Journal of Neurology (2020) 267:369–379
https://doi.org/10.1007/s00415-019-09573-w

ORIGINAL COMMUNICATION

Non-motor symptoms are relevant and possibly treatable in hereditary spastic paraplegia type 4 (SPG4)

Tim W. Rattay[1,2] · Andreas Boldt[1] · Maximilian Völker[1] · Sarah Wiethoff[1,2] · Holger Hengel[1,2] · Rebecca Schüle[1,2] · Ludger Schöls[1,2]

Received: 31 July 2019 / Revised: 24 September 2019 / Accepted: 3 October 2019 / Published online: 23 October 2019

Abstract

Hereditary spastic paraplegias (HSP) share as cardinal feature progressive spastic gait disorder. SPG4 accounts for about 25% of cases and is caused by mutations in the *SPAST* gene. Although HSP is an upper motor neuron disease, the relevance of non-motor symptoms is increasingly recognized because of the potential response to treatment. Our study sets out to evaluate non-motor symptoms and their relevance with regard to health-related quality of life. In 118 genetically confirmed SPG4 cases and age- and gender-matched controls, validated questionnaires were used to evaluate fatigue, depression, pain, and restless legs syndrome. In addition, self-reported medical information was collected concerning comorbidities and bladder, bowel, and sexual dysfunction. In a sub-study, cognition was evaluated using the CANTAB® test-battery and the Montreal Cognitive Assessment in 26 SPG4 patients. We found depression and pain to be significantly increased. The frequency of restless legs syndrome varied largely depending on defining criteria. There were no significant deficits in cognition as examined by CANTAB® despite a significant increase in self-reported memory impairment in SPG4 patients. Bladder, sexual, and defecation problems were frequent and seemed to be underrecognized in current treatment strategies. All identified non-motor symptoms correlated with health-related quality of life, which was reduced in SPG4 compared to controls. We recommend that clinicians regularly screen for depression, pain, and fatigue and ask for bladder, sexual, and defecation problems to recognize and treat non-motor symptoms accordingly to improve quality of life in patients with SPG4.

Keywords Non-motor symptoms · SPG4 · Hereditary spastic paraplegia (HSP) · Depression · Pain · Quality of life · Fatigue

Introduction

The hallmark feature of hereditary spastic paraplegia (HSP) is progressive spastic gait disorder with lower limb spasticity and weakness. There is considerable genetic heterogeneity with more than 80 HSP genes described so far [1]. Mutations in the *SPAST* gene cause hereditary spastic paraplegia type 4 (SPG4) which accounts for more than 25% of all HSP cases and more than 50% of autosomal dominant HSP families [2]. Being an upper motor neuron disease, most therapeutic approaches target the improvement of motor features [3]. Non-motor symptoms, however, are becoming increasingly recognized because of their therapeutic implications. In genetically non-stratified HSP cohorts, depression [4] and restless legs syndrome (RLS) [5] have been previously described. In 30 genetically confirmed SPG4 cases, fatigue, pain, and depression were increased [6]. Frequent psychiatric comorbidity was also shown in SPG4 [7]. With regard to higher cognitive functions, there is some controversy concerning dementia [8, 9] vs. subtle cognitive impairment [10]. A single study found abnormalities in social cognition in SPG4 [11] matching MRI findings of volumetric changes in the parietal region [12].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09573-w) contains supplementary material, which is available to authorized users.

✉ Tim W. Rattay
tim.rattay@uni-tuebingen.de

[1] Department of Neurodegenerative Disease, Hertie-Institute for Clinical Brain Research, and Center for Neurology, University of Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany

[2] German Center of Neurodegenerative Diseases (DZNE), Tübingen, Germany

As pain, restless legs syndrome, depression, neurogenic bladder impairment, and disturbed sexual function are symptomatically treatable, we set out to determine the frequency, the burden of disease, and the health-related quality of life in a large cohort of patients with genetically confirmed SPG4.

Material and methods

Study population and inclusion criteria

The NMS (non-motor symptoms) in HSP study (ClinicalTrials.gov identifier: NCT03204773) was conducted as a web-based questionnaire using LamaPoll (LamaPoll Berlin, Germany). Patients were recruited via the HSP outpatient clinic in Tübingen, Germany, and via two German patient support groups (HSP Hilfe e.V. and HSP Selbsthilfegruppe Deutschland e.V.). Controls were recruited among spouses, family members or friends of patients and medical staff. Inclusion criteria for SPG4 patients required (1) age of 18–70 years, and (2) clinical diagnosis of hereditary spastic paraplegia. Controls inclusion criteria required (1) age of 18–70 years, and (2) lack of neurological diseases except for RLS or depression. Only HSP patients with genetically confirmed SPG4 ($n = 118$) were included. An identical number of age and gender-matched controls were recruited. Written informed consent was obtained from all study participants. The study was approved by the local institutional review board (vote 568/2017BO2) as well as the sub-study regarding cognition (vote 210/2017BO2) and, therefore, performed in accordance with Declaration of Helsinki.

Demographic data and disease-specific characteristics

Demographic data were collected from all participants via the online questionnaire including age, height, weight, highest school degree, highest professional qualification, sum of all educational years (school, professional training, and college/university), as well as further self-reported medical information including concomitant diseases and current medications. Also, the inventory of complicating signs and symptoms [13] was assessed in combination with some additional questions to systematically gather information about cataract, retinal abnormalities, occurrence of epilepsy, psychiatric comorbidities, hearing impairment, memory impairment, dysphagia, speech abnormalities, sensory impairment, "trembling", bladder disturbances, and problems with defecation.

From HSP patients, additional questions targeted age at onset, maximum walking distance, use of walking aids, and current as well as any previous HSP-specific medications such as anti-spastic drugs, urological spasmolytics, analgesics, and others such as antidepressants, anticonvulsants, 4-Aminopyridine [14], levodopa, dopamine agonists, and magnesium.

Non-motor symptom scales

Five categories of non-motor symptoms were investigated using standardized questionnaires in German. Quality of life was examined by the EQ-5D [15], an instrument developed by the EuroQol Group [16] as a measure of health-related quality of life. Frequency of restless legs symptoms was evaluated using the 2014 Revised IRLSSG Diagnostic Criteria for RLS [17]. The severity and frequency of depressive symptoms were determined by Becks Depression Inventory (BDI-V) [18]. Fatigue was investigated with the help of the Modified Fatigue Impact Scale (MFI) [19]. Pain was measured using the Brief Pain Inventory (BPI) [20].

