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**Patient expertise indicates that physical activity
improves inherited spastic paraplegias**

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Patient expertise indicates that physical activity improves inherited spastic paraplegias

Abstract

Objective

Our aim was to understand the clinical variability in hereditary spastic paraplegias from the patient's perspective. Our goal was to identify individual and environmental factors that influence the progression of the disease and derive interventions which could improve spasticity.

Methods

The MODIFSPA study was based on self-assessments with questions on nominal and ordinal scales completed by patients with hereditary spastic paraplegias.

Results

Among the 325 responders, most were SPG4/SPAST patients (n=182, 56.0%) with a mean age at onset of 31.7 ± 16.7 years and a mean disease duration of 23 ± 13.6 years at the time of participation. The two factors identified as improving spasticity for more than 50% of the responders were physiotherapy for 59% (193/325) and superficial warming 55.8% (172/308). Half of the responders (n=164, 50.5%) performed physical activity at least once a month and up to once a week. Patients who reported physiotherapy as effective were significantly more satisfied with three or more sessions per week. Psychologically stressful situations and cold temperatures exacerbated spasticity for the majority of patients: 77.1% (246/319) and 63.3% (202/319) respectively.

Conclusion

Physiotherapy improved spasticity with a much greater impact than other medical interventions according to patients with hereditary spastic paraplegias. Therefore, patients should be encouraged to practice physical activity at least three times per week. This study reported patients' opinion, as in hereditary spastic paraplegias only functional treatments exist, the patient's expertise is of particular importance.

Keywords : 1. spasticity, 2. physical activity, 3. hereditary spastic paraplegias, 4. survey, 5. symptoms coping

Abbreviations :

- HSP : hereditary spastic paraplegias
- PSQI : Pittsburg Sleep Quality Index

Article

Introduction

Phenotypical variability is a consistent finding in neurogenetics, particularly with regard to dominantly inherited diseases. Identifying reasons for this variability is a challenge because neurogenetic diseases are rare and genetically heterogenous, making it difficult to conduct studies with sufficiently large sample sizes. There are 80 genes implicated in Hereditary Spastic Paraplegias (HSP) (1). Some forms are identifiable by their complex phenotype, such as SPG11 which is characterized by a thin corpus callosum in addition to intellectual deficiency and early onset (2). The most common form of HSP: SPG4/*SPAST-linked* (3), accounts for about 25% of HSPs. It is transmitted in an autosomal mode, presenting with a pyramidal syndrome in the lower limbs and decreased sensation to vibration in the ankles. The variability in age at onset and progression in SPG4/*SPAST-linked* exists even in patients 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 has been found to be bimodal and has recently been explained by the underlying mutation; missense mutation carriers have a significantly lower age at onset, truncated mutation carriers have a later age at onset (4). This finding was possible because the population included was very large (842 HSP-affected patients included).

Genetic modifiers, such as additional *SPAST* variants (c.131C>T/p.(Ser44Leu) for example) are known to impact age at onset and phenotype severity (4).

Improved molecular genetic techniques have led to better identification of diseases, increasing understanding but also leading to awareness that not all variations in phenotype can be explained by genetics alone (5). In addition to genetic modifiers, it's possible that environmental agents change disease course or onset. Temperature is a factor known to influence spasticity. For multiple sclerosis, cold is known to improve patients' gait (6,7), but in HSP cold decreased walking speed like for controls, but also increased spasticity (8). Environmental factors (for example : tobacco, alcohol, and pesticides) are known to worsen diseases such as cardiovascular disorders or allergies (9,10). However, in Parkinson disease smoking is known to be a protective factor (11–13). Such environmental factors have not yet been described in HSP both with regard to overall development and the evolution of spasticity.

Currently, there is no consensus on how best to manage spasticity for HSP. Only a few studies (mainly case reports) specifically address symptomatic treatment of spasticity in HSP, such as with botulinum toxin injection (14–18), intrathecal baclofene pump (19–21) or a specific rehabilitation protocol (22–24). A review of the literature concluded that actual studies are of low or very low quality and controlled therapeutic trials are needed (25).

With this in mind, we surveyed patients with HSP regarding their lifestyle, spasticity management and coping strategies for symptoms. We aim to use patients' expertise to understand variability and derive interventions which could improve spasticity.

Material and methods

Standard Protocol Approvals, Registrations, and Patient Consents

In the MODIFSPA study we analyzed a self-administered questionnaire which was completed by HSP patients. The questionnaire was produced in French by the investigative team and distributed during patients' regular follow up in the Genetic Department at the Pitié-Salpêtrière University Hospital (www.brain-team.fr) as well as via the websites of two lay organisations (ASL: Association Strümpell-Lorrain Hereditary Spastic Paraplegia France (www.asl-hsp-france.org) and APSHE: Association Paraplégie Spastique Héritaire et nos Enfants (www.apshe.net)).

The study has been validated by an ethics committee and declared to the CNIL (n°1776346). Written consent was obtained from each participant and their consent included permission to recontact by the rehabilitation doctor for further information.

