Annals of Physical and Rehabilitation Medicine 66 (2023) 101732

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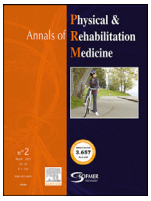

Original article

Individual perception of environmental factors that influence lower limbs spasticity in inherited spastic paraparesis

Pauline Lallemant-Dudek MD[a,b,*], Livia Parodi PhD[a], Giulia Coarelli MD[a,c], Anna Heinzmann MD[a,c], Perrine Charles MD PhD[c], Claire Ewenczyk MD, PhD[c], Silvia Fenu MD[a], Marie-Lorraine Monin MD[a], Philippe Corcia MD PhD[d,e], Christel Depienne PhD[a,f], Fanny Mochel MD, PhD[a], Jean Benard PhD[g], Sophie Tezenas du Montcel MD[h], Alexandra Durr MD, PhD[a,c]

[a] *Sorbonne Université, Paris Brain Institute (ICM Institut du Cerveau), INSERM, CNRS, Assistance Publique-Hôpitaux de Paris (APHP), University Hospital Pitié-Salpêtrière, Paris, France*
[b] *Sorbonne Université, Pediatric Physical Medicine and Rehabilitation Department, Hospital Armand Trousseau, Paris, France*
[c] *Sorbonne Université, Genetic Department, University Hospital Pitié-Salpêtrière, Paris, France*
[d] *Centre SLA, University Hospital Bretonneau, Tours, France*
[e] *Inserm Unit UMR U1253, iBrain, France*
[f] *Institute of Human Genetics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany*
[g] *Association ASL-HSP France, France*
[h] *Sorbonne Université, Biostatistics and Medical Informatics Unit and Clinical Research Unit, University Hospital Pitié-Salpêtrière, UMR S1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France*

ARTICLE INFO

Article History:
Received 30 March 2022
Accepted 28 October 2022
Available online xxx

Keywords:
Spasticity
Physiotherapy
Hereditary spastic paraparesis
Survey
Physical activity
Coping

ABSTRACT

Background: Phenotypic variability is a consistent finding in neurogenetics and therefore applicable to hereditary spastic paraparesis. Identifying reasons for this variability is a challenge. We hypothesized that, in addition to genetic modifiers, extrinsic factors influence variability.
Objectives: Our aim was to describe the clinical variability in hereditary spastic paraparesis from the person's perspective. Our goals were to identify individual and environmental factors that influence muscle tone disorders and derive interventions which could improve spasticity.
Methods: This study was based on self-assessments with questions on nominal and ordinal scales completed by participants with hereditary spastic paraparesis. A questionnaire was completed either in-person in the clinic or electronically via lay organization websites.
Results: Among the 325 responders, most had SPG4/*SPAST* (n = 182, 56%) with a mean age at onset of 31.7 (SD 16.7) years and a mean disease duration of 23 (SD 13.6) years at the time of participation. The 2 factors identified as improving spasticity for > 50% of the responders were physiotherapy (193/325, 59%), and superficial warming (172/308, 55%). Half of the responders (n = 164, 50%) performed physical activity at least once a month and up to once a week. Participants who reported physiotherapy as effective were significantly more satisfied with ≥ 3 sessions per week. Psychologically stressful situations (246/319, 77%) and cold temperatures (202/319, 63%) exacerbated spasticity for most participants.
Conclusion: Participants perceived that physiotherapy reduced spasticity and that the impact of physiotherapy on spasticity was much greater than other medical interventions. Therefore, people should be encouraged to practice physical activity at least 3 times per week. This study reported participants' opinions: in hereditary spastic paraparesis only functional treatments exist, therefore the participant's expertise is of particular importance.

Introduction

Phenotypic variability is a consistent finding in neurogenetics, particularly for dominantly inherited diseases. Identifying reasons for this variability is a challenge because neurogenetic diseases are rare and genetically heterogeneous, thus studies with sufficiently large

Abbreviations: HSP, hereditary spastic paraparesis; PSQI, pittsburg sleep quality index

* Corresponding author at: Paris Brain Institute (ICM), Hôpital Pitié Salpétrière, CS21414, 75546, Paris 13 CEDEX, France.
E-mail address: pauline.lallemant@icm-institute.org (P. Lallemant-Dudek).

https://doi.org/10.1016/j.rehab.2023.101732
1877-0657/

sample sizes are difficult to conduct. Eighty genes are implicated in Hereditary Spastic Paraparesis (HSP) [1]. Some forms are identifiable by their complex phenotypes, such as SPG11, characterized by a thin corpus callosum, intellectual deficiency and early onset [2]. First and second motor neuron involvement occurs in many forms, for example, cerebellar ataxia, peripheral neuropathy, and optic atrophy [3]. The most common form of HSP: SPG4/*SPAST-linked* [4], accounts for about 25% of HSPs. It is transmitted in an autosomal mode, presenting with a pyramidal syndrome in the lower limbs and decreased response to vibration of the ankle joints. The variability in age at onset and progression in SPG4/*SPAST-linked* is even found in individuals from the same family, with the same pathogenic variant. The great clinical heterogeneity with unpredictable ages at onset and evolution within the same family is puzzling. The distribution of age at onset is bimodal and has recently been explained by the underlying mutation; missense mutation carriers induce a significantly lower age at onset, and truncated mutation carriers induce a later age at onset [5]. This result could be found because the number of people included was very large (842 HSP-affected participants included). Therefore, we were motivated to question individuals directly about the factors that they believed influenced the onset and the intensity of the spasticity.