Exploring cognitive functions using MoCA and CANTAB®

In a subgroup of 26 SPG4 patients (ClinicalTrials.gov Identifier: NCT03104088), we assessed cognitive function in comparison to age- and gender-matched controls using the Montreal Cognitive Assessment (MoCA) [21] as a screening tool for mild cognitive impairment and the CANTAB® Cognitive assessment software (Cambridge Cognition, 2019, Cambridge, United Kingdom. All rights reserved. https://www.cantab.com), a tablet-based neurocognitive test battery. The following tests were used in standard configuration if not otherwise specified: paired association learning (PAL) high functioning, verbal recognition memory (VRM), one touch stockings of Cambridge (OTS), multitasking test (MTT), emotion recognition task (ERT) long version, spatial working memory (SWM) high functioning version, rapid visual processing (RVP) of three targets, and delayed match to sampling (DMS). The test battery aims to evaluate the following cognitive domains: visual memory (including short-term visual recognition), verbal memory, new learning, executive functions (strategy, spatial planning, and working memory), multitasking, emotion recognition, sustained attention, and visual matching ability. Detailed information on all tests including neurophysiological correlates and outcome measures can be found online.[1]

Statistics

For descriptive statistics, we used IBM SPSS Statistics, version 25 (IBM, Armonk, NY). Only fully completed

[1] Information retrieved from the CANTAB® website on 03.07.2019. https://www.cambridgecognition.com/cantab/cognitive-tests

Table 1 Biographic parameters: non-motor symptoms in SPG4 study

	Age in years	Sex		BMI [kg/m^2]	Age at onset [years]	Disease duration [years]	Duration from disease onset to diagnosis [years]	Max. walking distance [m]
		♂	♀					
Total: mean (SD) [range] ($n=236$)	46.1 (10.7) [20–69]	118	118	26.02 (4.9) [15.7–26.0]				
SPG4 patients ($n=118$)	50.4 (9.4) [20–64]	59	59	25.9 (5.1) [15.7–50.8]	29.1 (15.7) [0–57]	21.3 (14.1) [1–61]	8.8 (11.3) [0–54]	1184.5 (2068.2) [0 m–12 km]
Controls ($n=118$)	47.8 (11.7) [31–69]	59	59	26.2 (4.8) [17.7–40.6]				
Gaussian variable	No	No		No	No	No	No	No
p value <0.017	0.110	1.000		0.513				

Data are presented as mean (standard deviation) [range with lowest and highest value]. Gaussian distribution of data was tested using the Shapiro–Wilk test as $3<n<3000$. For the baseline statistics, Gaussian distributed variables were tested by a two-sided t test, non-Gaussian distributed variables by the Mann–Whitney U test and nominal variables by Chi-square test. p values after Bonferroni correction below 0.017 were considered to be statistically significant

BMI body mass index, *SD* standard deviation

questionnaires were included in the analysis. Gaussian distribution of the data was tested using the Shapiro–Wilk test as $3<n<3000$. For baseline statistics, Gaussian distributed variables were tested by a two-sided t test, non-Gaussian distributed variables by the Mann–Whitney U test and nominal variables by Chi-square test. The primary endpoints were significant changes in the sum scores of the five questionnaires/scales to identify relevant non-motor symptoms in SPG4. A p value <0.05 was considered statistically significant which was adjusted accordingly by Bonferroni correction for multiple testing. Correlations were calculated according to Pearson. All non-motor symptoms as evaluated by standardized scores/scales were correlated to quality of life and to biographic (age) and disease-specific (age of onset, disease duration, and maximum walking distance) parameters.

Results

Biometric data

No significant difference was found between the SPG4 group and the control group concerning age (50.4 vs. 47.8 years; $p=0.110$), gender (both groups equal 59 males vs. 59 females, $p=1.0$), or body-mass index (BMI; 25.9 vs. 26.2 kg/m^2; $p=0.513$) when correcting the p value threshold according to Bonferroni. The SPG4 cohort had a mean age of onset at 29.1 years (defined as onset of gait disturbance), with a mean disease duration of 21.3 years. The time from onset of gait disturbance until clinical diagnosis of HSP took on average 8.8 years. The maximum walking distance (based on interview) was on average 1184.5 m with a range of 0 m up to 12 km. Details are given in Table 1. 36.4% of SPG4 patients and 100% of controls were able to walk without a walking aid. Walking sticks were regularly used by 49.2%, walkers by 25.4%, and wheelchair by 39.8% of SPG4 patients (multiple answers possible).

Self-reported medical information

Self-reported medical information showed significantly higher rates of comorbidities in SPG4 compared to controls (60.2% vs. 32.2%; $p<0.001$). Especially trembling (40.7% vs. 3.4%; $p<0.001$), memory impairment (28% vs. 11%; $p<0.001$), RLS (18.6% vs. 0.8%; $p<0.001$), impairment of upper extremity (8.5% vs. 1.7%; $p<0.001$), and cataract (7.6% vs. 2.5%; $p<0.001$) were reported more frequently in SPG4 patients than in controls (Table 2). Psychiatric disorders excluding depression (5.1% vs. 1.7%; $p=0.150$), speech abnormalities (5.9% vs. 0.8%; $p=0.031$), and dysphagia (6.8% vs. 0%; $p=0.004$) were more frequent in SPG4 patients, but did not differ significantly.