The questionnaire (translated in English for the publication, appendix 2) 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 where participants could respond freely.

Demographic data were collected including sex, weight, height, date of birth, location of residence, alcohol and tobacco consumption habits, sleep quality via the PSQI (Pittsburg Sleep Quality Index), professional activity, comorbidities, and information regarding pregnancies (cf Questionnaire Annexed).

A medical history of 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 the questionnaire, and completed if missing by the rehabilitation doctor (PLD). A physical activity index was calculated with both sport and physiotherapy frequency rated from 0 (never) to 5 (everyday). The sum of the two frequencies gives the physical activity index.

Patients with a score greater than 5 practiced at least one physical activity per day on average.

Double entry of each questionnaire and final quality control ensured data entry consistency. Data are reported as frequencies (per cent) for qualitative variables and mean (SD) for quantitative variables. Quantitative variables were compared using chi-square tests and quantitative variables using t-tests. Results were statistically significant for $p \leq 0.05$. We estimated the odds ratio (OR) and 95% confidence intervals by using logistic regression to account for the correlation between physiotherapy efficiency 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 questionnaires between December 2014 and March 2019. Sixteen questionnaires were excluded due to the absence of signed consent or multiple submissions by the same patient (figure 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 in Paris and 133 via internet through patients' associations (table 1).

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

The mean age at completion was 56.9 years \pm 13.6 ranging from 14.1 to 78.7 years. A majority were men (181 versus 144). The mean body mass index was 25 kg/m². The primary residence for most participants was urban (n=179, 55.1%), followed by countryside (n=116, 35.7%), seaside (n= 10, 3.1%) and mountains (n=3, 0.9%). Most were employed outside their home (n=303, 93.2%) and of these, most (n=127, 39.1%) were salaried employees.

Among self-reported risk factors: 50 (15.4%) were regular smokers, 32 (9.8%) smoked daily; 91 (28.0%) patients consumed alcohol, with 37 (11.4%) consuming daily. 95/144 (66.0%) of women had had at least one pregnancy.

Co-morbidities included cardiovascular disease in 66 (20.3%), previous or current cancer in 31 (9.5%), and diabetes in 14 (4.3%).

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

The underlying causal gene was indicated for 283 (87.1%) patients and missing for 42 (12.9%). Pathogenic variants in *SPG4/SPAST* were the most frequent (n=182, 56.0%) followed by *SPG7/SPG7* (n=16, 4.9%) and other exceptional forms (Table 1).

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

A subgroup of 72 patients (22.2%) 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%) patients, with 197 patients specifying the time of day when spasticity was the most bothersome: in the evening for 123 (62.4%), morning 68 (34.5%) or midday 6 (3.0%).

The overall functional stage assessed for 263 (80.9%) patients was moderate (3, cannot run) to severe (4, walking with one cane) with a mean of 3.2 (1.5) ranging from no functional handicap (0) to bedridden (7).

Most of the responders (n=164, 50.5%) engaged in physical activity between once a month and once a week, the mean physical activity index was 4.3 (2.7) (on a scale of 0 to 9); 61 patients (18.8%) reported no physical activity at all or with a frequency of less than

once a month; and 100 (30.8%) patients reported one or more physical activity sessions per week (sport or physiotherapy).

Multiple-choice questions about the worsening or improvement of spasticity (with weather conditions -cold, or heat -, stress and intercurrent infections) indicated that psychologically stressful situations and cold temperatures most strongly exacerbated HSP at 77.1% (246/319) and 63.3% (202/319) respectively with no difference between SPG4/*SPAST* and non-SPG4. Two factors improved spasticity for more than 50% of the responders: physiotherapy for 59% (193/325) and hot weather for 55.8% (172/308). Figure 2 summarizes factors that influenced the degree of spasticity as reported by patients.

Among 325 patients, 261 (70.8%) were treated for spasticity: with physiotherapy for 219 (83.4%), oral medications for 140 patients (53.6%), and botulinum toxin injections for 75 (28.7%). These treatments were deemed effective overall by 230 patients (88.1%), for oral medications: 80 (30.7%) and botulinum toxin injection 51 (19.5%) patients. The oral medications prescribed were: baclofene (n= 44), dantrolene (n=13), clonazepam (n=5), gabapentine (n=5), pregabalin (n=3), levodopa (n=2), thiocolchiside (n=2), bromazepam (n=1), fampiridine (n=1), citalopram (n=1), diazepam (n=1). Nine (2.8%) patients received baclofene by intrathecal pump.

Physical stress, such as an intercurrent infection, increased spasticity for 107/317 patients (33.9%) but most often had no effect (210/317 patients (66.5%)). Although fatigue was not specifically indicated as an exacerbating factor in the questionnaire itself, it was reported spontaneously by 91 patients. Several origins for fatigue are known, one obvious reason is bad sleep quality. Patients filled a PSQI score to assess sleep quality.

