The Spastic Paraplegia Rating Scale (SPRS)

Endorsed by ERN-RND: 26.07.2018

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- Atypical Parkinsonism and genetic Parkinson's Disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Choreas
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

Recommendation for clinical use:

The European Reference Network for Rare Neurological Diseases strongly recommends the use of the Spastic Paraplegia Rating Scale (SPRS) as best clinical practice for the assessment and rating of patients with Spastic Paraplegia.

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METHODOLOGY

The endorsement process has been performed by the Disease group for Ataxia and Hereditary Spastic Paraplegias of ERN-RND.

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Endorsement process:

- Mapping of used disease scales by disease group – June – December 2017
- Proposal for endorsement of rating scale by ERN-RND disease group coordinators – 15/05/2018
- Discussion in ERN-RND disease group during annual meeting – 08/06/2018
- Consent on endorsement of disease scale during ERN-RND annual meeting 2018 – 08/06/2018
- Consent on endorsement by whole disease group – 13/07/2018

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SCALE

(1) Walking distance without pause
Due to history, walking aids allowed

0: Normal, unlimited
1: Abnormal exhaustion due to spasticity after more than 500m
2: Walking distance less than 500m
3: Walking distance less than 10 m
4: Unable to walk

(2) Gait quality
Patient is asked to walk as fast as possible a 10 meter distance including one turn

0: Normal
1: Mild stiffness, running still possible
2: Clearly spastic gait, interfering with running
3: Spastic gait requiring use of canes/walker
4: Unable to walk for a 10 meter distance even with maximal support

(3) Maximum gait speed
Time for a 10 meter distance including one turn, taken by stop watch

0: Normal
1: Slightly reduced (10m: $\geq$ 5s)
2: Moderately reduced (10m: $\geq$ 10s)
3: Severely reduced (10m: $\geq$ 20s)
4: Unable to walk for a 10m distance or time $\geq$ 40s

(4) Climbing stairs
5 steps upstairs - turn - 5 steps downstairs

0: Normal: needs no support of the banister
1: Mild impairment: needs intermittent support of the banister
2: Moderate impairment: needs permanent support of the banister
3: Severe impairment: needs support of another person or additional walking aid to perform task
4: Unable to climb stairs

(5) Speed of stair climbing
Time for 5 steps upstairs - turn - 5 steps downstairs, taken by stop-watch

0: Normal
1: Slightly reduced ($\geq$ 5s to perform task)
2: Moderately reduced ($\geq$ 10s to perform task)
3: Severely reduced ($\geq$ 20s to perform task)
4: Unable to climb stairs

(6) Arising from chair
Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest

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0: Normal
1: Slow, or may need more than one attempt.
2: Pushes self up from arms of seat.
3: Tends to fall back and may have to try more than one time but can get up without help.
4: Unable to arise without help.

(7) Spasticity -hip adductor muscles (Modified Ashworth scale)
Score more severely affected side

0: No increase in muscle tone
1: Slight increase in muscle tone, manifested by a catch and release
2: More marked increase in muscle tone through most of the range of motion
3: Considerable increase in muscle tone - passive movement is difficult
4: Limb stiff in adduction

(8) Spasticity -knee flexion (Modified Ashworth scale)
Score more severely affected side

0: No increase in muscle tone
1: Slight increase in muscle tone, manifested by a catch and release
2: More marked increase in muscle tone through most of the range of motion
3: Considerable increase in muscle tone - passive movement is difficult
4: Limb stiff in flexion or extension

(9) Weakness -hip abduction (Medical Research Council 1976)
0: No weakness
1: Mild weakness (4/5)
2: Moderate weakness (3/5)
3: Severe weakness (1-2/5)
4: Plegia (0/5)

(10) Weakness -foot dorsiflexion (Medical Research Council 1976)
0: No weakness
1: Mild weakness (4/5)
2: Moderate weakness (3/5)
3: Severe weakness (1-2/5)
4: Plegia (0/5)

(11) Contractures of lower limbs
Score in supine position

- *Hip extension: lumbar spine and thighs touch the underlay.*
  Hip abduction: abduction up to an angle of >60° between the legs possible
- *Knee extension: thigh and calf touch the underlay*
- *Ankle dorsal extension: > 10° possible.*
  Ankle pronation: > 10° possible

