 % of patients.

Electrophysiologically defined neuropathies were further classified as axonal, demyelinating, and mixed neuropathy.
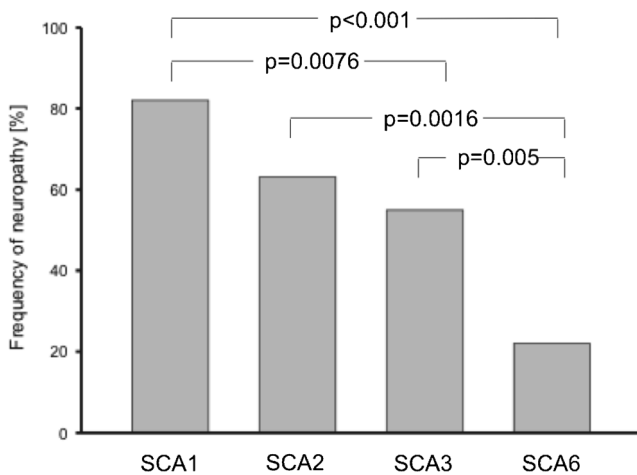
Fig. 1 Frequency of neuropathy by electrophysiological means in different SCA subtypes. Data are shown as percent. For criteria of electrophysiologically defined neuropathy, see the "Patients and Methods" section

Frequency of these types of neuropathy differed between genotypes (Fig. 2).

Analysis of sensory and motor nerve affection revealed sensorimotor neuropathy as the by far most common form in all SCA genotypes, ranging from 94 % in SCA1 to 69 % in SCA3 patients (Fig. 3) with no statistical differences between SCA type (Fisher exact test, $p=0.10$).

Potential determinants of the appearance of electrophysiologically defined neuropathy were investigated by employing a logistic regression analysis. The only significant determinants in univariate analyses were the SARA score in SCA2 patients with an odds ratio of 1.17 [1.03; 1.34] per each additional point for the SARA score and age of onset with an odds ratio of 0.94 [0.88; 0.99] (Table 2). Multivariate analysis for SCA2 and SCA3 data did not pinpoint any additional statistically significant explanatory covariates. In order to avoid unreliable results due to overfitting, a multivariate analysis could not be performed for SCA1 and SCA6 patients due to the small number of SCA1 patients without neuropathy and SCA6 patients with neuropathy.

Table 3 summarizes the Z-scores of nerve conduction parameters for SCA1, 2, 3, and 6. Group comparisons of Z-scores with ANOVA followed by Tukey-Kramer adjustment of p values for significant post hoc comparisons revealed slower nerve conduction velocities of SCA1 patients compared to patients with other genotypes (Fig. 4). As expected from slower nerve conduction velocities, F wave latencies were longer in SCA1 than in other subtypes in the ulnar nerve ($p<0.0001$ for all genotypes) as well as the tibial nerve (SCA1 vs SCA2, $p<0001$; SCA1 vs SCA3, $p=0.0002$; SCA1 vs SCA6, not significant). Interestingly, distal latencies did not differ between genotypes neither in the ulnar nor in the tibial nerve. Moreover, SCA6 patients revealed less axonal