Genetic modifiers, such as additional *SPAST* variants c.131C>T/p.(Ser44Leu), are known to impact age at onset and phenotype severity [5].

Advances in molecular genetic techniques have improved the identification of diseases, increasing understanding but also leading to the awareness that not all phenotypic variations can be explained by genetics [6]. In addition to genetic modifiers, environmental agents may change the disease course or onset. Temperature is known to influence spasticity. For multiple sclerosis, cold temperatures improve gait [7,8], but in HSP, cold decreases walking speed similarly to healthy controls, but also increases spasticity [9]. Environmental factors (e.g., tobacco, alcohol, and pesticides) worsen diseases such as cardiovascular disorders or allergies [10,11]. However, in Parkinson's disease, smoking is a protective factor [12–14]. Such environmental factors have not yet been described in HSP, neither for the overall development nor the evolution of spasticity, but we assume that extrinsic factors play a role in addition to known genetic modifiers.

Currently, there is no consensus on how best to manage spasticity for HSP since clinical variability is not explained solely by the causal genotype. We hypothesized that, in addition to the genetic cause and possible genetic modifiers, environmental factors would influence spasticity and thus its management. Only a few studies (mainly case reports) specifically addressed the symptomatic treatment of spasticity in HSP, including botulinum toxin injection [15–19], intrathecal baclofen pump [20–22] or a specific rehabilitation protocol [23–25]. A literature review concluded that current studies are of low or very low quality and controlled therapeutic trials are needed [26]. With this in mind, we surveyed participants with HSP regarding their lifestyle, spasticity management and coping strategies for symptoms. We aimed to use participants' expertise to understand variability and derive interventions which could reduce spasticity.

Material and methods

Standard protocol approvals, registrations, and participant consent

We analyzed a self-administered questionnaire that was completed by individuals with HSP. The reporting follows STROBE guidelines. The questionnaire was produced in French by the investigative team. This questionnaire was based on person-related observations about symptoms and factors influencing their symptoms among protective or aggravating factors reported for other neurological diseases [12].

Two modes of administration were used: in-person (participants who were present in the National reference center for rare diseases in the Genetic Department at the Pitié-Salpêtrière University Hospital [www.brain-team.fr]) and electronically through lay organization websites (ASL: Association Strümpell-Lorrain Hereditary Spastic Paraparesis France (www.asl-hsp-france.org) and APSHE: Association Paraplégie Spastique Héréditaire et nos Enfants (www.apshe.net).

The study was validated by an ethics committee CCTIRS (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le Domaine de la Santé) and declared to the National Commission for Data Protection and Liberties (CNIL: n°1,776,346). Written consent was obtained from each participant and their consent included permission to be re-contacted by phone by the investigator to assess their degree of autonomy or disability stage. The disability stage is a score established by the Spatax network [27] to report the degree of walking autonomy from 0 to 7. 0: no functional disability, 1: no functional disability but signs at examination, 2: mild, able to run, unlimited walking, 3: moderate, unable to run, limited walking without aids, 4: severe, walks with one stick, 5: walks with two sticks, 6: unable to walk, requires a wheelchair, 7: confined to bed.

The questionnaire (translated to English for the publication, Appendix 1) consisted of ordinal and nominal questions. The nominal questions were composed of questions with dichotomous answers, multiple-choice questions with one or several possible answers, and open-ended questions to which participants could respond freely.

Demographic data collected were sex, weight, height, date of birth, location of residence, alcohol and tobacco consumption habits, sleep quality (Pittsburg Sleep Quality Index [PSQI]), professional activity, comorbidities, and information regarding pregnancies (Appendix 1).

The medical history of the HSP was collected: age at onset, age at the beginning of medical follow-up, symptom triggers, and physical activity. In addition, the underlying genetic variant, if identified, was requested, as well as clinical severity at the time of questionnaire completion, this was completed by the investigator if missing (phone call and medical file if the participant gave permission). Both physiotherapy and personal physical activity were reported in the questionnaire. No details were asked about the type of physiotherapy or the duration of the exercises. A physical activity index was calculated by summing the frequency of physical activity rated from 0 (never) to 5 (every day) (cf questionnaire, Question B 4) and physiotherapy with the transcription of the free text (cf questionnaire, Question B 6) according to the same scale used for physical activity. On average, participants with a physical index > 5 practiced at least 1 physical activity per day.

Double entry of each questionnaire and final quality control ensured data entry consistency. Data are reported as frequencies (percent) for qualitative variables and means (SD) for quantitative variables. Quantitative variables were compared using chi-square tests and quantitative variables using t-tests. $P<0.05$ was considered statistically significant. We estimated odds ratios (OR) and 95% confidence intervals with logistic regression to account for the correlation between physiotherapy effectiveness and genetic variants or physiotherapy frequency. Statistical analysis was performed using SAS software (V.9.4; SAS Institute, Cary, North Carolina, USA).