0: No contractures
1: Mild, not fixed abnormal position of one joint (unilaterally or bilaterally)
2: Fixed contracture of one joint (unilaterally or bilaterally)
3: Fixed contracture of two joints (unilaterally or bilaterally)

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4: Fixed contracture of more than two joints (unilaterally or bilaterally)

(12) Pain due to SP related symptoms

0: None
1: ≤ 50% of waking day present AND intensity 0 - 3 points on visual analogue scale
2: ≤ 50% of waking day present AND intensity 4 - 10 points on visual analogue scale
3: > 50% of waking day present AND intensity 0 - 3 on visual analogue scale
4: > 50% of waking day present AND intensity 4 - 10 points on visual analogue scale

(13) Bladder and bowel function

0: Normal bladder and bowel function
1: Urinary or fecal urgency (difficulties to reach toilet in time)
2: Rare and mild urge incontinence (no nappy required)
3: Moderate urge incontinence (requires nappy or catheter when out of the house)
4: Permanent catheterization or permanent nappy

Annex - Original publication

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The Spastic Paraplegia Rating Scale (SPRS)

A reliable and valid measure of disease severity

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Abstract—*Objective:* To develop and evaluate a clinical Spastic Paraplegia Rating Scale (SPRS) to measure disease severity and progression. *Methods:* A 13-item scale was designed to rate functional impairment occurring in pure forms of spastic paraplegia (SP). Additional symptoms constituting a complicated form of SP are recorded in an inventory. Two independent patient cohorts were evaluated in a two-step validation procedure. *Results:* Application of SPRS requires less than 15 minutes and does not require any special equipment, so it is suitable for an outpatient setting. Interrater agreement of SPRS was high (intraclass correlation coefficient = 0.99). Reliability was further supported by high internal consistency (Cronbach $\alpha = 0.91$). SPRS values were almost normally distributed without apparent floor or ceiling effect. Construct validity was shown by high correlation of SPRS to Barthel Index and the International Cooperative Ataxia Rating Scale (convergent validity) and low correlation to Mini-Mental Status Examination (discriminant validity). *Conclusion:* The Spastic Paraplegia Rating Scale is a reliable and valid measure of disease severity.

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Spastic paraplegias (SPs) share the key symptom of lower extremity spasticity and weakness due to progressive degeneration of the corticospinal tract.[1-3] In pure SP, symptoms are restricted to pyramidal motor system malfunction. In complicated SP, the degenerative process affects multiple parts of the nervous system and presents clinically with additional features like neuropathy, ataxia, cognitive impairment, seizures, optic atrophy, amyotrophy, or extrapyramidal involvement.[2,4]

At present, 29 genes or loci for SP, termed *SPG1–30*, are known, including 11 loci for autosomal dominant SP, 14 loci for autosomal recessive disease, and 4 loci for X-linked forms.[5,6] Identification and first steps in the functional characterization of 11 SP genes over the last decade have shown similarities in the pathophysiology of a number of clinically heterogeneous genetic forms of SP. Seven of the 11 SP genes known so far are thought to impair axonal transport processes. Effective axonal transport of cellular cargoes like mitochondria, structural proteins, and neurotrophic factors is vital to neurons. Motor neurons of the corticospinal tract that contain the longest axonal processes of the whole nervous system seem to be especially vulnerable to its disturbances.[7]

At present, no curative treatment is available for SP. To evaluate potential new treatments, clinicians will critically depend on appropriate clinical measures of disease severity. However, to date, no rating scale for SP is available.

In 2003 the German Network for Hereditary Movement Disorders (GeNeMove) was founded to research rare genetic movement disorders in Germany. Here we report results of a multicenter trial performed by the GeNeMove SP task force to develop and validate a clinical SP Rating Scale (SPRS).

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 8 issue to find the title link for this article.