PSQI scores were below 8 in 78 % (n=183) with a median score of 6 ± 2.6 , ranging from 0 to 17, indicating good sleep quality. Those who reported fatigue as an exacerbating factor of spasticity had a similar PSQI score of 6.3 (2.8) (ranging from 1 to 13, 82 patients

(34.9%)) indicating overall good sleep quality. Among these 82, only 15 reported a PSQI >8 indicating poor sleep quality as an aggravating factor in spasticity. Sleep quality was independent of disease severity (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 (figure 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 fewer than 10% of the responders.

Tobacco and alcohol consumption were mostly found to have no effect on spasticity: 97 (29.8%) reported an effect for smoking and 153 (47.1%) for drinking.

SPG4/SPAST-HSP linked responders

In order to analyze responses from this genetically homogenous subgroup, we compared SPG4/SPAST patients ($n=182$) to the others ($n=101$). The latter included patients with illness from unknown genetic causes but for whom pathogenic variants in *SPAST* had been excluded ($n=42$), and patients with other identified HSP forms ($n=59$): for most SPG7/SPG7 ($n=16$) and SPG3A/ALT1 ($n=12$) (Table 1).

SPG4/SPAST and non SPG4/SPAST were comparable for sex ratio ($p=0.192$), body mass index ($p=0.067$) and sedentarity index ($p=0.643$) as well as disability stage ($p=0.282$) (Table 2). Mean age at participation of SPG4/SPAST patients was significantly older than in the non SPG4/SPAST group (56.21 years (13.78) versus 52.49 years (13.98); $p=0.034$). Age at onset was later in SPG4/SPAST ($p<0.0001$) as was the age at the beginning of medical care ($p<0.0001$) (Table 2). Despite these differences, mean disability stage was similar between both 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 was significantly different between the two groups ($p=0.0035$) (Figure 3). In the SPG4/SPAST group, disability stage progressed significantly by 1 disability stage per 20 years ($0.049 / \text{year}$ (0.01) ($p<0.001$)), whereas no worsening was visible in the Non- SPG4/SPAST group ($0.009 / \text{year}$ (0.01) ($p=0.34$)).

Spasticity treatments

There were no differences between SPG4/SPAST and Non-SPG4/SPAST groups based on type or frequency of reported treatments (physiotherapy, oral treatment, and botulinum toxin injection). Nevertheless, physiotherapy was more effective for Non-SPG4/SPAST (OR = 0.413 (0.195 to 0.877)). Among patients who reported physiotherapy as being effective ($n=170$), practicing at least three sessions of physical therapy per week improved effectiveness (OR = 1.568 (1.304 to 1.886)). Physiotherapy is effective regardless of the patient's disability stage (OR = 1.071 (0.853 to 1.346)) (figure 4).

SPG4 and Non-SPG4 differed significantly with regard to fatigue, employment and reported trigger factors at onset: i) fatigue was reported significantly more by Non-SPG4/SPAST than SPG4/SPAST ($p= 0.0218$), ii) Non- SPG4/SPAST had more skilled jobs with less intense physical work than SPG4/SPAST ($p= 0.0111$), and iii) Non-SPG4/SPAST declared a trigger factor more often than SPG4/SPAST (31 versus 30, $p= 0.006$). The latter could be explained by less frequent familial history of the disease in the non SPG4/SPAST (13 patients had autosomal recessive transmission and 10 had autosomal dominant transmission).

Discussion

According to our hypothesis that environmental factors impact spasticity in addition to genetic modifiers in HSP, we explored self-reported lifestyle, spasticity management and coping with symptoms in this study. We observed that spasticity in HSP is perceived to be

improved by physiotherapy particularly when practiced 3 times a week or more. This is the first time that frequency for physical activity is clearly stated, and the perception of improvement is linked to frequency. French national guidelines for general population recommend physical activity for adults (from 18 to 74 years of age) 5 or more days per week with at least 30 minutes of moderate physical activity per day. In this study these recommendations are followed by 25% of participants which corresponds to a sedentarity index equal to or greater than 7 (n=82) (26). It seems essential that the healthcare providers treating these patients and the patients themselves become aware of the positive impact of physical activity. Indeed, in addition to physiotherapy with a professional, most patients should practice an adapted physical activity in order to reap the most benefits in reducing spasticity.

Furthermore, physical activity was reported as more frequently effective than intramuscular botulinium toxin injections. Only 75 patients were receiving intramuscular injection at the time of participation, while 64% (n=182) were from the same health care center. In this care center, injections are easily accessible by referral to clearly identified doctors, therefore the low uptake may reflect either the ineffectiveness of botulinum toxin or a rejection of this treatment by the patients. The SPASTOX trial included 55 patients with HSP for a double-blind randomized, placebo-controlled crossover trial (27).

Interestingly, injection of botulinum toxin type A did not improve functional outcomes. This absence of clinical and functional efficacy may be a reason to discontinue treatment. This is the only randomized attempt to test botulinum toxin in HSP and it would be useful to engage a study including stratification on progression profiles.