Fig. 2 Distribution of neuropathies (axonal, demyelinating, and mixed) by electrophysiological means in different SCA subtypes. For criteria of different forms of neuropathy, see the "Patients and Methods" section
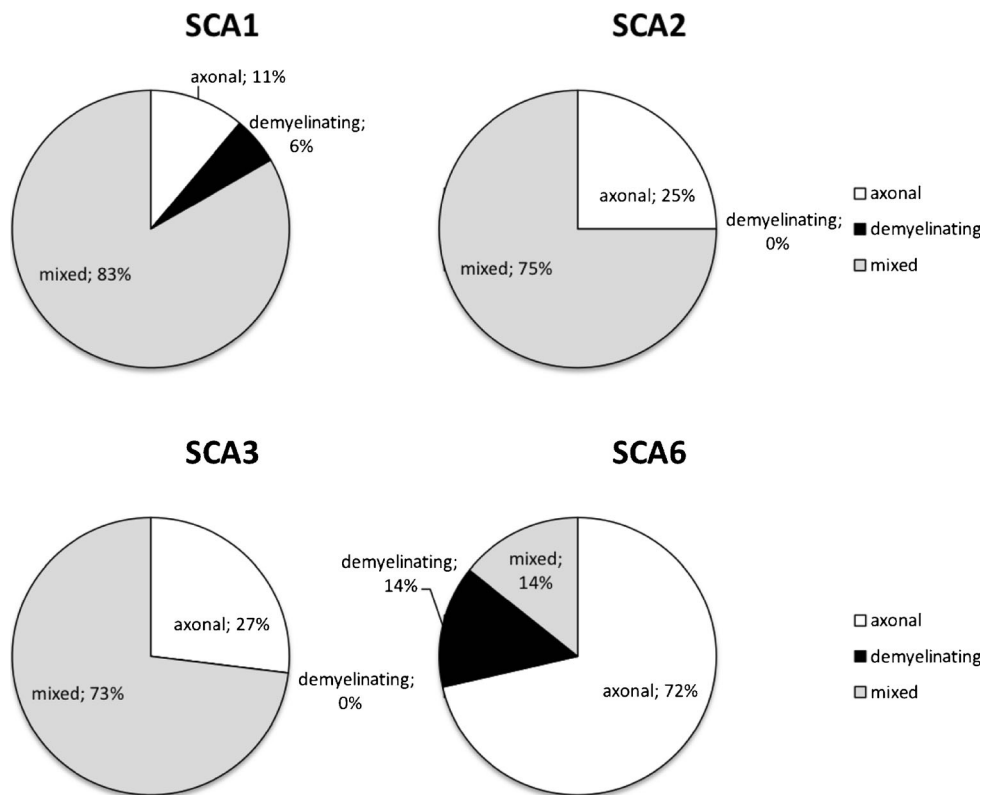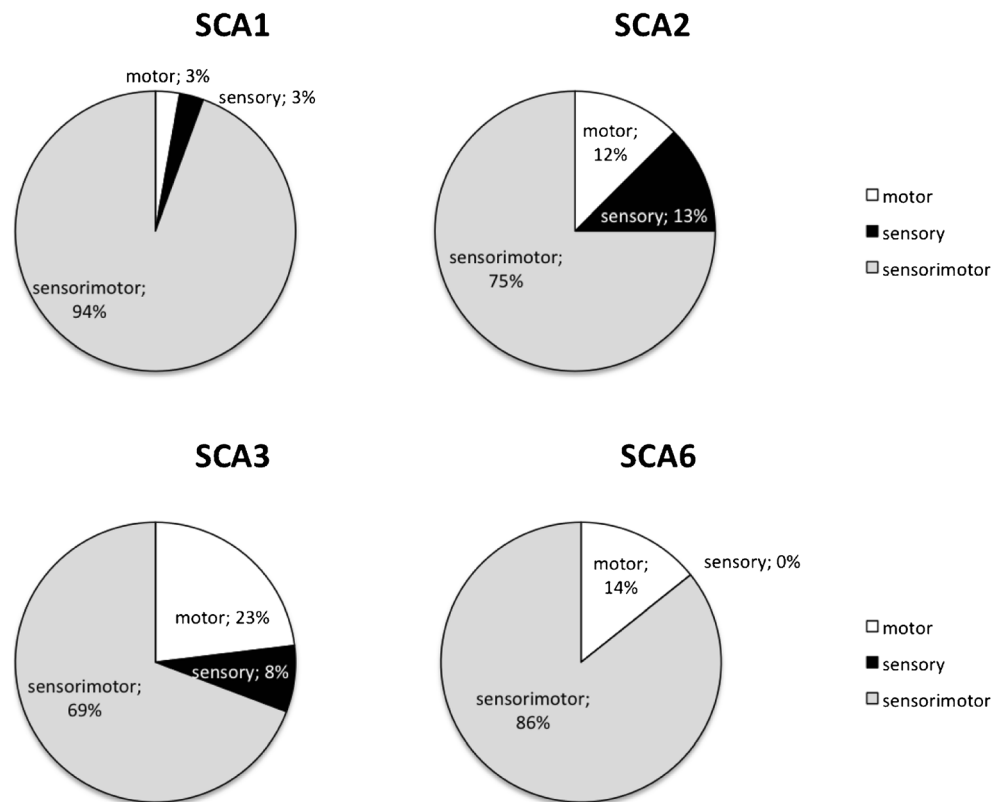
Fig. 3 Distribution of motor, sensory, and sensorimotor neuropathy by electrophysiological means in different SCA subtypes. For criteria of different forms of neuropathy, see the "Patients and Methods" section

SCA1
motor; 3%
sensory; 3%
sensorimotor; 94%

SCA2
motor; 12%
sensory; 13%
sensorimotor; 75%

☐ motor
■ sensory
☐ sensorimotor

SCA3
motor; 23%
sensory; 8%
sensorimotor; 69%

SCA6
motor; 14%
sensory; 0%
sensorimotor; 86%

☐ motor
■ sensory
☐ sensorimotor

neuropathy in lower extremities than patients with other subtypes ($p \leq 0.01$ for sural SNAP and tibial CMAP in comparison of SCA6 versus SCA1, SCA2, and SCA3; Table 3).