Bladder symptoms occurred more often in SPG4 compared to controls (78.0% vs. 8.5%; $p<0.001$) including urge in 55.1%, incontinence in 38.1%, and/or voiding in 33.1%. Incontinence pads were required by more than one-third of patients (37.3%); 22.9% used them daily, 4.2% used them only when leaving the house, and 10.2% used them occasionally. Problems of defecation were more frequent in SPG4 (31.4% vs. 3.4%; $p<0.001$); 4.2% of patients reported urge, 13.6% incontinence, 11.9% obstipation, and/or 1.7% others defecation problems. Disturbed sexual function was more common in SPG4 (23.7% vs. 4.2%; $p<0.001$) and occurred in females ($n=12/48$) as well as in males ($n=16/54$). The questionnaire did not allow for the distinction of problems with erection or ejaculation in men. Female patients ($n=11$)

Table 2 Self-reported medical history

	Any comorbidity	Arterial hypertension / coronary angiopathy	Diabetes mellitus	Polyneuropathy / Dysesthesia	RLS	Depression	Dementia/ memory impairment	Trembling	Impairment arms or hands	Retinal abnormalities / cataract	Epilepsy	Psychiatric disorder without depression	Hearing abnormality AOO < 40 years	Dysphagia	Speech abnormalities	Bladder disturbance (urge/incontinence/voiding /use of pads)	Defecation disturbance (urge/incontinence/ obstipation/other)	Disturbed sexual function
Present in % of cases ($n=236$)	46.2	26.3/2.1	5.1	4.2/16.9	9.7	14.0	1.7/19.5	22.0	16.9	0.8/5.1	0.8	3.4	3.8	3.4	3.4	43.2 (29.2/21.2/16.9/21.2)	17.4 (2.1/6.8/7.2/1.3)	14.0
SPG4 patients ($n=118$)	60.2	27.1/0.8	5.1	7.6/32.2	18.6	24.6	3.4/28.0	40.7	29.7	0.8/7.6	1.7	5.1	4.2	6.8	5.9	78.0 (55.1/38.1/33.1/36.3)	31.4 (4.2/13.6/11.9/1.7)	23.7
Controls ($n=118$)	32.2	25.4/3.4	5.1	0.8/1.7	0.8	3.4	4.2/11.0	3.4	4.2	0.8/2.5	0	1.7	3.4	0	0.8	8.5 (3.4/4.2/0.8/5.1)	3.4 (–/–/2.5/0.8)	4.2
p value < 0.00227	**<0.0001**	0.96/0.30	0.93	0.03/**<0.0001**	**<0.0001**	**<0.0001**	0.1/**<0.0001**	**<0.0001**	**<0.0001**	0.04/**<0.0001**	.131	0.150	0.319	0.004	0.031	**<0.0001**	**<0.0001**	**<0.0001**

For all nominal values, the two-sided p value was evaluated using cross-tables and Chi-square testing. Bonferroni correction for all tested baseline values was performed (22 items) and significant findings (p values < 0.00227) are highlighted in bold

AOO age of onset, *SD* standard deviation, *RLS* restless legs syndrome, *SPRS* spastic paraplegia rating scale

chose not to answer this question more than twice as often as males ($n=5$).

Bladder modifying medication (mostly antimuscarinic medication) was taken in 19.5% of cases, antidepressants by 16.9%, analgesics in 16.1%, dopa-agonists in 4.2%, levodopa by 2.5%, anticonvulsants by 3.4% (including use as pain modifier), and anti-dementia drugs by 1.7% of SPG4 patients. No patient received medication addressing disturbed sexual function such as PDE5 inhibitors.

Motor symptoms were addressed rather frequently with 23.7% of SPG4 patients taking baclofen (61.0% had taken this medication previously), 4.2% tizanidine (previous: 22%), 12.8% tolperisone (previous: 28%), 10.2% botulinum toxin (previous: 21.2%), 1.7% benzodiazepines (previous: 7.6%), and 6.8% cannabis (including cannabis flowers, dronabinole, and nabiximols (Sativex®) (previous: 5.9%). Additionally, magnesium was taken by 5.1% of cases and 4-aminopyridine in 2.5% (Table 3).

Non-motor symptoms

Frequencies of non-motor symptoms including self-reported symptoms in SPG4 patients are provided in Fig. 1 and Table 4. When calculating a bivariate correlation after Pearson with the two variables age and number of symptoms, there was a negative but non-significant correlation −0.032; $p=0.730$. The same applies for age at onset of the hereditary spastic paraplegia and the number of non-motor symptoms: −0.073, $p=0.431$.

Health-related quality of life was reduced in SPG4 patients compared to controls (EQ-5D index: 0.70 vs. 0.96; $p<0.001$). The EQ-5D index in SPG4 correlated with the maximum gait distance (Pearson 0.311; $p=0.001$) and inversely with the MFI (Pearson −0.502; $p<0.001$), pain severity (Pearson −0.517; $p<0.001$), pain interference with function (Pearson −0.459; $p<0.001$), and the BDI-V (Pearson −0.418; $p<0.001$) but not with the RLS *IRLSSG 2014 Diagnostic Criteria Score* (Pearson −0.128; $p=0.168$).

Fatigue was increased in SPG4 patients compared to controls (MFI total score: 33.2 vs. 17.4; $p<0.001$) with 37 patients being positively diagnosed with fatigue (> 38 points in the MFI) compared to 9 controls. In SPG4 patients, MFI total score correlated inversely with maximum walking distance (Pearson −0.288; $p=0.002$). There was no correlation with age (Pearson 0.064; $p=0.491$), age at onset (Pearson 0.054; $p=0.559$), or disease duration (Pearson −0.018; $p=0.848$).

Pain severity (2.0 vs. 0.62; $p<0.001$), as well as pain interference with daily living (2.5 vs. −0.02 $p<0.001$), was increased in SPG4 patients compared to controls. In SPG4 patients, pain severity correlated with pain medication (Pearson 0.456; $p<0.001$) and pain interference with daily activities (Pearson 0.814; $p<0.001$) and inversely with disease

Table 3 Self-reported medication

Spasticity related medication	Baclofen	Tizanidine	Tolperisone	Botulinum toxin	Benzodiazepine	Cannabis medication
Current/previous % of SPG4 patients ($n=118$)	23.7%/61.0%	4.2%/22.0	12.7%/28.0%	10.2%/21.2%	1.7%/7.6%	6.8%/5.9%
Further symptomatic medication	Bladder medication (antimuscarinic)	Pain medication	Levodopa	dopamine agonist	Antidepressant	Anticonvulsant	4-Aminopyridine	Magnesium	Anti-dementiva
Current/previous % of SPG4 patients ($n=118$)	19.5%/13.6%	all: 16.1%/16.9% NSAID: 13.6%; Metamizole: 2.5% Opioid: low: 3.4%/high 1.7% potent	2.5% 4.2%	n.a n.a	16.9%/n.a	3.4%/n.a	2.5%/n.a	5.1%/n.a	1.7%/n.a