The main causes indicated for the worsening of spasticity were psychological stress (77.1%), 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 for HSP. For

comparison, in a study of 29 patients suffering from stroke and multiple sclerosis: 59% and 90% described stress and anxiety as worsening spasticity respectively (28). To explain the effect of stress, a study reported electromyogram recordings in 32 healthy women and showed that stress could modulate muscular contraction with uncorrelated response bursts (29). In addition to the fact that the perception of stress varies from one individual to another, it is unclear whether stressful situations modify just the perception of spasticity or if the muscle itself contracts differently in the case of perceived stress.

Fatigue, which was not proposed as a factor in the questionnaire, was spontaneously cited as the most important factor to increase spasticity. It was reported as an additional symptom in SPG4 for 31.4% of 118 patients (30) with SPG4 patients scoring higher on the Modified Fatigue Impact Scale than controls (31). Fatigue was found to be independent from daytime sleepiness, and in our study, we could not link fatigue to sleep quality. Fatigue is frequently reported in other neurodegenerative diseases such as Friedreich ataxia or spinocerebellar ataxia (32,33) but unfortunately it is not currently medically managed.

Participants were comparable with the French population with regard to body mass index (25 kg/m² versus to 26.1 kg/m²) and residency (55.1% versus 50% in cities and, 35.7% versus 30% in the countryside). They reported being smokers less frequently (9% versus 25.4%) but had similar daily alcohol consumption rates (11% versus 10%) (34,35). Responders were representative of the known genetic heterogeneity of HSPs with a majority of *SPG4* and *SPG7* linked HSP (36). In 2010, 47% of the French population reported having sleep disorders. With the PSQI, 22% of the study population had a score corresponding to poor sleep quality. The SPG population is concordant on these criteria with the general French population (37).

Our study allowed for a comparison of the disease course between patients with SPG4/SPAST-HSP and other rarer forms of spasticity. The age at onset of symptoms in SPG4/SPAST-HSP is earlier than for other forms resulting in a longer disease course. Onset in HSP is difficult to define precisely (gait difficulties, or stiffness, falls etc.) and assessed retrospectively. Since in HSP there is mostly a very slowly and gradual onset of symptoms, the exact age is seldom accurate since the functional discomfort depends on the individual experience and coping. The loss of autonomy in SPG4 patients is earlier than in Non-SPG4 patients.

This study has several limitations. There is potential for a recruitment bias 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 sectors of the HSP population. A self-administered questionnaire precludes objective measurements. Because the only treatments available to HSP patients are symptomatic, we thought it would be of interest to inquire about which treatments they deemed effective. As these treatments are functional or “comfort” treatments, the patient's opinion is of particular importance and should perhaps take priority over medical opinion.

Two frequent physical ailments in the HSP population have not been explored: bladder and bowel disorders and pain. These symptoms have a negative impact on patients' quality of life (38) but their prevalence has been evaluated by very few studies within the HSP population (36,38,39). There is no current correlation between genotype and phenotype, but this should probably be more systematically evaluated.

Physiotherapy improved symptoms for a larger portion of patients than oral anti-spasticity treatment and botulinum toxin injection together. However, this study could not determine the proportion of patients who have tested anti-spasticity oral treatment or botulinum toxin injection. There is no data available in the literature to compare frequency of use or comparative efficacy of these treatments.

This study highlights an important environmental factor in the experience and management of spasticity: physical activity and the frequency with which it is performed. Another study using a self-administered questionnaire reported that SPG patients engaged in physical activity for only a small amount of time in the day, if at all (40). It would be interesting in further studies to compare the efficacy of different types of physical exercise and the time needed for maximum benefits. Finally, future studies would ideally have an objective means of evaluating spasticity according to the physical activity practiced. This would make it possible to correlate patients' opinions with objective physical assessments.

Conclusions

In the HSP population, spasticity or its perception are modified by intrinsic and extrinsic factors: mainly stressful situations, weather and physical activity. This finding points to the need for patients to have access to help in order to cope with stressful or difficult situations as well as a need to minimize risks (at work, crowded places, public transport etc.). Knowing the particular importance of physical activity in reducing perceived spasticity, healthcare professionals can be better equipped to promote physiotherapy and physical activity and encourage a minimal frequency of 3 times per week.