Results

We received 341 responses between December 2014 and March 2019. Sixteen questionnaires were excluded because of no signed consent or multiple submissions by the same participant (Fig. 1). Among the 325 valid questionnaires, 192 were completed during clinical visits at the National Reference center for Rare Disease at Pitié Salpêtrière University Hospital and 133 via the internet through lay associations (Table 1).

- *All participants (n = 325), demographic description*

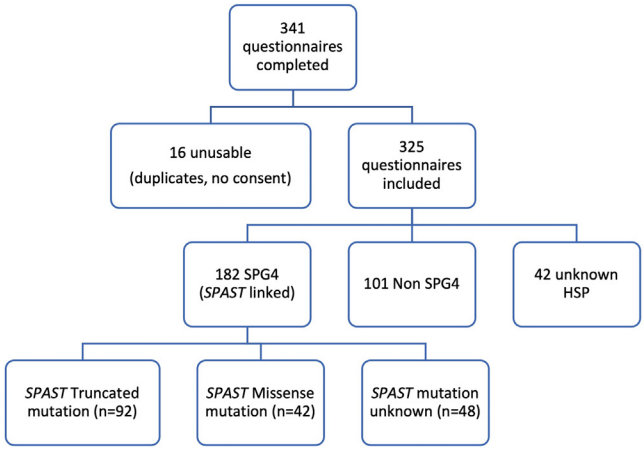

Fig. 1. Flowchart of study participants. HSP: Hereditary Spastic Paraparesis.

The mean age at completion was 56.9 (SD 13.6) years, range 14.1 to 78.7 years. The majority were male (181 versus 144). The mean body mass index was 25 kg/m^2. The primary location of residence for most participants was urban (n = 179, 55%), followed by countryside (n = 116, 36%), seaside (n = 10, 3%) and mountains (n = 3, 1%). Most were employed outside their home (n = 303, 93%) and of these, most (n = 127, 39%) were salaried employees. These criteria did not differ between the data collected via the internet or in the clinic.

Among self-reported health risk factors, 50 (15%) participants were regular smokers, 32 (10%) smoked daily; 91 (28%) consumed alcohol, with 37 (11%) consuming daily. In total, 95/144 (66%) of women had at least 1 pregnancy.

Co-morbidities included cardiovascular disease for 66 (20%) participants, previous or current cancer for 31 (9%), and diabetes for 14 (4%).

- *HSP genetics and symptoms of all participants (n = 325)*

The underlying causal gene was indicated for 283 (87%) participants and missing for 42 (13%). Pathogenic variants in SPG4/*SPAST* were the most frequent (n = 182, 56%) followed by SPG7/*SPG7* (n = 16, 5%) and other exceptional forms (Table 1).

The mean age at onset for all participants was 31.7 (SD 16.7) years (ranging from birth up to 70 years) and the mean age at the beginning of medical care was 35.1 (15.9) years (from 0 to 73 years). The questionnaire was completed after a mean disease duration of 23 (13.6) years (from 1 to 73 years).

A subgroup of 72 participants (22%) indicated that they believed the onset of their symptoms had been triggered by a particular life event: a physical health problem, an emotional or psychological shock, a vaccine, or another event.

Spasticity fluctuated throughout the day for 316 (97%) participants, with 197 participants specifying the time of day when spasticity was the most bothersome: in the evening for 123 (62%), morning 68 (34%) or midday 6 (3%).

The overall disability stage assessed for 263 (81%) participants was moderate (3, could not run) to severe (4, walking with one cane) with a mean stage of 3.2 (SD 1.5) ranging from no functional handicap (0) to bedridden (7).

Most of the responders (164/325, 50%) engaged in physical activity between once a month and once a week, the mean physical activity index score was 4.3 (2.7) (on a scale of 0 to 9); 61 participants (19%) reported no physical activity at all or a frequency of < once a month, and 100 (31%) participants reported one or more physical activity sessions per week (sport or physiotherapy).

Multiple-choice questions about aggravation or reduction of spasticity (with hot or cold weather, stress or intercurrent infections) indicated that psychologically stressful situations and cold temperatures most strongly exacerbated spasticity for 246/319 (77%) and 202/319 (63%) respectively, with no difference between SPG4/*SPAST* and non-SPG4. Two factors reduced spasticity for more than 50% of the responders: physiotherapy for 193/325 (59%) and hot weather for 172/308 (56%). Fig. 2 summarizes the participant-reported factors that influenced the degree of spasticity.

Table 1
Genetic and demographic characteristics of the 325 survey participants.