Tetrazepam marketing authorization was suspended on April 24th 2013 across the EU and was taken previously by 4.2% of patients

n.a. not available

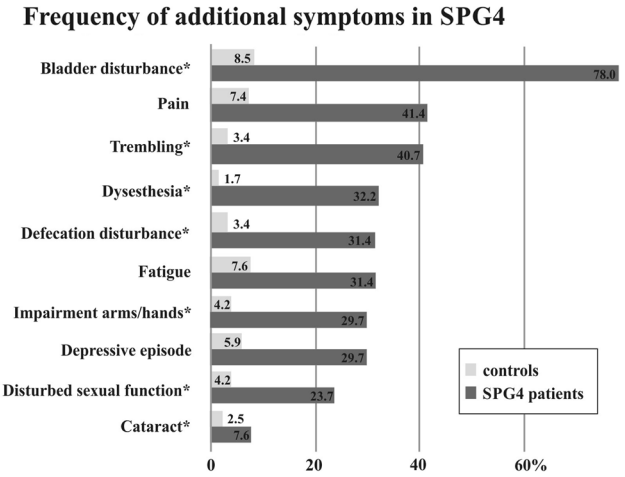

Fig. 1 Frequency of additional symptoms in SPG4. The frequency of additional symptoms including non-motor symptoms in 118 SPG4 patients (dark grey) and 118 age- and gender-matched controls (light grey) is shown. The Becks Depression Inventory (BDI-V) was used to diagnose an episode of depression if ≥ 35 points were achieved. Pain levels were evaluated using the Brief Pain Inventory (BPI). The question asking for pain occurrence associated with the underlying disease [in this case hereditary spastic paraplegia type 4 (SPG4) or any other disease] in controls was used to compare pain occurrence between SPG4 patients and controls. Fatigue was diagnosed using the Modified Fatigue Impact Scale (MFI) with scores > 38 points. All further symptoms marked with an * are self-reported, and the others as previously described were objectively evaluated using established scores, scales, or questionnaires

duration (Pearson −0.211; $p=0.022$) and maximum walking distance (Pearson −0.270; $p=0.003$). No correlation was found for age (Pearson −0.045; $p=0.628$) or age at onset (Pearson 0.163; $p=0.078$).

Depression is more present in SPG4 patients ($n=37$, 31.3%) than in controls ($n=7$, 5.9%), as recognized by the BDI-V (≥ 35 points) with a mean BDI-V score of 26.6 in SPG4 patients vs. 14.3 in controls ($p<0.001$). In the self-reported medical information, depression had a higher frequency as a comorbidity in SPG4 than in controls (24.6 vs. 3.4%; $p<0.001$), as well. Twenty patients were taking antidepressants including eight patients with a BDI < 34 points. Twenty-nine SPG4 patients reported depression as diagnosis of which only 15 took an antidepressant and a total of 17 patients received psychotherapy. Twenty-four of twenty-nine self-reported depressive patients had a BDI score ≥ 35 points fulfilling the criteria of an episode of depression. Of all 37 SPG4 patients with a BDI score ≥ 35 points (manifest depressive episode), only 54% received a form of therapy: antidepressant treatment ($n=6$), psychotherapy ($n=8$), and a combination of both ($n=6$). No correlations were found for BDI-V total score with maximum walking distance (Pearson −0.138; $p=0.138$), age (Pearson −0.120; $p=0.195$), age at onset (Pearson −0.045; $p=0.629$), disease duration (Pearson −0.030; $p=0.746$), or gender (Pearson −0.174,

Table 4 Objectively evaluated non-motor symptoms

	Fatigue	Quality of life	Pain		Depression	Restless legs
			Severity	Interference with daily living		
Total: mean (SD) [range] ($n=118$)	25.3 (16.1) [2–76] >38 points $n=46$	0.83 (0.21) [0.016–1.00]	1.3 (2.0) [0–8]	1.2 (2.8) [−2–9.3]	20.4 (17.4) [0–96] ≥35 points $n=44$	1.14 (0.73) [0–4] 5 points $n=4$
SPG4 patients ($n=118$)	33.2 (15.8) [2–76] >38 points $n=37$	0.70 (0.21) [0.016–1.00]	2.0 (2.3) [0–8]	2.5 (3.1) [−2–9.3]	26.6 (18.9) [2–82] ≥35 points $n=37$	1.05 (1.63) [0–4] 4 points $n=20$
Controls ($n=118$)	17.4 (12.0) [4–67] >38 points $n=9$	0.96 (0.10) [0.069–1.00]	0.62 (1.3) [0–6.25]	−0.02 (1–7) [−2–5.3]	14.3 (13.1) [0–96] ≥35 points $n=7$	1.14 (0.73) [0–5] 5 points $n=4$ 4 points $n=0$
Gaussian variable	No	No	No	No	No	No
p value < 0.00833	**<0.00001**	**<0.00001**	**<0.00001**	**<0.00001**	**<0.00001**	**<0.00001**
Test/scale/criteria used	MFI (modified fatigue impact scale) [19]	EQ-5D index [15]	BPI (brief pain inventory) [20]		BDI-V (becks depression inventory) [18]	Revised IRLSSG diagnostic criteria for RLS [17]

Data are presented as mean (standard deviation) and [range: lowest and highest values]. Gaussian distribution was tested by Shapiro–Wilk test due to $n>3<3000$. Non-Gaussian variables were tested by Mann–Whitney U test. Bonferroni correction for all tested values considered all p values below an alpha of 0.833% (six items) to be statistically significant and are highlighted in bold

SD standard deviation

$p=0.060$). Gender and BDI-V ≥ 35 points were not significantly associated.

When using the *2014 Revised IRLSSG Diagnostic Criteria for RLS,* there is a significant difference in the presence of RLS with no SPG4 patients fulfilling the diagnostic criteria (=5 points) compared to four individuals in the control group. SPG4 patients had a significantly lower total score than controls (1.05 vs 1.14 points; $p<0.001$). To be able to differentiate a spastic clonus as "passively moving legs" from RLS, a number of additional questions were asked. In SPG4, 45.8% of patients reported to know what a "spastic clonus" is. In contrast, only 34.7% were confident to be able to differentiate RLS from spastic clonus as determined with a separate question. When asking the remaining 65.3% (which were not confident to differentiate RLS from spastic clonus) for the concrete definition of a spastic clonus, only 10.2% of SPG4 patients replied that the definition of a spastic clonus was known to them. In the questionnaire, specific definitions of spastic clonus and RLS were presented to the participants. Even after introducing the spastic clonus and RLS definitions with specifically naming the differences between both, still more than a fourth (26.3%) were not able to differentiate RLS from a spastic clonus. Spastic clonus occurred in 33 SPG4 patients (=28%) and had a clear time-related accumulation ($n=30$) in the second half of the daytime when asking for time of occurrence: 6.8% mentioned clonus before getting out of bed in the morning and 3.4% in the morning, 4.2% around noon, 11.9% in the evening, 6.8% before going to bed, 11% when trying to go to sleep, and 6.8% while sleeping (multiple replies were possible).