Discussion

Peripheral neuropathy is frequent in all common subtypes of spinocerebellar ataxias. In this large European study, we found electrophysiological evidence for the affection of the peripheral nervous system in the majority of SCA patients. This is consistent with earlier studies in several substantially smaller cohorts published for single genotypes [8–19]. A strength of our multicenter approach is that we were able to recruit representative cohorts of all common SCA genotypes and to compare neurophysiological parameters across genotypes. However, the involvement of centers in several

Table 2 Determinants of EMG neuropathy for SCA1, SCA2, and SCA3 patients (univariate logistic regression analysis)

Variable	SCA1		SCA2		SCA3		SCA6	
	n	OR [95 % CI]	*n*	OR [95 % CI]	*n*	OR [95 % CI]	*n*	OR [95 % CI]
Gender (m)	44	0.64 [0.14; 2.97]	39	1.46 [0.39; 5.4]	47	0.69 [0.21; 2.20]	32	0.18 [0.02; 1.73]
Age	44	0.98 [0.90; 1.06]	39	0.95 [0.89; 1.00]	47	1.03 [0.97; 1.08]	32	1.02 [0.93; 1.12]
Age at onset	42	0.99 [0.90; 1.09]	38	0.94 [0.88; 0.99]	43	1.00 [0.94; 1.05]	31	1.02 [0.93; 1.12]
Duration of disease	43	1.09 [0.88; 1.35]	38	1.04 [0.94; 1.16]	46	1.11 [0.99; 1.25]	31	0.93 [0.78; 1.13]
INAS count	41	1.26 [0.85; 1.88]	35	1.53 [0.93; 2.52]	37	1.17 [0.89; 1.54]	26	1.71 [0.69; 4.20]
SARA total	44	1.06 [0.91; 1.25]	39	1.17 [1.03; 1.34]	47	1.06 [0.97; 1.16]	32	1.00 [0.82; 1.23]
Disease stage	44	3.08 [0.34; 28.13]	39	4.64 [0.85; 25.30]	47	1.28 [0.41; 4.06]	32	3.18 [0.52; 19.64]
Longer CAG repeat length	42	1.09 [0.90; 1.32]	35	1.32 [0.98; 1.78][a]	43	0.93 [0.80; 1.08]	32	0.40 [0.04; 3.70]
Shorter CAG repeat length	41	1.37 [0.78; 2.43]	35			41	0.91 [0.76; 1.08]	32	1.03 [0.46; 2.31]

Data are given as odds ratio (OR) and the 95 % confidence interval (95 % CI)

SCA spinocerebellar ataxia, *SARA* Scale for the Assessment and Rating of Ataxia [3], *INAS* Inventory of Non-Ataxia Symptoms [6]

[a] Due to the complete separation of the data, the odds ratio cannot be estimated

Table 3 Z-scores (mean and standard deviation) of electrophysiological parameters, global p values, and significant differences in group comparisons between SCA subtypes (analysis of variance and Tukey-Kramer adjustment of p values)