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Figures and tables titles and legends

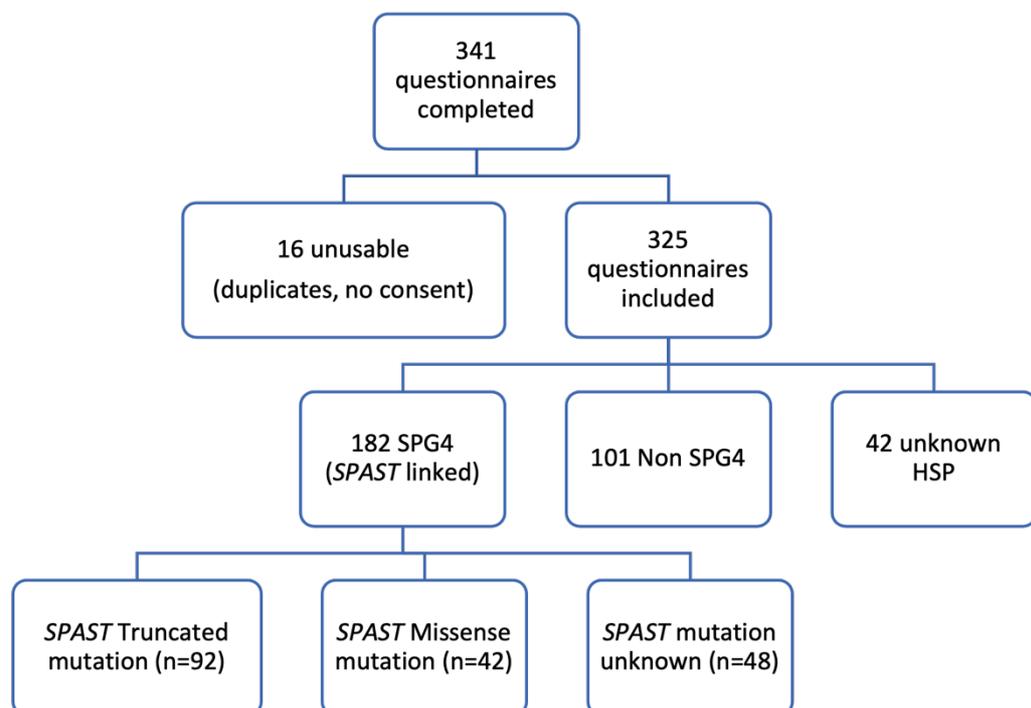


Figure 1: Flowchart of all participants to MODIFSPA

Abbreviation: HSP = Hereditary Spastic Paraplegia

Underlying Genes with pathogenic variants	N (%)	Sex Women /Men	Median age at response Years (range)	Where patients received the survey:		
				Out patients genetics clinic	Lay organisations**	
SPG4 (SPAST linked)	182 (56%)	79/103	0.77	57.8 (23.6 - 89.6)	119 (65%)	63 (35%)
Non SPG4	101 (31.1%)	51/ 50	1.02	55.1 (14.1 – 78.7)	61 (60%)	40 (40%)
- SPG4 excluded *	42 (12.9%)	19/23	0.83	63.9 (28.0 - 78.7)	17 (40%)	25 (60%)
- Other HSP	59 (18.2%)	32/27	1.19	51.9 (14.1 - 78.7)	44 (75%)	15 (25%)
SPG7 (SPG7 linked)	16 (4.9%)	8/8	1.00	63.4 (38.1-72.1)	9 (56%)	7 (44%)
SPG3A (ALT1 linked)	12 (3.7%)	9/3	3.00	43.0 (14.1-64.8)	11 (92%)	1 (8%)
SPG5 (CYP7B1 linked)	6 (1.8%)	3/3	1.00	59.3 (29.4-67.4)	5 (83%)	1 (17%)
SPG31 (REEP1 linked)	5 (1.5%)	2/3	0.67	49.9 (29.8-67.8)	5 (100%)	0 (0%)
SPG10 (KIF5A linked)	4 (1.2%)	2/2	1.00	48.1 (37.6-58.0)	4 (100%)	0 (0%)
SPG30 (KIF1A linked)	4 (1.2%)	3/1	3.00	40.8 (29.1-42.9)	4 (100%)	0 (0%)
SPG8 (WSHC5 linked)	3 (0.9%)	1/2	0.50	70.1 (55.0-78.4)	2 (67%)	1 (33%)
SPG9 (ALDH18A1 linked)	3 (0.9%)	2/1	2.00	40.7 (35.1-62.0)	2 (67%)	1 (33%)
SPG15 (ZFYVE26 linked)	2 (0.6%)	1/1	1.00	34 (29.8-38.2)	0 (0%)	2 (100%)
SPG6 (NIPA1 linked)	1 (0.3%)	0/1		29.1	0 (0%)	1 (100%)
SPG11 (SPG11 linked)	1 (0.3%)	0/1		35.2	0 (0%)	1 (100%)
SPG12 (RTN2 linked)	1 (0.3%)	1/0		61.7	1 (100%)	0 (0%)
SPG48 (AP5Z1 linked)	1 (0.3%)	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 (12.9%)	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 (59.1%)	133 (40.9%)

Table 1: Genetic and demographic characteristics of 325 participants of the survey on modifying factors of spastic paraplegias.

* The SPG4 excluded population is composed of: 32 patients SPG4 excluded (9.8%), 4 patients SPG3 4 6 8 31 42 excluded (1.2%), 1 patient SPG4 7 excluded (0.3%), 1 patient SPG3 4 7 10 31 64 excluded (0.3%), 1 patient SPG4 7 8 17 31 42 excluded (0.3%), 1 patient SPG3 4 8 31 42 49 55 59 excluded (0.3%), 1 patient SPG4 42 excluded (0.3%), 1 patient SPG4 8 31 42 excluded (0.3%).