Disease burden of additional symptoms including non-motor symptoms in SPG4

To estimate disease burden, including non-motor symptoms, the following objectifiable measurements ($n=3$) used in this study (Fig. 1—all results presented without*) to evaluate fatigue, depressive episodes, and occurrence of pain were combined with self-reported symptoms occurrence ($n=8$) (bladder dysfunction, "trembling", dysesthesia, defecation dysfunction, impairment of arms and/or hands, disturbed sexual function, and cataract). The evaluated RLS occurrence was not used due to difficulties with the recent diagnostic criteria. This is discussed in great detail below. The result of this burden of disease analysis is presented in Fig. 2. There was a significant difference of disease burden between SPG4 patients and controls ($U=1497$, $p<0.001$). Symptom burden (including eight non-motor symptoms and additionally impairment of arms and/or hands and "trembling") correlated inversely with quality of life as measured by the EQ-5D index (Pearson −0.643; $p<0.001$). There was a significant correlation of gender and number of non-motor symptoms, in favor of females 0.195, $p=0.034$.

Cognition in SPG4

Cognitive assessment has been restricted to a subgroup of 26 SPG4 patients. Biographic characteristics of patients and controls are given in supplementary Table 1. There were no significant differences in the eight CANTAB® tests (PAL, VRM, OTS, MTT, ERT, SWM, RVP, and DMS) between

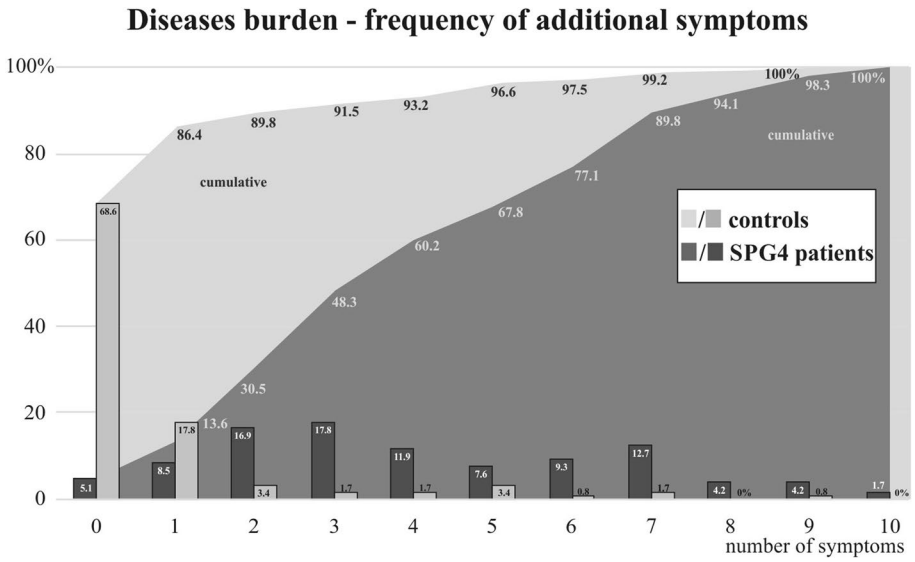

Fig. 2 Disease burden—cumulative frequency of all additional symptoms. The diagram shows the burden of additional symptoms and non-motor symptoms in 118 SPG4 patients (dark grey) and 118 age- and gender-matched controls (light grey). The colored areas underneath the curve are representing the cumulative occurrence of simultaneously present additional symptoms starting from zero up to ten additional symptoms. The frequency of the simultaneous occurrence in 118 SPG4 and 118 controls is shown in bar graphs (slightly darker colored) on the bottom of the diagram. The spectrum reaches from zero up to ten additional symptoms. All ten in this study as relevant identified symptoms were used for burden analysis. Three objectively evaluated symptoms (without the fourth objective rated symptom: restless legs syndrome) using established questionnaires like the BDI-V, BPI (here only pain occurrence associated with the underlying disease was used), and MFI. Further seven self-reported symptoms (and therefore subjective measurements) were included into this burden analysis which were identified in this study (compare Table 2) as relevant non-motor symptoms

SPG4 patients and the matched control group. Details are provided in supplementary Table 2. In the MoCA, patients reached an average of 25.2 out of 30 points, whereas the control group reached 27.0 points ($p = 0.042$); this difference was no longer significant after correction for multiple testing according to Bonferroni. MoCA scores did not correlate with SPRS total score (Pearson: −0.048, $p = 0.814$) as a measure for disease severity, age (Pearson 0.149, $p = 0.467$), disease duration (Pearson −0.125, $p = 0.544$), or total educational years as measure for educational level.

Discussion

This study set out to assess the frequency of non-motor symptoms in SPG4, a rare disease of the primary motor neuron. SPG4 is usually recognized as a purely hereditary spastic paraplegia according to Harding [22], which was recently confirmed in a large cohort of 842 SPG4 patients [23]. We found non-motor symptoms to be present in the majority of patients (62.9%), with more than 15% of patients reporting problems in more than two of the four categories assessed by scores (RLS, depressive episodes, pain, and fatigue). With a looser definition compared to Harding's definition of pure hereditary spastic paraplegia using the ten identified relevant symptoms (including urinary urge for example as mentioned by Anita Harding previously), our burden analysis found additional symptoms in 94.9% of SPG4 patients compared to 33.1% in controls (Fig. 2—cumulative data are presented as the curve in the background). It also showed that approximately 90% of patients suffer from at least seven additional symptoms (main symptom: the progressive spastic paraparesis with gait disturbance) and about 60% from four additional symptoms.