Variable	SCA1 n	SCA1 Mean±SD	SCA2 n	SCA2 Mean±SD	SCA3 N	SCA3 Mean±SD	SCA6 n	SCA6 Mean±SD	Global p value	Significant differences in group comparisons
Radial SNAP amplitudes	44	−2.03±0.90	37	−2.25±0.94	46	−1.51±0.96	32	−0.52±1.27	<0.0001	SCA1 versus SCA6: <0.0001; SCA2 versus SCA3: 0.006; SCA2 versus SCA6: <0.001; SCA3 versus SCA6: 0.0002
Radial SNCV	44	−2.27±1.54		−1.32±1.12		−1.34±1.68		−0.99±1.62	0.0017	SCA1 versus SCA2: 0.03; SCA1 versus SCA3: 0.0242; SCA1 versus SCA6: 0.0022
Sural SNAP amplitudes		−1.26±0.87		−1.34±0.87		−1.13±0.96		−0.44±1.20	0.0006	SCA1 versus SCA6: 0.0021; SCA2 versus SCA6: 0.0009; SCA3 versus SCA6: 0.0123
Sural SNCV		−1.82±1.22		−0.89±1.55		−1.19±1.39		−1.02±2.02	0.0320	SCA1 versus SCA2: 0.0328
Tibial CMAP amplitudes		−0.77±1.12		−0.65±1.26		−0.72±1.18		0.22±0.83	0.0008	SCA1 versus SCA6: 0.0014; SCA2 versus SCA6: 0.0082; SCA3 versus SCA6:0.0024
Tibial DL		0.76±1.19		0.78±1.30		1.36±1.55		1.19±1.48	0.1236	
Tibial F	43	3.58±2.04		1.64±1.00		1.73±2.40		2.63±1.83	<0.0001	SCA1 versus SCA2: <0.0001; SCA1 versus SCA3: 0.0002
Tibial MNCV	41	−2.84±1.43		−0.82±1.48		−1.55±1.60		−1.38±1.30	<0.0001	SCA1 versus SCA2: <0.0001; SCA1 versus SCA3: 0.0011; SCA1 versus SCA6: 0.0035
Ulnar CMAP amplitudes		−0.69±1.34		−0.52±1.47		−0.39±1.46		0.06±1.08	0.1210	
Ulnar DL		0.97±2.58		0.43±1.96		1.12±2.13		1.05±1.44	0.4690	
Ulnar F	42	3.97±2.36		1.03±1.21		1.84±1.57		1.67±2.05	<0.0001	SCA1 versus SCA2: <0.0001; SCA1 versus SCA3: <0.0001; SCA1 versus SCA6: <0.0001;
Ulnar MNCV	43	−3.29±1.27		−0.49±1.45		−1.59±1.17		−1.17±1.59	<0.0001	SCA1 versus SCA2: <0.0001; SCA1 versus SCA3: <0.0001; SCA1 versus SCA6: <0.0001; SCA2 versus SCA3: 0.0042

For abbreviations, see the "Patients and Methods" section

Fig. 4 Z-scores of nerve conduction velocities (mean and standard deviation) in SCA1, 2, 3, and 6. For abbreviations, see the "Patients and Methods" section. Group (SCA1, 2, 3, and 6) comparisons of Z-scores (differences of least squares means) were performed with analysis of variance and Tukey-Kramer adjustment of p values (*** adjusted $p < 0.005$ and * adjusted $p < 0.05$). Error bars indicate standard deviation
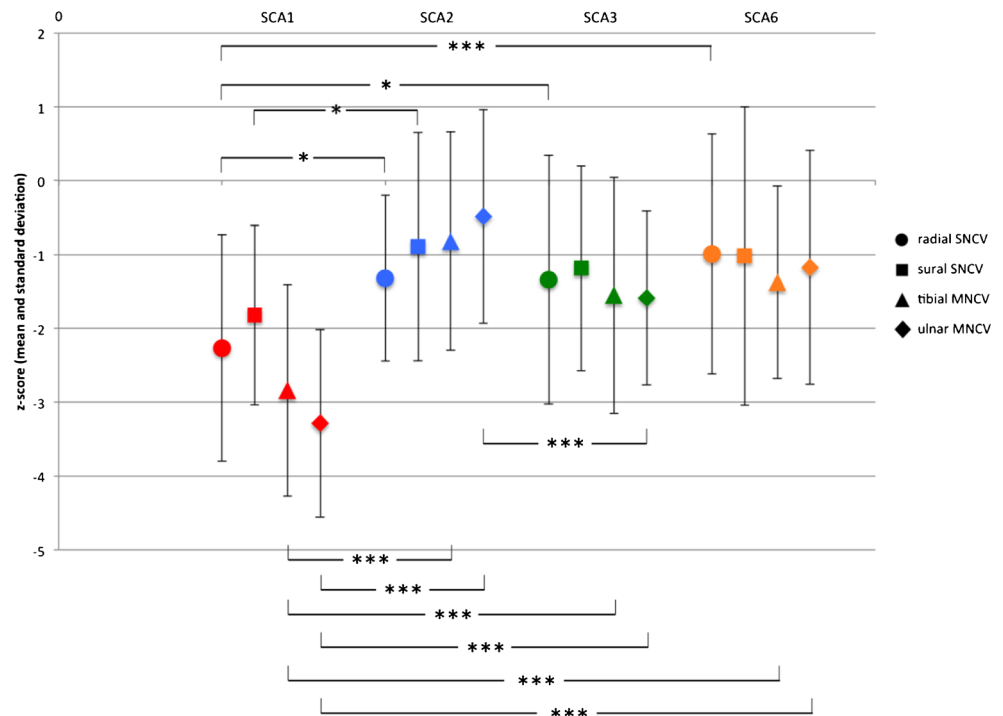
European countries required specific analyses including Z-score statistics to consider center effects.

