Received: 13 October 2024 | Accepted: 5 December 2024

DOI: 10.1111/ene.70003

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Hereditary spastic paraplegias: When to expect bladder dysfunction a genetic and urodynamic study

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Abstract

Background: The aim of this study was to characterize hereditary spastic paraplegias (HSP) patients' urodynamic profiles and development of bladder symptoms.

Methods: This is a multicentric retrospective study which included patients presenting with bladder disorders. We reviewed medical and urodynamic records in individuals with HSP and recorded age at onset of gait and bladder disorders, disability stage at the time of urodynamic assessment.

Results: We included 122 participants. They were mostly men ($n = 74$) with a median age at interview of 54.6 ± 13.0 [25–76] years. The underlying genetic cause was identified in 70% of participants, with 54 heterozygous mutations in *SPAST*, followed by 7 *SPG11* and 6 *SPG7*. The age at onset of motor disorder was significantly younger than for the beginning of bladder dysfunction (49.3 vs. 29.7 years-old, $p < 0.001$). Detrusor overactivity was present in most participants (72.1%), followed by detrusor-sphincter-dyssynergia (65.3%). Similar proportions were present in the *SPAST* group as well as the non-*SPAST* group. The *SPAST* group developed urinary symptoms later than the non-SPAST group as compared to the age at onset of spasticity (53.8 ± 11.3 and 44.1 ± 13.2 for the *SPAST* group vs. 44.1 ± 13.2 and 25.5 ± 17.3 for the non-SPAST group).

Conclusion: We have shown that the most common urodynamic pattern in HSP is detrusor overactivity associated with detrusor-sphincter dyssynergia, as would be expected for upper motor neuron lesions. We assessed the temporal window of onset, showing that urinary disorders are secondary to spastic gait in HSP and particularly frequent when walking capability deteriorates.

KEYWORDS
bowel disorders, hereditary spastic paraplegia, neurogenic bladder, SPG4/*SPAST*

INTRODUCTION

More than eighty genes are implicated in hereditary spastic paraplegias (HSP) [1]. The phenotypic presentation varies, with a core phenotype of spasticity in the lower limbs [2]. In a recent published survey [3], HSP patients reported that non-motor symptoms such as pain, fatigue, and/or bladder disorders are more bothersome than walking difficulties, however these problems are not systematically evaluated by urodynamic exploration [4, 5]. In different studies, the prevalence of urinary disorders was estimated to be between 72.4% and 77.6% [6, 7]. Urinary symptoms are not systematically considered or fully investigated in this population, and urodynamics are not described for most of people with HSP. Four major studies explored neurogenic lower urinary tract disorders in the HSP population [4, 7–9]. Urodynamic evaluations were performed in 3 of them for 8, 29 and 33 patients respectively [7–9]. However, genotype information was only partially known for two of these cohorts, SPAST mutation carriers ($n=9/49$ [7] and $n=34/78$ [4]). The aim of this study was to characterize HSP patients' urodynamic profile in a larger cohort and to explore the link between genotype and the onset of bladder disorders.

METHODS

This is a multicentric retrospective study including data from four medical centers with neuro-urology expertise from the University Hospitals of the Assistance Publique—Hôpitaux de Paris network in France. We reviewed medical records for symptomatology and/or urodynamics results in 122 individuals with HSP. Participants had been seen between 1995 and 2023 for a dedicated visit regarding neurogenic lower urinary tract disorders. Genetic testing results were obtained either through the diagnostic laboratory of the National Reference Center for rare neurological diseases in the Genetic Department at the Pitié-Salpêtrière University Hospital in Paris or through the research laboratory of the Paris Brain Institute. Genetic testing was done with either with panel studies, according to Morais et al [10], including 65 SPG genes in the diagnostic setting (including MLPA analysis) for index discovery, or Sanger sequencing if the index case had an identified variant, or exome analysis in research setting. The latter Whole-exome sequencing data was generated with the NovaSeq 6000 and S4 Reagent Kit V.1.5 (300 cycles, paired-end read length of 150 bases) (Illumina, San Diego, California, USA) after Twist V.2.0 (Twist Bioscience, San Francisco, California, USA) capture. DRAGEN Germline Pipeline (Illumina) was used to align the reads to the hg38 human reference genome. Data was collected with the consent of all patients under ethical review board authorization RBM 01–29 and IDRCB n°2021-A00989-32 (NCT 05034172), according to current French regulations (Comité de Protection des Personnes). Genetic testing allowed for comparison of the most frequent genotype (SPG4/*SPAST*) with other SPG genes present on the diagnostic panel.