Using systematic self-reporting of patients, we found a substantial number of non-motor symptoms to be significantly more frequent in SPG4 patients compared to controls. SPG4 patients reported speech abnormalities at a prevalence of ~6% and dysphagia in almost 13% which might be addressed by speech therapists to improve. In 65% of SPG4 patients, increased reflexes in the upper limb were reported in Parodi's cohort [23]. In SPG4, 8.5% of patients report impairment in their upper extremity (defined as interfering with daily activities) in this study which could be addressed by occupational therapy. This finding might be at least partially explained by a lower motor neuron rather than upper motor neuron involvement, since about 9% of ulnar nerve abnormalities were found in SPG4 by Karle and colleagues [24] who did not find any central motor conduction abnormalities in the upper extremity in 35 SPG4 patients. Also cataract may be more prevalent in SPG4 and not only in SPG9 or other complicated forms of HSP [25]. This

self-reported information of SPG4 patients is not substantiated by two contradicting studies. A small study did not find ophthalmological abnormalities in 10 SPG4 patients [26] and an optic coherence tomography (OCT) study revealed normal retinal nerve fiber layer thickness [27] in 13 SPG4 patients. We suggest to further investigate ophthalmological affection in a representative cohort of SPG4 patients.

As expected, health-related quality of life is reduced [6, 28, 29] in SPG4 which is currently an incurable neurodegenerative disease. We found quality of life in SPG4 to be directly related to the maximum walking distance, therefore, closely related to disease severity. This was shown in non-genetically stratified HSP with categorized walking ability (unaided > 500 m, with aid > 500 m, with aid < 500 m, not able to walk) by Klimpe and colleagues [28] previously. Our calculated burden of disease [sum of positive identified addition symptoms including non-motor symptoms (up to $n = 10$)] strongly correlates with quality of life. Therefore, optimal treatment of symptoms such as pain, depression, and bladder symptoms is likely to improve quality of life and should be in the focus of physicians dealing with this rare disease.

Although bladder disturbances are frequent in SPG4 patients (78%) and require incontinence pads in 37.3% of cases, only 19.5% of patients receive any medication to modify bladder emptying. In contrast, motor symptoms are frequently treated by anti-spastic agents (> 60% of patients). The same applies to defecation disturbances which occur in about one-third of SPG4 patients. Therapeutic options for fecal incontinence are limited, but there is positive evidence for biofeedback which is a recommended treatment according to the guideline of the American College of Gastroenterologists [30]. To the best of our knowledge, the effect of biofeedback has not yet been studied in SPG4. Fecal incontinence may be iatrogenic in some HSP patients due to anticholinergics prescribed to treat urinary incontinence [31] or muscle relaxants and anti-spastic drugs prescribed to treat spasticity, e.g., baclofen [31]. Baclofen-induced fecal incontinence has been described in patients with multiple sclerosis [32]. For clinicians, it will be important to observe if fecal incontinence occurs after introduction of anti-spastic or spasmolytic medication and to identify contributing agents. Disturbed sexual function occurred in about every fourth patient and seems to affect males as well as females. Since not a single patient of our series received any medication like PDE5 inhibitors, this topic seems to be insufficiently addressed in patient visits at least in Germany. Addressing sexual health and function and offering treatment to SPG4 patients may well help to reduce constraints caused by HSP, although disturbed sexual function did not correlate with quality of life in SPG4 patients (Pearson: 0.006; $p = 0.945$) in contrast to controls of our series (Pearson: −0.356; $p = 0.000078$). This may reflect the fact that other symptoms might be more severe and debilitating.

Fatigue is common in chronic diseases. It is hard to treat due to a lack of effective therapeutics and it has been shown to be increased in SPG4 patients [6]. We were able to reproduce this finding with 31% of patients ($n = 37$) fulfilling the diagnostic criteria (> 38 points) when applying the MFI. In a recently published meta-analysis, Menting and colleagues [33] showed that only 11% of the variance noted in fatigue severity was explained by the underlying disease (here common chronic diseases were used), but 55% when transdiagnostic factors like female sex, motivational and concentration problems, pain, sleep disturbance, physical functioning, reduced activity, and lower self-efficacy concerning fatigue were added. Thus, Menting et al. suggested that severely fatigued patients would benefit from a transdiagnostic approach targeting individual patient's needs rather than the underlying specific disease. In future therapeutic studies or interventional trials, fatigue may be used as a secondary endpoint to explore if improvements in the specific target on study also lead to an improvement in fatigue.

Pain is also frequent in SPG4 patients and is relevant in its interference with daily activities. 43.2% of SPG4 patients report pain related to HSP, but only 16.1% of patients receive analgesics. In our study, pain severity was positively correlated with age and had a negative impact on maximum walking distance (function) (). This may indicate that adequate treatment of pain may help to improve function in SPG4.

RLS is probably the most controversial topic addressed in this study. Even though RLS has important motor aspects we included it to non-motor symptoms due to its dominating sensory proportion. Sperfeld [5] described an increased frequency of RLS in a series of not genetically stratified HSP cases. This earlier published paper used the 2003 RLS diagnostic criteria [34] with four essential features which all needed to be fulfilled for a diagnosis of RLS. In the meantime, the updated 2014 IRLSSG Diagnostic Criteria were published [17] and were used in our study. There, an additional criterion was introduced and requires that the occurrences of restless legs suspicious features are not solely accounted for as symptoms primary to another medical or behavioral condition. The new criteria include conditions which are differential diagnosis of RLS like leg cramps, peripheral neuropathy, and myelopathy. Patients with hereditary spastic paraplegia have, per definition, a progressive inherited myelopathy and, therefore, cannot be diagnosed with a restless legs syndrome using the previously mentioned criteria due to the underlying disease. When applying the 2003 diagnostic criteria, we were able to reproduce Sperfeld's [5] findings in a genetically stratified SPG4 cohort (total score in SPG4 1.1 vs 0.25 in controls; $p < 0.001$). If the fifth criterion of the 2014 IRLSSG Diagnostic Criteria is applied, RLS can no longer be diagnosed in HSP patients

due to the underlying myelopathy. This matches the clinical observation that levodopa-sensitive symptoms like in common RLS are rarely seen in SPG4, although no formal studies have proven this observation to be true. A previously published article [35] identified problems of patients in differentiating clonus and spasticity using the word spasm for both entities. Additionally, there is a problem with the misperception in non-medical personnel, since "restless" is frequently misperceived in Germany as "passively moving" rather than "without rest". In this study, we addressed this misperception by asking questions about a specific definition of "restless legs" versus spastic clonus. Many patients (> 65%) cannot differentiate both and refer to spastic clonus as "restless legs". Even after getting both definitions presented, 25% of patients self-reported were still not able to differentiate a spastic clonus from RLS. Like in RLS, there is a time-related accumulation for spastic clonus during the evening or at night rather than during other times of the day hampering the selectivity of the RLS diagnostic criteria. For practical aspects, dopaminergic medication may be used as a probative treatment to differentiate between RLS and spastic symptoms.