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

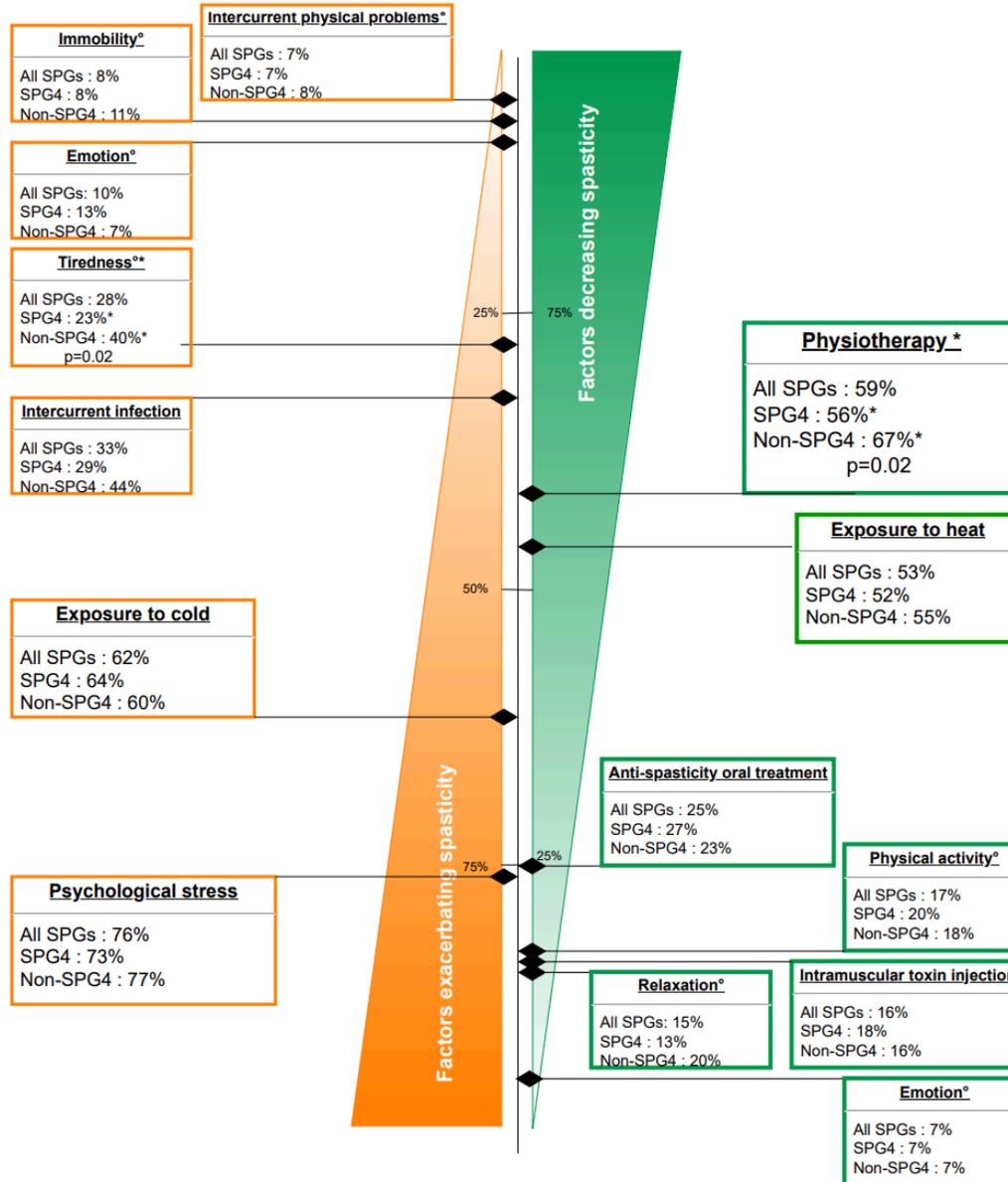


Figure 2: Factors exacerbating and improving spasticity with their proportions in the global population of HSP participating to MODIFSPA (n=325).

The SPG4-SPAST linked patients (n=182) and the Non-SPG4 population (n=101). Factors indicated with ° were factors freely cited by patients on answer after open-ended questions. Factors indicated with * are significantly different between SPG4 and Non-SPG4.