Methods. *Development of SPRS.* SPRS was developed by a task force of GeNeMove, consisting of movement disorder specialists from six German universities. The design of SPRS was based on the following: 1) SPRS should rate functional impairment and should therefore not include neurologic signs without functional implications like presence of extensor plantar reflex or brisk tendon reflexes. 2) SPRS should focus on key features of pure SP; complicating features should be recorded in an inventory of complicating signs and symptoms. 3) SPRS should be practicable. No special equipment should be necessary to administer the scale; items should be based on standard neurologic examination proce-

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Table 1 *Characteristics of patient and control sample*

	First validation step	Second validation step	Total	Controls
No.	21	42	63	10
Gender, M/F	17/4	22/20	39/24	5/5
Age, y				
Mean ± SD	44.7 ± 10.0	44.5 ± 18.1	44.6 ± 15.8	40 ± 25.3
Range	24–63	9–80	9–80	11–82
Age at onset, y				
Mean ± SD	25.2 ± 19.9	28.9 ± 18.3	27.6 ± 17.6	
Range	0–54	0–66	0–66	
Disease duration, y				
Mean ± SD	19.5 ± 11.7	15.6 ± 12.8	17.4 ± 12.7	
Range	3–44	2–53	2–53	
Pure/complicated SP	15/6	15/27	30/33	
Mode of inheritance, AD/F/S	10/1/10	23/5/14	33/6/24	
Landmarks of disability,* 1/2/3/4	10/5/6/0	22/7/11/2	32/12/17/2	

* See Methods.

SP = spastic paraplegia; AD = autosomal dominant; F = familial; S = sporadic.

dures. Existing scales like the Ashworth Scale[8,9] for rating of spasticity and the Medical Research Council Scale[10] for muscle strength assessment were used.[4] Each scale item should discriminate five grades (0 through 4), where 0 represents no affection and 4 most severe affection. The score result is calculated by adding single scores of each of the 13 items, resulting in a maximum score of 52.

Patients. Sixty-three patients of 50 families were recruited in seven GeNeMove SP outpatient clinics based on the following diagnostic criteria[4,11]: 1) pure SP or 2) spastic tetraparesis with earlier and more severe affection of lower limbs or 3) SP as an early (first 3 years of the disease) and prominent sign of a degenerative disease affecting several parts of the nervous system and 4) other causes of the presenting symptoms excluded.

Diagnosis of hereditary SP was considered definite in patients that reported a family history of spastic gait disturbances (39/63 patients) in addition to the above-mentioned criteria. In subjects with apparently sporadic disease (24/63 patients), diagnosis was considered probable. Molecular diagnosis was available in 20 of 63 patients; 12 of them carried mutations in the spastin gene (*SPG4*), in 6 patients mutations in *KIF5A* (*SPG10*) were identified, and 2 sisters of a family with autosomal recessive SP showed linkage to the *SPG11* locus.

The clinical characteristics of the sample are shown in table 1. Only children above age 9 were included. Patients were categorized as having pure or complicated SP according to presence of additional neurologic and nonneurologic features[12,13] as recorded in the inventory of complicating signs and symptoms. Only the following additional features were considered consistent with diagnosis of pure SP: impaired vibration or joint position sense, skeletal abnormalities (i.e., pes cavus), and urge incontinence.

Patients were examined on their individual medication (i.e., oral antispastics, botulinum toxin injections, etc.). Patients were grouped by a simple 4-grade severity scale (landmarks of disability) based on their walking abilities taken by history.

Landmarks of disability were as follows: 1 = able to walk >500 meters without walking aid, 2 = able to walk >500 meters with walking aid, 3 = able to walk <500 meters with walking aid, 4 = not able to walk.

Additionally, SPRS was performed in 10 healthy control subjects not aware of any neurologic diseases (table 1).

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

Evaluation of SPRS. SPRS was administered to patients by two experienced examiners. Each patient was examined by the local investigator running the SP outpatient clinic and the study coordinator who traveled to the GeNeMove centers. Items 1 through 6 were performed once and rated independently by both investigators; items 7 through 13 were administered and rated independently by both investigators. The inventory of complicating signs and symptoms as well as Mini-Mental State Examination (MMSE), International Cooperative Ataxia Rating Scale (ICARS),[14] and Barthel Index[15] were completed by the study coordinator.

SPRS was validated in a two-step procedure. A preliminary version that was designed by the GeNeMove task force was administered to 21 patients. Based on statistical pre-evaluation, the preliminary scale was modified. The resulting final version was administered to 42 patients in a second validation step. Final statistical evaluation relates to the second set of patients only. Subgroup analysis was done for patients with familial as opposed to sporadic disease and for patients with pure as opposed to complicated SP.