Self-reported memory impairment and a positive family history of cognitive impairment was increased in SPG4 patients than control individuals (supplementary Table 1). Since the BDI-V score significantly positively correlated with the self-reported memory impairment (in SPG4, Pearson 0.219, $p = 0.017$, and in controls, Pearson 0.528, $p < 0.001$), this may be influenced by a more pessimistic perspective view in patients. MoCA testing revealed minimal differences between SPG4 patients and controls ($p = 0.042$; not significant after correcting for multiple testing). This may be influenced by slightly lower education levels and increased depression in the patient group. In addition to the MOCA test, we used the CANTAB test battery to reevaluate previous findings from other studies [8-10] and to address hypotheses based on imaging results demonstrating parieto-temporal volume reduction in SPG4 [12], but did not find evidence for cognitive impairment in the SPG4 group (see supplementary Table 2). Single parameters as tested by CANTAB® (supplementary Table 2) were below an alpha of 5% including the MoCA with $p = 0.042$. Due to multiple testing and Bonferroni correction, these results were not interpreted as significant changes. Therefore, negative results for cognitive testing may result from the study design with multiple cognitive testing with the CANTAB® approach. In a large cohort, Parodi and colleagues [23] have recently found missense mutations to be more prone for intellectual disability than null mutations in *SPAST*. In contrast, two smaller studies [8, 10] did not find this effect. Further non-automated neuropsychological examinations by trained psychologists are probably needed to clarify the inconsistent findings of previous studies regarding higher cognitive functions in SPG4 and should be done considering the type of mutation. In contrast, there are other HSP subtypes like SPG35 with mutations in *FA2H* which manifest with a high prevalence of progressive cognitive deficits [36]

It is well known that depression is a major comorbidity for chronic diseases. In World Health Surveys of > 245,000 participants [37], depression was present between 9.3 and 23.0% of participants with at least one chronic physical disease. Depression appears to be underdiagnosed and incompletely recognized and treated in SPG4 patients. Some patients with BDI scores < 34 points (below the positive cut-off for depression) receive antidepressants ($n = 8$) or psychotherapy ($n = 3$), which may point to successful interventions, but longitudinal data for those cases are missing. When analyzing patients positively tested for depression by the BDI and gender, there was no significant difference in Chi-square testing ($x = 1$) $p = 0.840$ when testing for the gender. Given the huge impact of depression on quality of life, a more detailed longitudinal study is needed to generate data for more concise recommendations. For the time being, we suggest to include screening and therapy of depression in the daily assessment of SPG4 patients.

Conclusion

Non-motor symptoms such as bladder disturbances, disturbed sexual function, defecation disturbance, fatigue, pain, and depression are frequent and underrecognized in SPG4 patients. These conditions substantially affect quality of life and are often accessible for treatment. As a consequence, clinicians should regularly screen for depression, pain, and fatigue using validated scales to recognize, diagnose, and treat them accordingly. Especially when a cure for this progressive neurodegenerative disease still does not exist, optimizing current treatment strategies is likely to have direct impact on quality of life of SPG4 patients.

Acknowledgments We thank our patients and their families as well as all healthy controls for participating in this study. We would also like to thank our study nurses Katrin Dillmann-Jehn and Elke Feil for their support in recruiting patients. Finally, we thank Thilo Rattay for assistance in proofreading and language editing.

Author contributions LS and TWR designed the experiments. TWR, AB, MV, HH, SW, RS, and LS recruited the patients. TWR and AB analyzed the data. TWR wrote the first draft of the manuscript, with important contributions from HH, SW, RS, and LS. All authors provided input for the final manuscript and approved the final submitted version.

Funding This study was partially funded by the HSP Selbsthilfegruppe Deutschland e.V. (Grant to TWR, RS, and LS). TWR receives funding from the University of Tübingen, medical faculty, for the Clinician Scientist Program Grant: #386-0-0. SW is supported by the Ministry of Science, Research and the Arts of Baden-Württemberg

and the European Social Fund (ESF) of Baden-Württemberg (31-7635 41/67/1). TWR, HH, RS and LS are members of the European Reference Network for Rare Neurological Diseases (Project ID No 739510).

Compliance with ethical standards

Conflicts of Interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement The data sets for this manuscript are not publicly available, because raw data regarding human subjects (e.g., genetic raw data, personal data) are not shared freely to protect the privacy of the human subjects involved in this study; no consent for open sharing has been obtained. Requests to access the data sets should be directed to Dr. Tim W. Rattay.