	SPG4 (n=182)	Non SPG4 (n=101)	
Men: n (%)	103 (57%)	49 (49%)	p=0.192
Women: n (%)	79 (43%)	52 (51%)	
Body Mass Index: mean (STD)	25.3 (4.0)	24.3 (4.2)	p=0.067
min - max	18.4 - 38.5	17.1 - 38.1	
n	175	100	
Disability stage: mean (STD)	3.6 (1.5)	3.9 (1.4)	p=0.282
min - max	0 - 7	1 - 6	
n	103	67	
Sedentarity Index: mean (STD)	4.29 (2.63)	4.14 (2.69)	p=0.643
min - max	0 - 9	0 - 9	
n	182	101	
Age: mean (STD)	56.21 (13.78)	52.49 (13.98)	P=0.0343*
min - max	23 - 89	14 - 79	
n	178	97	
Age at onset: mean (STD)	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 (STD)	39.0 (16.25)	28.40 (16.60)	p<0.0001*
min - max	0 - 73	0 - 69	
n	147	87	
Duration disease: mean (STD)	20.42 (12.20)	27.36 (14.95)	p=0.0011*
min - max	1 - 73	1 - 65	
n	122	72	
Seated and small displacement: n (%)	95 (57.2%)	68 (73.1%)	p=0.0111*
Intense physical work: n (%)	71 (42.8%)	25 (26.9%)	

Table 2: Comparison of the SPG4 group to the Non-SPG4 group for the age description and pathology evolution.

SPG4/*SPAST*-linked patients are younger with a lower age at onset and beginning of the follow-up. No difference is found for sex, BMI, disability stage and sedentarity index between SPG4 and Non SPG4 patients.

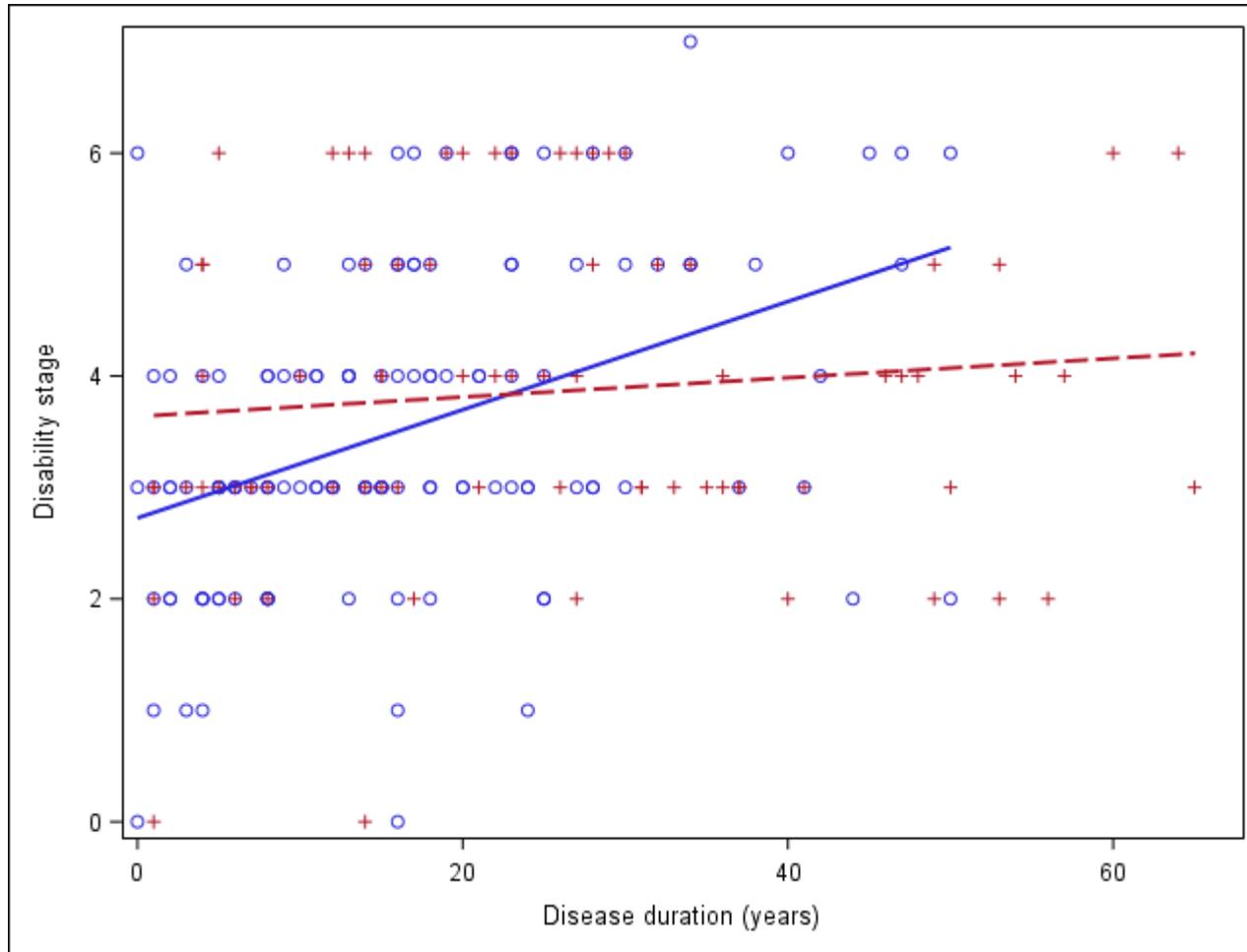


Figure 3: Evolution of the disability stage through the disease duration for the SPG4 group (blue) and the Non-SPG4 (red).