Underlying Genes with pathogenic variants	n	Sex		Median age at response	Where participants completed the survey:	
	(%)	Female /Male	Ratio	Years (range)	At genetics clinic	Internet via lay organisations**
SPG4 (*SPAST* linked)	182 (56%)	79/103	0.77	57.8 (23.6–89.6)	119 (65%)	63 (35%)
Non-SPG4	101 (31%)	51/ 50	1.02	55.1 (14.1–78.7)	61 (60%)	40 (40%)
- SPG4 excluded*	42 (13%)	19/23	0.83	63.9 (28.0–78.7)	17 (40%)	25 (60%)
- Other HSP	59 (18%)	32/27	1.19	51.9 (14.1–78.7)	44 (75%)	15 (25%)
SPG7 (*SPG7* linked)	16 (5%)	8/8	1.00	63.4 (38.1–72.1)	9 (56%)	7 (44%)
SPG3A (*ALT1* linked)	12 (4%)	9/3	3.00	43.0 (14.1–64.8)	11 (92%)	1 (8%)
SPG5 (*CYP7B1* linked)	6 (2%)	3/3	1.00	59.3 (29.4–67.4)	5 (83%)	1 (17%)
SPG31 (*REEP1* linked)	5 (2%)	2/3	0.67	49.9 (29.8–67.8)	5 (100%)	0 (0%)
SPG10 (*KIF5A* linked)	4 (1%)	2/2	1.00	48.1 (37.6–58.0)	4 (100%)	0 (0%)
SPG30 (*KIF1A* linked)	4 (1%)	3/1	3.00	40.8 (29.1–42.9)	4 (100%)	0 (0%)
SPG8 (*WSHC5* linked)	3 (1%)	1/2	0.50	70.1 (55.0–78.4)	2 (67%)	1 (33%)
SPG9 (*ALDH18A1* linked)	3 (1%)	2/1	2.00	40.7 (35.1–62.0)	2 (67%)	1 (33%)
SPG15 (*ZFYVE26* linked)	2 (1%)	1/1	1.00	34 (29.8–38.2)	0 (0%)	2 (100%)
SPG6 (*NIPA1* linked)	1 (<1%)	0/1		29.1	0 (0%)	1 (100%)
SPG11 (*SPG11* linked)	1 (<1%)	0/1		35.2	0 (0%)	1 (100%)
SPG12 (*RTN2* linked)	1 (<1%)	1/0		61.7	1 (100%)	0 (0%)
SPG48 (*AP5Z1* linked)	1 (<1%)	0/1		71.6	1 (100%)	0 (0%)
Identified genetic form of HSP	283	130/153	0.85	56.5 (14.1–78.7)	180 (64%)	103 (36%)
Unknown genetic HSP	42 (13%)	14/28	0.50	62.6 (22.7–88.5)	12 (29%)	30 (71%)
Total	325	144/181	0.80	56.9 (14.1–89.6)	192 (59%)	133 (41%)

* The SPG4 excluded cohort was composed of: 32 participants SPG4 excluded (9.8%), 4 participants SPG3 4 6 8 31 42 excluded (1.2%), 1 participant SPG4 7 excluded (0.3%), 1 participant SPG3 4 7 10 31 64 excluded (0.3%), 1 participant SPG4 7 8 17 31 42 excluded (0.3%), 1 participant SPG3 4 8 31 42 49 55 59 excluded (0.3%), 1 participant SPG4 42 excluded (0.3%), 1 participant SPG4 8 31 42 excluded (0.3%).

** 29 from the ASL (Association Strümpell-Lorrain) and 1 from APSHE (Association Paraplégie Spastique Héréditaire et nos Enfants).

HSP: hereditary spastic paraparesis.

Among the 325 participants, 261 (71%) were treated for spasticity: 219 (83%) had physiotherapy, 140 had oral medications (54%), and 75 (29%) had botulinum toxin injections. These treatments were deemed effective overall by 230 participants (88%): 80 (31%) for oral medications and 51 (19%) for botulinum toxin injections. The oral medications prescribed and perceived as effective were: baclofen (n = 44), dantrolene (n = 13), clonazepam (n = 5), gabapentin (n = 5), pregabalin (n = 3), levodopa (n = 2), thiocolchicoside (n = 2), bromazepam (n = 1), fampridine (n = 1), citalopram (n = 1), diazepam (n = 1), 2 participants did not answer. Nine (3%) participants received baclofen via an intrathecal pump.

Physical stress, such as an intercurrent infection, increased spasticity for 107/317 participants (34%) but most often had no effect (210/317, 66%). Although fatigue was not specifically indicated as an exacerbating factor in the questionnaire itself, it was reported spontaneously by 91 participants. Several origins of fatigue are known, one obvious reason is poor sleep quality. Participants rated their sleep quality with the PSQI. PSQI scores were < 8 for 183/235 (78%) with a median score of 6 points (Q1 4; Q3 8), range from 0 to 17, indicating good sleep quality. Those who reported fatigue as an exacerbating factor of spasticity had a similar median PSQI score of 6 (Q1 4; Q3 8) (range from 1 to 13, 82 participants, 35%) indicating overall good sleep quality. Among these 82, only 15 reported a PSQI >8 indicating poor-quality sleep as an aggravating factor of spasticity. Sleep quality was independent of disease severity (disability stage 3.5 for poor sleepers and 3.3 for good sleepers, p = 0.285).

Factors spontaneously reported to improve spasticity were physical activity, relaxation and being happy (Fig. 2). Negative emotions, immobility and other intercurrent physical problems (such as bladder and bowel disorders, osteoarthritis, dental pain etc.) were spontaneously reported as aggravating spasticity, but for < 10% of the responders.

Tobacco and alcohol consumption were mostly found to not affect spasticity: 97/323 (30%) reported an effect for smoking and 153 (47%) for drinking.