Statistical analysis. All statistical analyses were done using SAS 8.02. Internal consistency of the various score components was investigated using Cronbach α coefficient.[16] In addition, a factor analysis was performed using principal component analysis.[17]

Reliability of SPRS was assessed as interrater agreement calculating intraclass correlation coefficients (ICCs).[18] These coefficients calculate the ratio between interpatient variation and total variation (interpatient + interrater), thus giving a measure of what percentage of the score variation is real signal compared to noise.

To validate that increasing SPRS values reflect increasing disease severity in terms of increasing impairment, we used a simple four-step severity scale (landmarks of disability) as an external criterion for validation. Validity of the score was further investigated by correlating SPRS with ICARS, MMSE scores, and Barthel Index. As the score seemed to show an approximately normal distribution and all associations with other quantities seemed to be nearly linear, Pearson correlation coefficient and associated tests were used.

Results. *Evaluation of preliminary score version and score modification.* A preliminary version of SPRS was administered to 21 patients. The preliminary scale contained 17 items; maximum score was 68. Mean SPRS was 17.8 ± 7.6 (5 to 34). As a measure of interrater agreement, ICC was acceptable (ICC > 0.8) for all items with two exceptions. The "dorsal column sensation" item (ICC = 0.78) was subsequently removed from the score. A detailed instruction was added to the "contractures" item (ICC = 0.65). Two items concerning spasticity and weakness of the upper extremities were removed from the score as a full score in both items would imply complete paralysis and

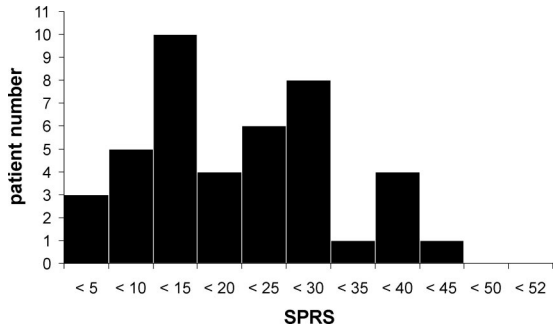

Figure 1. Distribution of Spastic Paraplegia Rating Scale (SPRS) scores. SPRS scores were grouped in bins of five for clarity reasons. SPRS scores show an approximately normal distribution in our sample.

stiffness of the upper extremities and would therefore contradict diagnosis of SP. Two items evaluating pain intensity and duration were condensed into one single item.

The final version of SPRS is provided in appendix E-1 on the *Neurology* Web site (go to www.neurology.org).

Description of the sample. Final version of SPRS was administered to 42 patients and 10 healthy control subjects. In healthy control subjects, SPRS scores ranged from 0 to 2 points. All but the three eldest control individuals had a score of 0. Controls received pathologic ratings for slow walking (item 3), stair climbing (item 5), and arising from chair (item 6).

Mean SPRS in patients was 20.0 ± 10.2 (1 to 43). Distribution of SPRS is presented in figure 1. SPRS shows an only slightly skewed and approximately normal distribution in our sample.

SPRS showed moderate correlation with disease duration (correlation coefficient = 0.44, $p = 0.004$; figure 2).

Reliability. To assess internal consistency, Cronbach α (average correlation between all items in the score) was calculated and found to be 0.91 for the total score, indicating that the score components do measure a common concept (though with some redundancy). To further investigate this, a factor analysis was performed and resulted in one main factor representing items 1 to 10, which explained 54% of the variation in the data (Eigenvalue = 7.1), and two barely relevant factors, which covered items 12 and 13 (10% of variation, Eigenvalue = 1.4) and item 11 (9% of variation, Eigenvalue = 1.1). Thus, items 1 to 10 can be said to represent closely related aspects of the main concept, whereas items 11 to 13 describe two somewhat distinct additional areas.

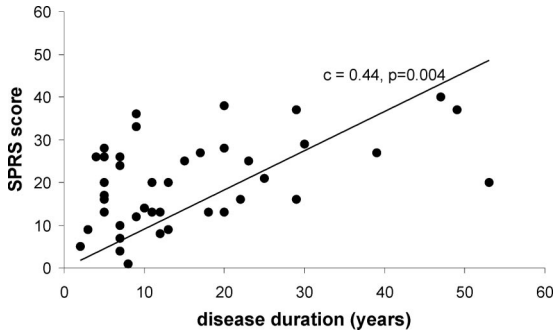

Figure 2. Correlation between disease duration and Spastic Paraplegia Rating Scale (SPRS) scores. SPRS correlates moderately with disease duration.