For each individual, we recorded age at onset of gait disorder as well as bladder disturbances. The Spatax network's definition of disability stage was used 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 cane, 5: walks with two canes, 6: unable to walk, requires a wheelchair, 7: confined to bed [11].

Each patient's first urodynamic evaluation is reported in this study. The evaluation included filling and voiding cystometry as well as pressure profilometry using multi-channel pressure recording technology, following the International Continence Society's (ICS) recommendations [12]. The occurrence of detrusor-sphincter-dyssynergia (DSD) during the voiding phase was recorded. We assessed symptoms at the first interview according to ICS terminology [13] as follows: (i) Increased daytime urinary frequency: exceeding 8 times in 24 h. (ii) Nocturia: waking to pass urine during the main sleep period. (iii) Urgency: the sudden compelling and difficult to defer desire to pass urine. (iv) Urinary incontinence: involuntary loss of urine. Urodynamic observations were described using the definitions above [13]: (i) Neurogenic detrusor overactivity (NDO), or involuntary detrusor contractions during the filling phase; (ii) high pressure detrusor overactivity (if above 40 cm H_20), (iii) bladder compliance impairment (if under 20 mL/cm H_20); (iv) cystometric capacity, bladder volume at the end of filling cystometry. Post void residue was observed after urodynamic investigation, and defined as significant when it exceeded 100 mL.

Statistical analysis was performed using Rstudio software (version 2023.06.1 + 524, Posit Software, PBC, 2022). The Chi-square and Mann–Whitney tests were used to assess the associations between qualitative and quantitative variables respectively. A p value less than 0.05 was defined as statistically significant.

RESULTS

All participants ($n = 122$)

All participants presented with urinary symptoms and had a dedicated interview. There were 48 women (39%), and the median age at examination was 55 ± 13.0 [25–76] years without a significant difference between men and women. The underlying pathogenic causal variant was known for 85 (70%) with variants in SPG4/*SPAST* in 44% ($n=54$), followed by SPG11/*SPG11* in 6% ($n=7$), and SPG7/*SPG7* in 5% ($n=6$) (Table 1).

The median age at the beginning of gait difficulties was 28.5 ± 18.9 [birth–65] years and age at onset of bladder dysfunction was 51 years ±13.6 [16–74] years. The age at the beginning of motor disorder was significantly younger than the onset of bladder dysfunction ($p=0.000003$).

After the dedicated consultation, 104 of the 122 patients underwent urodynamic evaluation. The first urodynamic evaluation was carried out more than 5 years after the first complaint and approximately 6 months after a clinical visit dedicated to bladder and bowel disorders (Table 1). The most frequent urinary symptom was urinary urgency in 88.0% (81/92), then voiding dysfunction in 76.7% (66/86) and incontinence in 64.3% (45/70) (see Table 2). Many reported

TABLE 1 Genetic and demographic characteristics of the 122 participants included after complain of bladder disorders.