SPG4/*SPAST-HSP* linked responders

To analyze responses from this genetically homogenous subgroup, we compared participants with SPG4/*SPAST* (n = 182) to those with other forms of HSP (n = 101). Other forms included participants with illness from unknown genetic causes but for whom pathogenic variants in *SPAST* had been excluded (n = 42) and participants with other

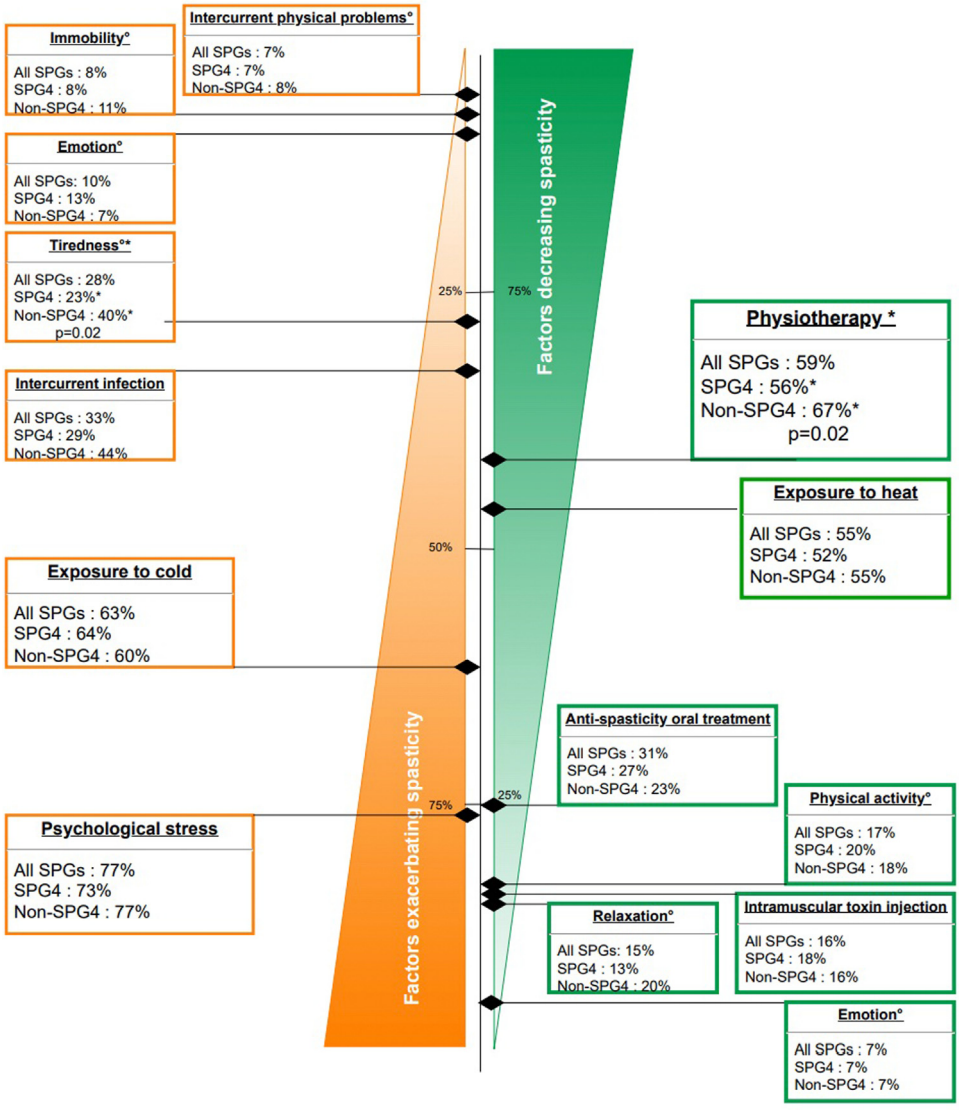

Fig. 2. Factors that exacerbated or reduced spasticity and their frequencies as reported by participants with HSP (n = 325). SPG4-SPAST linked participants: n = 182 and non-SPG4 participants n = 101; °: spontaneously cited factors in the open-ended questions; *: significant difference between SPG4 and non-SPG4 groups.

Table 2
Comparison of demographic and clinical characteristics between the SPG4 and non-SPG4 groups.

	SPG4 (n = 182)	Non SPG4 (n = 101)	
Male: n (%)	103 (57%)	49 (49%)	p = 0.192
Female: n (%)	79 (43%)	52 (51%)	
Body Mass Index: mean (SD) min; max	25.3 (4.0) 18.4; 38.5	24.3 (4.2) 17.1; 38.1	p = 0.067
n	175	100	
Disability stage: mean (SD) min; max n	3.6 (1.5) 0; 7 103	3.9 (1.4) 1; 6 67	p = 0.282
Sedentarism Index: mean (SD) min; max n	4.29 (2.63) 0; 9 182	4.14 (2.69) 0; 9 101	p = 0.643
Age: mean (SD) min; max n	56.21 (13.78) 23; 89 178	52.49 (13.98) 14; 79 97	P = 0.0343*
Age at onset: mean (SD)	36.1 (15.19)	24.53 (15.64)	p<0.0001*
min; max	0; 70	0; 65	
n	126	76	
Age at the beginning of follow-up: mean (SD)	39.0 (16.25)	28.40 (16.60)	p<0.0001*
min; max	0; 73	0; 69	
n	147	87	
Duration disease: mean (SD)	20.42 (12.20)	27.36 (14.95)	p = 0.0011*
min; max	1; 73	1; 65	
n	122	72	
Short distance mobility: n (%)	95 (57%)	68 (73%)	p = 0.0111*
Intense physical work: n (%)	71 (43%)	25 (27%)	
* indicates a significant between-group difference			

identified HSP forms (n = 59): SPG7/*SPG7* (n = 16) and SPG3A/*ALT1* (n = 12) (Table 1).