Table 2 *Spastic Paraplegia Rating Scale interrater agreement*

Item	ICC
1. Walking distance without pause	0.95
2. Gait quality	0.97
3. Maximum gait speed	1.00
4. Climbing stairs	1.00
5. Speed of stair climbing	1.00
6. Arising from chair	0.97
7. Spasticity, hip adductor muscles	0.87
8. Spasticity, knee extension	0.83
9. Weakness, hip abduction	0.93
10. Weakness, foot dorsiflexion	0.90
11. Contractures of lower limbs	0.87
12. Pain due to SP-related symptoms	0.97
13. Bladder and bowel function	0.95

ICC = intraclass correlation coefficient; SP = spastic paraplegia.

Interrater agreement based on results obtained in 42 patients assessed by two investigators was high with an ICC of 0.99. Detailed ICCs for single items are given in table 2. ICC was excellent (ICC ≥ 0.90) for 10 of 13 items and acceptable (ICC ≥ 0.80) for the remaining three items.

Validity. Criterion-related validity. To examine criterion-related validity, we chose landmarks of disability, a simple four-step severity scale based on walking abilities, as main external criterion. SPRS increased ($p < 0.001$) with the disease stage. Correlation of SPRS total score with landmarks of disability was 0.83 ($p < 0.001$).

Figure 3 gives details on SPRS score in dependence on landmarks of disability.

Construct validity. To prove construct validity, discriminant and convergent validity were calculated. Correlation of SPRS total score to MMSE was low, as expected, demonstrating discriminant validity (−0.04, n.s.). Convergent validity was demonstrated by a correlation between SPRS and Barthel Index (−0.73; $p < 0.001$) as well as SPRS and ICARS (0.81; $p < 0.001$), a motor scale developed for rating of ataxia.

Subgroup analyses. To confirm feasibility of SPRS for

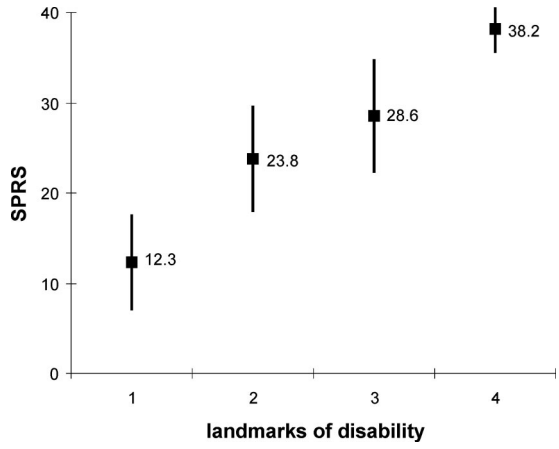

Figure 3. Spastic Paraplegia Rating Scale (SPRS) in dependence of landmarks of disability as defined in Methods (mean; whiskers indicate standard deviation). SPRS total score increases with disease stage ($p < 0.001$).

Table 3 *Reliability and validity of Spastic Paraplegia Rating Scale in subgroups of SP patients*

	ICC	Cronbach α	Correlation to landmarks of disability/Barthel Index/ICARS/MMSE
Pure SP, n = 15	0.99	0.86	0.72*/−0.74*/0.80*/−0.03
Complicated SP, n = 27	0.99	0.89	0.84*/−0.71*/0.76*/0.09
Positive family history, n = 28	0.99	0.91	0.84*/−0.81*/0.84*/−0.03
Negative family history, n = 14	0.98	0.90	0.85*/−0.48/0.77*/−0.08
All, n = 42	0.99	0.91	0.83*/−0.73*/0.81*/−0.04

* $p < 0.05$.

SP = spastic paraplegia; ICC = intraclass correlation coefficient; ICARS = International Cooperative Ataxia Rating Scale[14]; MMSE = Mini-Mental Status Examination.

the whole spectrum of SP, we performed subgroup analyses for pure and complicated forms as well as hereditary and apparently sporadic variants of SP. Reliability and validity of SPRS was quite similar for all subgroups (table 3).