Underlying Genes with pathogenic variants	*N* (%)	Sex Women/Men	Mean age at onset Years (range) (*n*)	Mean age for motor involvement Years (range) (*n*)	Average duration of disease progression Years (range) (*n*)	Mean age for urological involvement Years (range) (*n*)	Average duration of disease progression Years (range) (*n*)	Mean age for the 1st urodynamics Years (range) (*n*)	Average duration of disease progression Years (range) (*n*)
Total	122	48/74	26.4 (0–65)	29.7 (0–65) (121)	1.9 (0–40) (111)	49.3 (16–74) (122)	22.1 (0–62) (75)	54.6 (25–76) (104)	26.4 (0–66) (94)
SPAST	54	20/34	28.9 (0–65) (54)	32.7 (0–65) (54)	2.5 (0–40) (48)	53.8 (25–74) (54)	23.2 (1–62) (31)	56.7 (32–76) (47)	24.1 (0–66) (39)
SPG11	7	4/3	15.7 (7–35) (7)	18.0 (8–35) (6)	1.6 (0–11) (7)	30.5 (16–47) (7)	14.8 (3–23) (4)	35.3 (25–55) (7)	19.6 (12–26) (7)
SPG3A	5	2/3	7.8 (1–20) (4)	8.0 (1–20) (4)	0.3 (0–1) (4)	46.0 (40–52) (2)	32.0 (32) (2)	52.8 (40–76) (4)	45.0 (34–56) (4)
SPG7	6	1/5	36.0 (15–5) (6)	36.0 (15–55) (6)	0.0 (0) (6)	51.3 (41–58) (6)	19.3 (0–43) (3)	59.3 (44–75) (6)	29.5 (16–48) (4)
SPG5	3	3/0	33.7 (24–44) (3)	44.0 (1)	0.0 (1)	55.5 (55–56) (2)	17.0 (11–23) (2)	63.0 (62–64) (2)	24.5 (18–31) (2)
SPG8	2	1/1	50 (1)	50 (1)	0 (1)	53 (1)	3 (1)	62.0 (1)	12 (1)
KIF5A	1	0/1	14 (1)	14 (1)	0 (1)	30 (1)	16 (1)	(0)	(0)
SPG31	2	2/0	35.0 (20–50) (2)	38.5 (20–57) (2)	3.5 (0–7) (2)	55.0 (47–63) (2)	20.0 (13–27) (2)	68.0 (2)	33.0 (17–49) (2)
SPG72	1	0/1	4 (1)	4 (1)	0 (1)	46 (1)	42 (1)	47 (1)	43 (1)
SPG76	1	1/0	23 (1)	28 (1)	5 (1)	40 (1)	17 (1)	40 (1)	17 (1)
UBAP1	1	1/0	5 (1)	5 (1)	0 (1)	39 (1)	34 (1)	43 (1)	38 (1)
UBQLN2	1	0/1	2 (1)	(0)	(0)	(0)	(0)	47 (1)	(0)
AP4B1	1	1/0	1 (1)	2 (1)	0 (1)	19 (1)	17 (1)	45 (1)	43 (1)
SPAST excluded	11	3/8	27.6 (0–60) (11)	32.6 (10–60) (11)	2.3 (0–16) (9)	55.0 (50–60) (11)	26.0 (16–36) (3)	59.2 (9)	26.9 (12–63) (9)
KIF5A excluded	1	0/1	1 (1)	3 (1)	2 (1)	53 (1)	52 (1)	53 (1)	52 (1)
No genetic exploration	25	9/16	28.0 (18–38) (2)	41.7 (20–56) (3)	(0)	28.0 (26–71) (4)	(0)	53.2 (3–76) (14)	13.0 (1)

bowel disorders such as constipation or fecal incontinence (64.1%, 50 out of 78 to whom the question was asked). Sexual dysfunction was reported by 62.5% participants, but the question was only asked to half (25/40). Women reported increased voiding frequency significantly more often than men (22/29 vs. 25/50, $p=0.015$). Men were more likely than women to complain of sexual dysfunction (21/26 vs. 4/14 $p=0.006$). The sexual symptoms reported were erectile dysfunction in 20 men, orgasmic dysfunction in 4 women and dyspareunia in a 5th participant.

Urodynamic parameters are reported in Table 3. Neurogenic detrusor overactivity (NDO) was diagnosed in 72.1% (75/104) of patients. Detrusor-sphincter-dyssynergia (DSD) was observed in 65.3% (64/98) of patients. Men were more at risk of developing NDO ($p=0.001$), DSD ($p=0.001$) and high detrusor pressure than women ($p=0.002$).

Before their first urodynamic evaluation only 6% (4/60) of patients had received an anticholinergic treatment for overactive bladder symptoms and no patient practiced intermittent urinary catheterization. After the urodynamic test, anticholinergic medication was prescribed for 40% (42/104) and 21% (21/104) were informed of the need to perform intermittent self-catheterization.

No significant difference was found for symptoms or urodynamic parameters according to degree of disability nor disease duration. Nevertheless, the higher the disability stage the more treatments were required. Only 3% of patients who required anticholinergics could still run and only 26% could walk without aid (Figure 1).

TABLE 2 Bladder, bowel and sexual symptoms described by patients with hereditary spastic paraparesis at the first visit.

Symptoms	All ($n=122$)	Women ($n=48$)	Men ($n=74$)	p
Mean age (years)	54.0 [25–76] (122)	53.8 [31–73] (48)	54.1 [25–76] (74)	
Mean duration of disease progression (years)	26.2 [3–65] (93)	27.4 [7–65] (33)	25.5 [3–56] (60)	
Mean disability scale (0–7)	4.4 [2–6] (60)	4.4 [2–6] (15)	4.3 [2–6] (41)	
Bladder symptoms (%)				
Storage symptoms				
Urgency	88.0% (81/92)	91.6% (33/36)	85.7% (48/56)	0.406
Frequency	59.5% (47/79)	75.9% (22/29)	50.0% (25/50)	0.015*
Nocturia	35.5% (22/62)	38.1% (8/21)	34.1% (14/41)	0.681
Voiding symptoms				
Voiding dysfunction	76.7% (66/86)	71.0% (22/31)	80.0% (44/55)	0.224
Incontinence	64.3% (45/70)	69.2% (18/26)	61.4% (27/44)	0.354
Bowl symptoms (%)	64.1% (50/78)	72.7% (24/33)	57.8% (26/45)	0.213
Sexual dysfunction (%)	62.5% (25/40)	28.6% (4/14)	80.8% (21/26)	0.006*

Note: Difference is statistically significant.