The SPG4/*SPAST* and non-SPG4/*SPAST* groups were comparable for sex ratio (p = 0.192), body mass index (p = 0.067) and physical index (p = 0.643) as well as disability stage (p = 0.282) (Table 2). The mean age at participation of the SPG4/*SPAST* group was significantly higher than that of the non-SPG4/*SPAST* group (56.2 (13.8) years versus 52.5 (14) years; p = 0.034). Age at onset was later in the SPG4/*SPAST* group (p<0.0001), as was the age at the beginning of medical care (p<0.0001) (Table 2). Despite these differences, mean disability stage was similar between groups (p = 0.282), indicating slower disease progression in the non-SPG4/*SPAST* group. The progression of disability stage according to the duration of the disease differed significantly between the 2 groups (p = 0.0035) (Fig. 3). In the SPG4/*SPAST* group, disability stage progressed significantly by 1 disability stage per 20 years (0.049 / year, SD 0.01, p<0.001), whereas no worsening was found for the non-SPG4/*SPAST* group (0.009 / year, SD 0.01, p = 0.34).

Spasticity treatments

There were no differences between the SPG4/*SPAST* and Non-SPG4/*SPAST* groups for type or frequency of reported treatments (physiotherapy, oral treatment, and botulinum toxin injection). Nevertheless, physiotherapy was considered as more effective by the non-SPG4/*SPAST* group (OR 0.413 [95%CI 0.195; 0.877]). Among participants who reported physiotherapy as being effective (170/325),

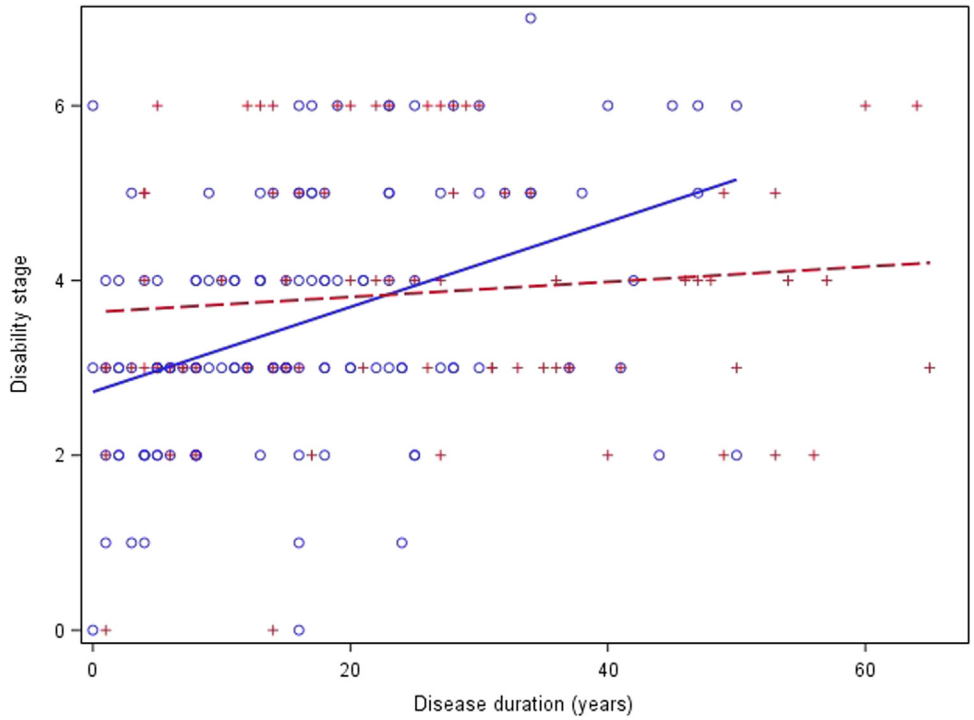

Fig. 3. Progression of disability stage as a function of disease duration for the SPG4 and non-SPG4 groups. Progression of disability stage differed between groups (p = 0.0035): for the SPG4 group (blue line and blue dots) (n = 134), progression was 0.049 points / year, SD 0.01 (p<0.001), whereas no progression was found for the non-SPG4 group (red line and red dots) (n = 76): 0.009 / year (0.01) (p = 0.34).