We found nerve conduction velocities of SCA1 patients to be slower compared to those of the other genotypes. This was especially prominent in motor nerves (Table 3 and Fig. 4). Second, SCA6 patients revealed less axonal neuropathy than patients with other subtypes especially in sensory and motor nerves of lower extremities. This matches with earlier studies [20] and the notion that SCA6 is rather a "pure" type of cerebellar degeneration [16, 19] classified as ADCA type III according to Harding [21] whereas SCA1, 2, and 3 frequently present with non-cerebellar affection qualifying for ADCA type I.

Nerve conduction studies allow quantification of peripheral nerve involvement in a non-invasive, readily available, and repeatable test. This suggests nerve conduction studies as quantitative parameters for the assessment of disease severity and disease progression in SCA. In this respect, it is of importance that in accordance with the literature [22], not only a small subgroup but also the majority of SCA patients presented with electrophysiological abnormalities. It may be speculated that even patients with normal values in the present evaluation may develop abnormalities when the disease progresses.

At the first glance, the rather poor agreement of clinical and electrophysiological diagnoses of peripheral nervous system involvement is unexpected. However, given the multisystem involvement in SCA1, 2, and 3, clinical signs of peripheral neuropathy may find alternative explanations. For example, sensory loss may be caused by dorsal column pathology rather than peripheral nerve affection. Similarly, muscle atrophy may be secondary to inactivity or lower motor neuron affection rather than affection of the peripheral nerves [1, 23]. Additionally, nerve conduction studies do not necessarily depict the fibers of peripheral nerves that are responsible for clinical symptoms and especially sensory deficits. While nerve conduction studies primarily assess the largest, myelinated fibers, sensory symptoms may derive from thin or unmyelinated fibers that escape standard nerve conduction studies. Histopathological studies of peripheral nerves in genetically defined SCA cases are scarce and depicted reduction in density of myelinated and unmyelinated fibers and loss of large myelinated fibers and distal axonopathy with relative hypomyelination in SCA3 but with substantial interindividual variability [24–27].

One shortcoming of this study is that it did not look for neuronopathy in discrimination to distal peripheral neuropathy [20]. Such differentiation would have required needle EMG that is even more difficult to standardize in a multicenter setting than nerve conduction studies and is likely to reduce compliance of patients due to pain associated with the procedure.

Apart from an association of disease severity and age at onset in SCA2, we largely failed to identify significant determinants of peripheral nerve involvement in univariate logistic regression analysis taking into account CAG repeat length, gender, age at onset, disease duration, age, and disease severity. In this multicenter approach, we could not confirm a study in German SCA3 patients that found CMAP and SNAP amplitudes to be determined by age [28] and a study in Cuban

SCA2 patients describing SNAP amplitudes of sural nerve to correlate with disease duration and disease severity as assessed by the International Cooperative Ataxia Rating Scale (ICARS) [29]. This may be explained by larger variability in our study due to multiple centers involved and a broad ethnical background. Our findings are in agreement with a Dutch study that did not observe an influence of age, disease duration, or ataxia severity as well [20]. This study and our findings establish peripheral neuropathy as an independent manifestation of the disease process in SCA. Whether electrophysiological parameters in nerve conduction studies are suitable surrogate markers to monitor disease progression is questionable given the poor correlation with severity of ataxia as assessed by SARA. This issue requires prospective data from longitudinal electrophysiological assessment for a definitive answer.

Conclusion

Our study proves peripheral neuropathy as a frequent manifestation in spinocerebellar ataxias type 1, type 2, and type 3. In contrast, neuropathy is less prominent in SCA6. Furthermore, neuropathy is different in SCA1 compared to other genotypes in that it goes along with substantially slowed nerve conduction. Longitudinal studies are needed to further evaluate electrophysiological parameters as biomarkers for disease progression that may be assessable in interventional trials in SCA in the future.

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