The 2 groups have a different evolution of their disability stage ($p=0.0035$): for the SPG4 group (blue line and blue dots) ($n=134$), the evolution is 0.049 / year (0.01) ($p<0.001$), whereas no evolution is visible in the Non-SPG4 group (red line and red dots) ($n=76$): 0.009 / year (0.01) ($p=0.34$).

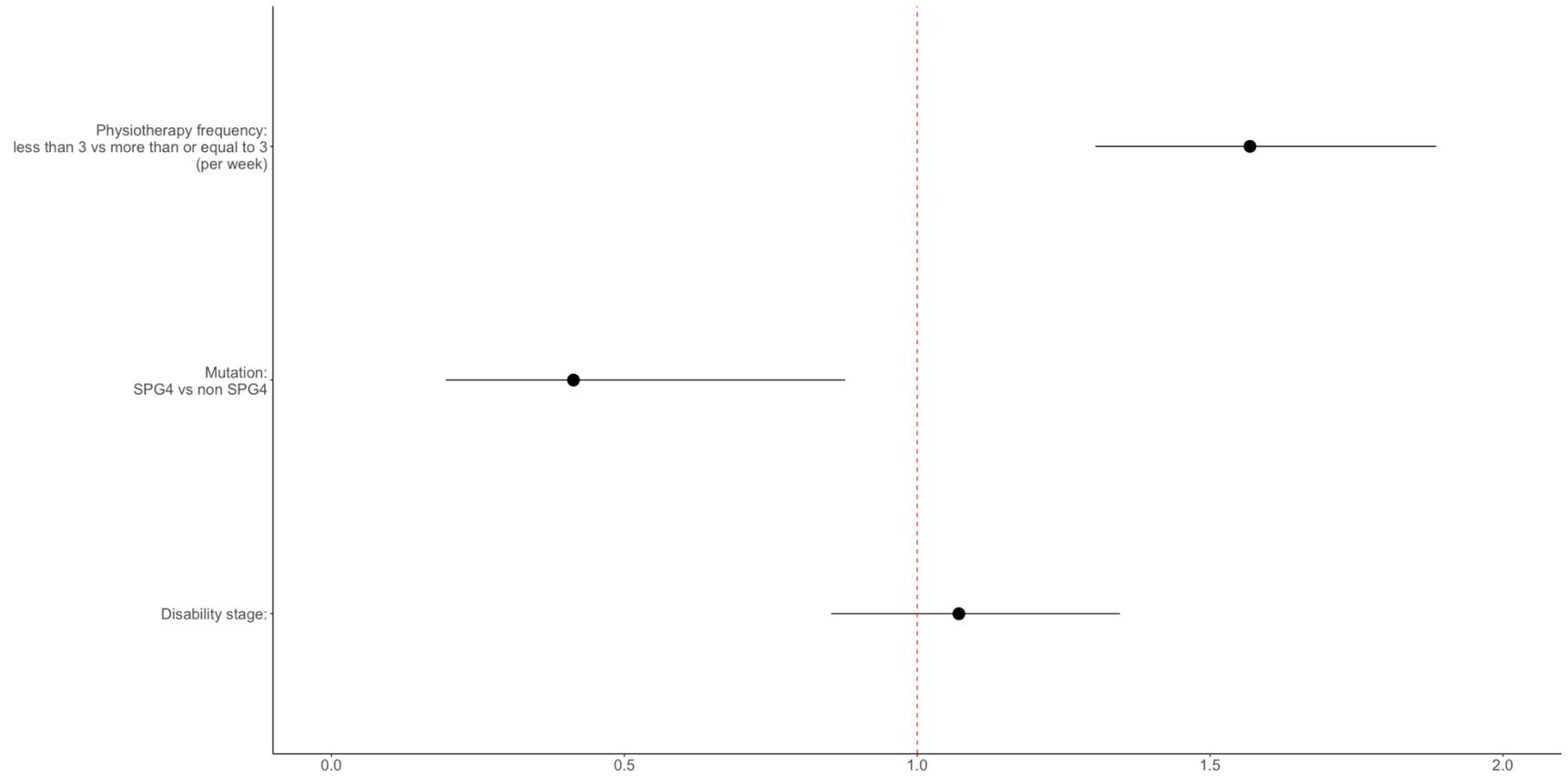


Figure 4: Predictors of physiotherapy efficacy

Logistic regression model: the horizontal lines indicate the 95% confidence intervals of the estimates. The points represent the summary odds ratio. Physiotherapy is significantly more efficient with 3 or more sessions per week (OR= 1.071 [1.304-1.889], $p < 0.0001$), for non-SPG4 patients (OR=0.413 [0.195-0.877], $p = 0.0213$). Physiotherapy is effective regardless of the patient'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.