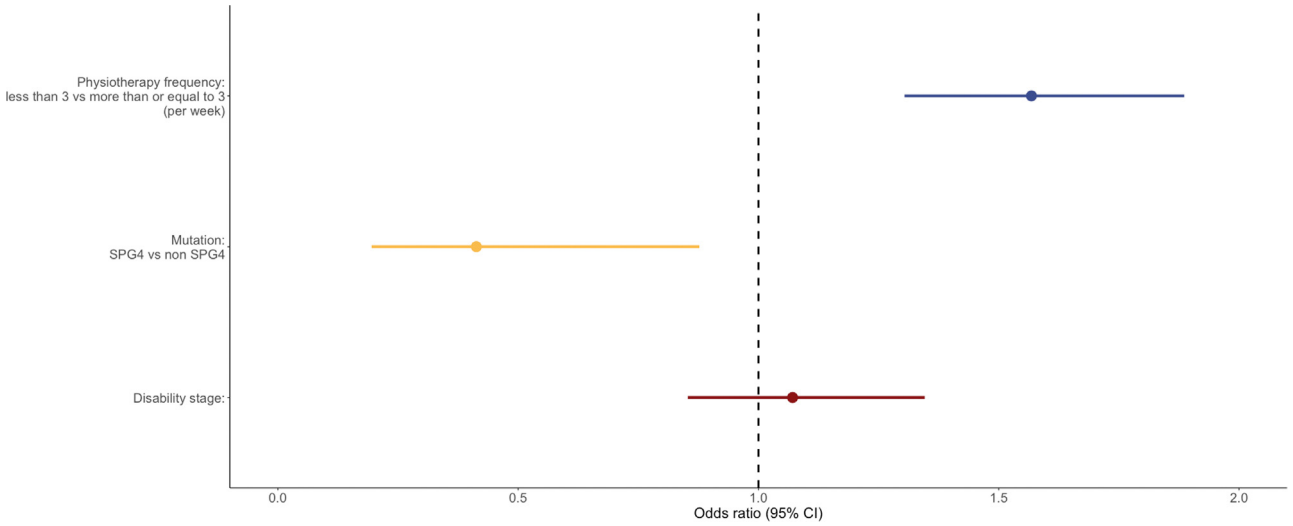

Fig. 4. Predictors of physiotherapy efficacy. Logistic regression model: the horizontal lines indicate the 95% confidence intervals of the estimates. The points represent the summary odds ratios. Physiotherapy is significantly more effective with ≥ 3 sessions per week (OR 1.071 [1.304;1.889], $p<0.0001$), for non-SPG4 participants (OR 0.413 [0.195; 0.877], $p = 0.0213$). Physiotherapy was effective regardless of the participant's disability stage (OR 1.071 [0.853; 1.346], $p = 0.5537$). Odds ratio (OR) and adjusted p-values were calculated with 95% confidence intervals.

practicing at ≥3 sessions of physical therapy per week reinforced the feeling of improvement in lower limb stiffness (OR 1.568 [1.304; 1.886]). Physiotherapy was perceived as effective independently of disability stage (OR = 1.071 [0.853; 1.346]) (Fig. 4).

The SPG4 and non-SPG4 groups differed significantly for fatigue, employment and reported trigger factors at onset: i) fatigue was reported significantly more frequently by the non-SPG4/*SPAST* than SPG4/*SPAST* group (p = 0.0218), ii) the non-SPG4/*SPAST* group more often had skilled jobs with less intense physical work than the SPG4/*SPAST* group (p = 0.011), and iii) the non-SPG4/*SPAST* group declared a trigger factor more often than SPG4/*SPAST* (31 versus 30, p = 0.006).

Discussion

To verify our hypothesis that environmental factors impact muscle tone disorder in addition to genetic modifiers in HSP, we explored self-reported lifestyle, spasticity management and coping with symptoms. We found that spasticity in HSP is perceived to be improved by physiotherapy, particularly when practiced ≥3 times a week. This is the first time that an effective frequency of physiotherapy has been clearly stated, with the perception of improvement linked to the frequency of sessions. French national guidelines for the general population recommend that adults (from 18 to 74 years of age) perform at least 30 min of moderate physical activity 5 days per week. These recommendations were followed by 25% of participants in the present study, according to our physical index score (≥7 points (n = 82) [28]. It seems essential that the healthcare providers treating these participants and the participants themselves become aware of the positive impact of physical activity. Indeed, in addition to physiotherapy with a professional, most individuals should perform exercises independently to maximize the impact on spasticity.

Furthermore, physical activity was more frequently reported as effective than intramuscular botulinum toxin injections. Only 75 participants were receiving intramuscular injections at the time of participation, 64% (n = 182) of whom were from the same health care center. In that care center, injections are easily accessible by referral to clearly identified doctors, therefore the low uptake may reflect low efficacy, acceptance, or use of botulinum toxin by the participants or the staff. The SPATOX double-blind randomized, placebo-controlled crossover trial included 55 participants with HSP [29]. Interestingly, injection of botulinum toxin type A did not improve functional outcomes. This is the only randomized trial to have evaluated botulinum toxin in HSP and studies designed with stratification on progression profiles are needed.

The main causes indicated for the worsening of spasticity were psychological stress (77%), followed by cold weather (62%). Unfortunately, the questionnaire did not directly assess non-motor symptoms such as depression or pain, and this did not allow us to precisely define psychological stress. Anxiety is known to affect other pathologies, such as stroke and multiple sclerosis, and is particularly prominent in HSP. For comparison, in a study of 29 participants with stroke or multiple sclerosis, 59% and 90% of participants respectively described stress and anxiety as worsening spasticity [30]. Another study reported electromyogram recordings in 32 healthy women and showed that stress could modulate muscle contractions with uncorrelated response bursts [31]. In addition to the fact that the perception of stress varies from one individual to another, it is unclear whether stressful situations only modify the perception of spasticity or if the muscle itself contracts differently in the presence of stress.