TABLE 3 Urodynamic parameters of patients with hereditary spastic paraparesis.

Urodynamic parameters	All ($n=104$)	Women ($n=42$)	Men ($n=62$)	p
Mean age (years)	54.6 [25–76] (104)	53.4 [31–73] (42)	54.4 [25–76] (62)	
Mean duration of disease progression (years)	26.8 [3–65] (60)	27.4 [4–65] (16)	26.5 [3–56] (36)	
Mean disability scale (0–7)	4.4 [2–6] (57)	4.4 [2–6] (15)	4.3 [2–6] (38)	
Storage parameters (mean)				
Neurogenic detrusor overactivity	72.1% (75/104)	54.8% (23/42)	83.9% (52/62)	0.001*
Maximal detrusor pressure >40 cmH_20	45.6% (41/90)	25.0% (9/36)	59.3% (32/54)	0.002*
Reduced detrusor compliance	5.9% (5/85)	5.7% (2/35)	6% (3/50)	1
Functional bladder capacity (mL)	366 [35–750] (62)	381.4 [90–620] (17)	357.9 [35–750] (38)	
Urethral pressure closure (cmH_20)	86 [20–196] (65)	66.6 [20–140] (16)	97.7 [40–196] (41)	
Voiding parameters (mean)				
Detrusor sphincter dyssynergia	65.3% (64/98)	47.5% (19/40)	79.3% (46/58)	0.001*
Post-void residue (>100 mL)	41.5% (34/82)	37.5% (12/31)	43.1% (22/51)	0.598

Note: Difference is statistically significant.

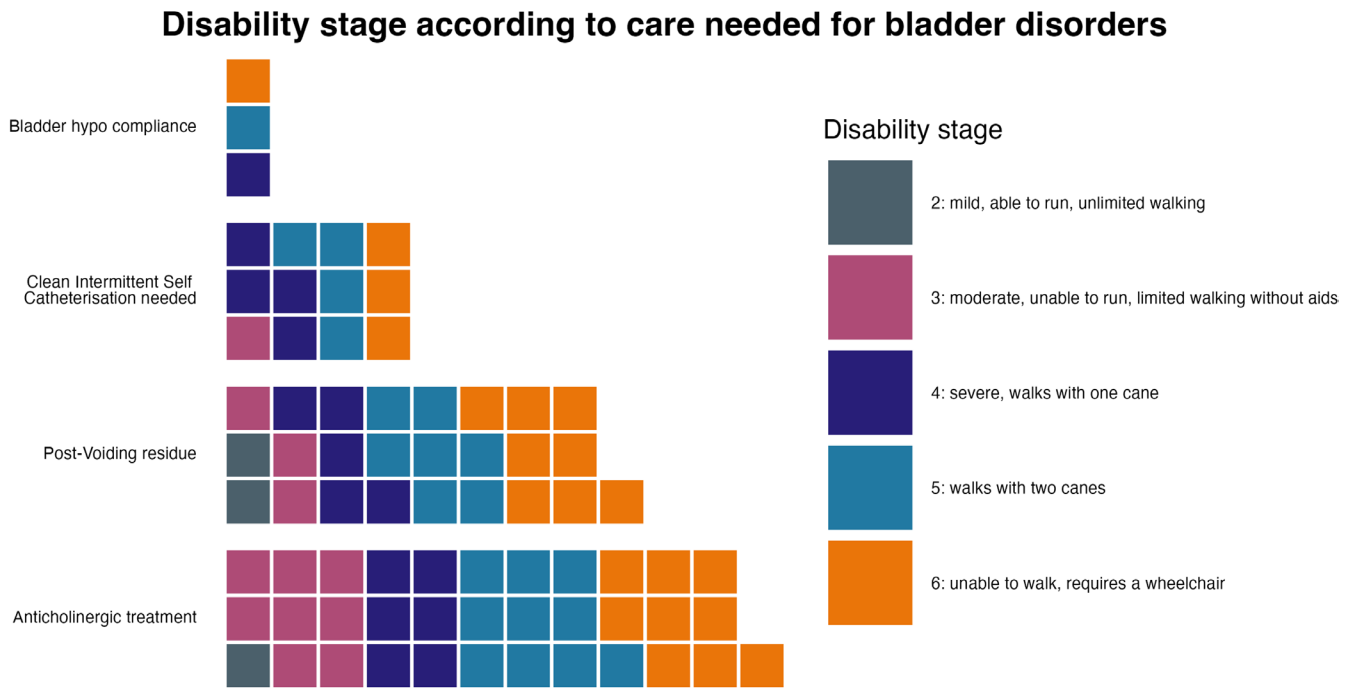

FIGURE 1 Disability stage according to care needed for bladder disorders. Each square represents one patient.