Inventory of complicating signs and symptoms. Skeletal abnormalities were present in 21 of 63 patients, most commonly lumbar hyperlordosis and pes cavus. Sensory deficits were present in 38 of 63 (60.3%) patients. In 24 of those patients, sensory deficits were restricted to reduction of vibration or joint position sense; the remaining 14 patients showed affection of additional sensory qualities like touch sense or temperature discrimination. Only the latter led to classification of SP as complicated (see Methods for details). Signs and symptoms of cerebellar involvement were present in 14 of 63 patients; the most common signs and symptoms in this subgroup were gaze-evoked nystagmus (8/14) and dysarthria (7/14).

The inventory of complicating signs and symptoms is provided in appendix E-1 on the Neurology Web site.

Discussion. The lack of validated measures for disease severity is a barrier to therapeutic trials in orphan diseases. Scientifically rigorous and clinically meaningful rating scales are essential to measure treatment impact, especially in diseases in which conventional laboratory markers of disease activity are missing. Recently, effort has been undertaken to develop new rating scales like the Unified Multiple System Atrophy Rating Scale[19] and evaluate widely used scores like the ICARS retrospectively.[20-22]

To the best of our knowledge, SPRS is the first score evaluated for SP. SPRS is suitable for all subtypes of SP including familial and sporadic forms as well as pure and complicated phenotypes. As SPRS uses standard neurologic examination procedures in most of its items, instructions for test performance and scoring could be kept short for most items without endangering interrater reliability. Completion of SPRS required less than 15 minutes and did not depend on any special equipment. The variety of signs and symptoms that accounts for clinical variability in complicated forms of SP is listed in an inventory. This inventory thus provides a standardized tool to document multisystem involvement of the disease. The inventory is adapted to a routine neurologic examination and avoids additional time-consuming tests. Taken together, these characteristics make SPRS particularly suitable for an outpatient setting.

We excluded infants from the SPRS evaluation process. Milestones of motor development taking place in the first decade of life are inseparably interwoven with a possible disease progression in affected children; a differentiated depiction of these complex interrelations in a score not specialized for this purpose seems impossible. Consequently, SPRS is not suitable to differentiate between developmental and age-related changes of the motor system and changes due to disease progression. When applying SPRS in future studies, it will be necessary to carefully compare age-matched groups.

We evaluated SPRS in a two-step validation procedure with independent cohorts of patients. This approach enabled us to optimize several items according to the results of the preliminary analysis. Adjustment of several items after the first validation step might have led to unintended adaptation of the scale to our special patient sample; therefore, we validated the final scale version in a second, independent patient cohort. This procedure resulted in a scale with high reliability and validity. An interrater agreement of 0.99 for the total score proves SPRS as a robust measure for disease severity. We recommend SPRS for upcoming interventional studies as its high reproducibility will substantially help to reduce patient numbers required to prove therapeutic effects. Validity of SPRS has been shown in concordant and discriminant direction. Comparison of SPRS with 1) landmarks of disability, 2) ICARS as a well established rating scale for another movement disorder (ataxia), and 3) Barthel Index as a measure of impairment in activities of daily living revealed high correlations and supports the relevance of SPRS to monitor functional impairment in SP. Construct validity is further supported by poor correlation to MMSE as a test for cognitive function that is not usually impaired at least in pure forms of SP, demonstrating discriminant validity.

For every single item, full score has been reached by individual patients. However, no patient reached the maximum sum score of 52 points. This design helps to prevent that patients receive maximal SPRS score before the final stage of the disease is reached (ceiling effect) as SPRS should be able to depict progression even in very late disease stages. SPRS separates almost perfectly between SP patients and healthy controls. Only the mildest affected patient (9-year-old girl) had a score value lower than the highest scoring control subject (82-year-old woman). SPRS is able to detect SP symptoms even in early disease stages. None of our patients received a 0 score value. Together with an almost normal distribution of SPRS values in our sample, this argues strongly against a significant floor effect.

SPRS correlated only moderately with disease duration. This result was expected as a broad spectrum of SP subtypes has been included in this cross-sectional analysis. Variability in disease progression between subtypes results in variable impairment after a fixed duration of the disease and reduces correlation of disease severity and duration. Clinicogenetic studies comparing SPRS in different genotypes and prospective longitudinal analyses will help to identify specific progression profiles in SP subtypes.

Longitudinal studies are necessary to analyze the sensitivity of SPRS to depict changes in disease severity and to monitor progression of the disease. A natural history study is ongoing by GeNeMove that will use SPRS to provide data for progression of SP and power calculations concerning patient numbers and study duration in forthcoming therapeutic trials.

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