Fatigue, which was not proposed as a factor in the questionnaire, was spontaneously cited as the most important factor that increased spasticity. It was reported as an additional symptom for 31% of the 118 participants with SPG4 [32] This group had higher ratings on the Modified Fatigue Impact Scale than healthy controls [33]. Fatigue was found to be independent of daytime sleepiness, and in our study we were unable to link fatigue to sleep quality. Fatigue is frequently reported in other neurodegenerative diseases such as Friedreich's ataxia or spinocerebellar ataxia [34,35] but unfortunately, it is not currently medically managed.

Participants were comparable with the French population for body mass index (25 kg/m^2 versus 26.1 kg/m^2) and location of residence (55% versus 50% in cities and, 36% versus 30% in the countryside). Fewer smoked (9% versus 25%) but daily alcohol consumption rates were similar (11% versus 10%) [36,37]. Responders were representative of the known genetic heterogeneity of HSPs with a majority of *SPG4* and *SPG7* linked HSP [38]. In 2010, 47% of the French population reported having sleep disorders. According to the PSQI results, 22% of the study participants had poor-quality sleep. These results for participants with HSP are concordant with data for the general French population [39].

The design of our study allowed a comparison of the disease course between participants with SPG4/*SPAST*-HSP and other rarer forms of spasticity. The age at onset of symptoms in SPG4/*SPAST*-HSP was earlier than for other forms, resulting in a longer disease course.

The onset of HSP is difficult to define precisely (gait difficulties, stiffness, falls etc.) and is determined retrospectively. Furthermore, knowledge of another person with a dominantly inherited disease could change the interpretation of the individual regarding the role of environmental factors. Beliefs about an external trigger that would influence age at onset in non-dominant forms could be explained by the absence of a familial history of the disease. Since, in HSP, onset of symptoms is mostly very slow and gradual, the exact age is seldom accurate since the functional discomfort depends on the individual experience and coping mechanisms. According to the disability stage, loss of autonomy occurs earlier in people with SPG4 than non-SPG4 (Fig. 3).

This study has several limitations. Recruitment bias may be present as it is a self-administered questionnaire; people taking part are likely to be motivated or interested in the management of their disease and symptoms. It also concerns individuals who are already symptomatic and elderly, potentially leaving out other important groups of people with HSP. A self-administered questionnaire precludes any objective measurement of spasticity or a clear distinction between spasticity, stiffness and reduced muscle strength as well as changes in spasticity with physiotherapy. Nevertheless, we chose to use a self-report questionnaire to facilitate contact with people who do not attend the reference center and to increase the number of responses. To our knowledge, this is the largest qualitative study of spasticity in this disease [25,26,40,41]. Because the only treatments available to people with HSP are symptomatic, we thought it would be of interest to ascertain which treatments they deemed effective. As these treatments are functional or "comfort" treatments, the individual's opinion is of particular importance and must be considered for further steps.

Two common physical disorders associated with HSP were not explored: bladder and bowel disorders and pain. These symptoms have a negative impact on individuals' quality of life [42] but their prevalence in HSP has been little evaluated [38,42,43]. Genotype and phenotype are not considered to be correlated, but this should probably be more systematically evaluated.

Physiotherapy improved symptoms for a larger proportion of participants than oral anti-spasticity treatment and botulinum toxin injection together. However, this study could not determine the proportion of participants who had tested anti-spasticity oral treatment or botulinum toxin injections. No data are available in the literature to compare frequency of use or the efficacy of these treatments. Differences in standards of physiotherapy care in France, such as more spaced-out coaching sessions compared to individual, weekly sessions, should be considered before the generalization of these results to the international level. Nevertheless, the relative frequencies of genotypes in our study reflect those found in other European countries [44] and could generalize our treatment approach.

This study highlights an important environmental factor in the experience and management of spasticity: physiotherapy and the frequency at which it is performed. Another study using a self-administered questionnaire reported that people with HSP engaged in physical activity for only a small amount of time in the day, if at all [41]. It would be interesting for further studies to compare the efficacy of different types of physical exercise and the time needed for maximum benefits. Finally, future studies should include objective measurement of spasticity and evaluate the relationship with the type and intensity of physical activity practiced. This would allow correlation between participants' opinions and objective physical assessments.

Conclusions

In people with HSP, perceived spasticity is reported to be modified by intrinsic and extrinsic factors, mainly stressful situations, the weather and physiotherapy. This finding points to the need for people to cope with stressful or difficult situations as well as a need to minimize risks (at work, in crowded places, public transport etc.). The next step is to test the efficacy of intensive physiotherapy in people with homogenous genetic disorders and lower limb spasticity.

Funding information

The present work was funded by the VERUM Foundation for Behaviour and Environment and iCRIN by Paris Brain Institute.

Data availability

Data will be made available on request.

Declaration of Competing Interest

None.

Acknowledgements

Many thanks to the participants, their families and associations for their participation: Association ASL-HSP France and Association Paraplégie Spastique Héréditaire et Nos Enfants (APSHE). We would like to thank the clinical research associates: Elodie Petit, Lynda Benammar, Marie Biet, Rania Hilab and Hortense Hurmic.

The present work was funded by the VERUM Foundation for Behaviour and Environment and iCRIN by Paris Brain Institute.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rehab.2023.101732.

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