References

1. Bis-Brewer DM, Zuchner S (2018) Perspectives on the genomics of HSP beyond Mendelian inheritance. Front Neurol 9:958
2. Schule R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S, Klimpe S, Gallenmuller C, Kurzwelly D, Henkel D, Rimmele F, Stolze H, Kohl Z, Kassubek J, Klockgether T, Vielhaber S, Kamm C, Klopstock T, Bauer P, Zuchner S, Liepelt-Scarfone I, Schols L (2016) Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. Ann Neurol 79:646–658
3. Bellofatto M, De Michele G, Iovino A, Filla A, Santorelli FM (2019) Management of hereditary spastic paraplegia: a systematic review of the literature. Front Neurol 10:3
4. Vahter L, Braschinsky M, Haldre S, Gross-Paju K (2009) The prevalence of depression in hereditary spastic paraplegia. Clin Rehabil 23:857–861
5. Sperfeld AD, Unrath A, Kassubek J (2007) Restless legs syndrome in hereditary spastic paraparesis. Eur Neurol 57:31–35
6. Servelhere K, Faber I, Saute J, Moscovich M, D'Abreu A, Jardim L, Teive H, Lopes-Cendes I, Franca M (2016) Non-motor symptoms in patients with hereditary spastic paraplegia caused by SPG4 mutations. Eur J Neurol 23:408–411
7. Chelban V, Tucci A, Lynch DS, Polke JM, Santos L, Jonvik H, Groppa S, Wood NW, Houlden HJJNNP (2017) Truncating mutations in SPAST patients are associated with a high rate of psychiatric comorbidities in hereditary spastic paraplegia. J Neurol Neurosurg Psychiatry 88:681–687
8. Murphy S, Gorman G, Beetz C, Byrne P, Dytko M, McMonagle P, Kinsella K, Farrell M, Hutchinson M (2009) Dementia in SPG4 hereditary spastic paraplegia clinical, genetic, and neuropathologic evidence. Neurology 73:378–384
9. McMonagle P, Byrne P, Hutchinson M (2004) Further evidence of dementia in SPG4-linked autosomal dominant hereditary spastic paraplegia. Neurology 62:407–410
10. Tallaksen CE, Guichart-Gomez E, Verpillat P et al (2003) Subtle cognitive impairment but no dementia in patients with spastin mutations. Arch Neurol 60:1113–1118
11. Chamard L, Ferreira S, Pijoff A, Silvestre M, Berger E, Magnin E (2016) Cognitive impairment involving social cognition in SPG4 hereditary spastic paraplegia. Behav Neurol. https://doi.org/10.1155/2016/6423461
12. Lindig T, Bender B, Hauser T-K, Mang S, Schweikardt D, Klose U, Karle KN, Schüle R, Schöls L, Rattay TW (2015) Gray and white matter alterations in hereditary spastic paraplegia type SPG4 and clinical correlations. J Neurol 261:1961–1971
13. Schule R, Holland-Letz T, Klimpe S, Kassubek J, Klopstock T, Mall V, Otto S, Winner B, Schols L (2006) The spastic paraplegia rating scale (SPRS): a reliable and valid measure of disease severity. Neurology 67:430–434
14. Béreau M, Anheim M, Chanson J-B, Tio G, Echaniz-Laguna A, Depienne C, Collongues N, de Sèze J (2015) Dalfampridine in hereditary spastic paraplegia: a prospective, open study. J Neurol 262:1285–1288
15. Hinz A, Klaiberg A, Brahler E, Konig HH (2006) The quality of life questionnaire EQ-5D: Modelling and norm values for the general population. Psychother Psychosom Med Psychol 56:42–48
16. EuroQol-Group (1990) EuroQol-a new facility for the measurement of health-related quality of life. J Health policy 16:199–208
17. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB (2014) Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated international restless legs syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. Sleep Med 15:860–873
18. Schmitt M, Altstötter-Gleich C, Hinz A, Maes J, Brähler EJD (2006) Normwerte für das vereinfachte Beck-Depressions-Inventar (BDI-V) in der Allgemeinbevölkerung. 52:51–59
19. Smets E, Garssen B, Bonke Bd, De Haes J (1995) The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 39:315–325
20. Radbruch L, Loick G, Kiencke P, Lindena G, Sabatowski R, Grond S, Lehmann KA, Cleeland CS (1999) Validation of the German version of the brief pain inventory. J Pain Symptom Manag 18:180–187
21. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow HJ (2005) The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699
22. Harding AE (1983) Classification of the hereditary ataxias and paraplegias. Lancet 1:1151–1155
23. Parodi L, Fenu S, Barbier M, Banneau G, Duyckaerts C, Tezenas du Montcel S, Monin M-L, Ait Said S, Guegan J, Tallaksen CME, Sablonniere B, Brice A, Stevanin G, Depienne C, Dur Network AS (2018) Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. Brain 141:3331–3342
24. Karle KN, Schule R, Klebe S, Otto S, Frischholz C, Liepelt-Scarfone I, Schols L (2013) Electrophysiological characterisation of motor and sensory tracts in patients with hereditary spastic paraplegia (HSP). Orphanet J Rare Dis 8:158
25. Fink JK (2003) Advances in the hereditary spastic paraplegias. Exp Neurol 184:106–110
26. Guthrie G, Pfeffer G, Bailie M, Bradshaw K, Browning AC, Horvath R, Chinnery PF (2013) The neurological and ophthalmological manifestations of SPG4-related hereditary spastic paraplegia. J Neurol 260:906
27. Wiethoff, S., Zhour, A., Schols, L., et al., Retinal nerve fibre layer loss in hereditary spastic paraplegias is restricted to complex phenotypes. BMC Neurol, 2012. 12: p. 143
28. Klimpe S, Schüle R, Kassubek J, Otto S, Kohl Z, Klebe S, Klopstock T, Ratzka S, Karle K, Schöls L (2012) Disease severity affects quality of life of hereditary spastic paraplegia patients. Eur J Neurol 19:168–171
29. Braschinsky M, Rannikmäe K, Krikmann Ü, Lüüs S, Raidvee A, Gross-Paju K, Haldre S (2011) Health-related quality of life in patients with hereditary spastic paraplegia in Estonia. Spinal Cord 49:175
30. Wald A, Bharucha AE, Cosman BC, Whitehead WE (2014) ACG clinical guideline: management of benign anorectal disorders. Am J Gastroenterol 109:1141

31. Rao SSC (2004) Pathophysiology of adult fecal incontinence. Gastroenterology 126:S14–S22
32. Wiesel PH, Norton C, Glickman S, Kamm MA (2001) Pathophysiology and management of bowel dysfunction in multiple sclerosis. Eur J Gastroenterol Hepatol 13:441–448
33. Menting J, Tack CJ, Bleijenberg G, Donders R, Droogleever Fortuyn HA, Fransen J, Goedendorp MM, Kalkman JS, Strik-Albers R, van Alfen N, van der Werf SP, Voermans NC, van Engelen BG, Knoop H (2018) Is fatigue a disease-specific or generic symptom in chronic medical conditions? Health Psychol 37:530–543
34. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4:101–119
35. Bhimani R, Anderson L (2014) Clinical understanding of spasticity: implications for practice. Rehabil Res Pract 2014:279175
36. Rattay TW, Lindig T, Baets J, Smets K, Deconinck T, Söhn AS, Hörtnagel K, Eckstein KN, Wiethoff S, Reichbauer J, Döbler-Neumann M, Krägeloh-Mann I, Auer-Grumbach M, Plecko B, Münchau A, Wilken B, Janauschek M, Giese A-K, De Bleecker JL, Ortibus E, Debyser M, Lopez de Munain A, Pujol A, Bassi MT, D'Angelo MG, De Jonghe P, Züchner S, Bauer P, Schöls L, Schüle R (2019) FAHN/SPG35: a narrow phenotypic spectrum across disease classifications. Brain 142:1561–1572
37. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B (2007) Depression, chronic diseases, and decrements in health: results from the World health surveys. Lancet 370:851–858