Comparison between SPG4/SPAST ($n = 54$) group and the non-SPAST group ($n = 43$)

We compared participants with SPG4/*SPAST* ($n = 54$) to those with other forms of HSP ($n = 42$), including identified forms of HSP and unknown genetic forms where pathogenic variants in *SPAST* had been excluded ($n = 11$) (Table 1). The median age of onset of bladder dysfunction was significantly older for the SPG4/*SPAST* group (54 ± 11.3 years-old versus 44 ± 13.2 years-old, $p = 0.025$). No difference was found in the frequency of urinary symptoms (p-value ranging from 0.44 to 1). Urodynamic results showed that low bladder compliance was significantly more frequent in the *SPAST* group ($n = 3$) compared with the non-*SPAST* group ($n = 0$) ($p = 0.03$).

DISCUSSION

The current study reports on the assessment of non-motor symptoms of HSP patients in a large cohort form France. This is the largest retrospective study on bladder disorders with urodynamic assessment in HSP to date. Most of these patients presented neurogenic detrusor overactivity and detrusor-sphincter-dyssynergia, a condition known to be a risk factor for upper urinary tract damage. These symptoms are not inaugural symptoms but appear with progression of the disease. These symptoms are similar in the different genotype groups. The development of urinary symptoms therefore appears to be part of the standard evolution of different types of HSP. A recent study identified bladder disturbances in a Spg4 prodromal group [14]. These were not significantly different from the control group but were nevertheless higher and could therefore be present even before evident motor signs. However, the sequence of onset of symptoms is not identical between genotypes: the non-*SPAST* group developed bladder disorders sooner than the *SPAST* group. This could indicate that in more complex forms of HSP, such as the non-SPAST group, the urinary tract may deteriorate 10 years earlier than in less complex forms of the disease. HSP pathology is known for a "dying back" process in which axons degenerate progressively from their distal ends [15, 16], which could explain the secondary onset of micturition problems. Furthermore, a post-mortem study on 6 HSP patients (without genetic identification) reported substantial axonal loss in corticospinal and sensory tracts [17]. The mechanism of degeneration differs by genotype and the involvement of the mutation in the neurons. These mechanisms are not well understood, and the evolution of clinical symptoms is still not fully understood, even within homogeneous genotypes and families.

To explore the prevalence of bladder disorders in an HSP population, we compared our participants to HSP patients seen at the National reference center for rare diseases (Neurogenetics) based on activity in 2022 ($n = 208$). During that year, urodynamic investigations were performed for 42 patients with HSP. This represents 20% of the HSP patients seen during this period. The patients included individuals carrying pathogenic variants in *SPAST*, responsible for SPG4 (18 had urodynamic exam/55 consulted at the National reference center, 32.7%), SPG7/*SPG7* (6/32, 18.8%), SPG3/*ATLASTIN* (3/7, 42.9%), SPG11/*SPATACZIN* (1/7, 14.3%), SPG30/*KIF1A* (2/6, 33.3%) and unknown in 9.1% (7/77). No significant difference was observed in the distribution of genotypes of the participants who had urodynamic exams.

The most frequently reported urinary symptom was urgency (88.0%). This result is similar to 2 out of 4 other studies [8, 9]

regarding bladder disorders and HSP which found 72.4% and 69,7% respectively. In our cohort, the other most frequent symptoms were: (i) frequency (59.5%): reported by 40% of 71 participants in another study [7] and (ii) nocturia (35.5%): reported in 81.1% of 49 patient interviews [4]. Voiding frequency occurred more frequently in women in our cohort than in two other cohorts [4, 8]. This tendency does not reflect the findings of a European population ($n = 19,165$) based survey on lower urinary tract symptoms, where 6.8% of women described having frequency symptoms as well as 6.8% of men [18]. For all of these symptoms the overall prevalence is lower in the general population than in our HSP cohort. As an example, urgency was reported for 16.9% of men and 14.2% of women.

Bowel and sexual disorders were reported by more than half of the patients questioned. This is very similar to the findings of a study of 118 SPG4 patients where 78% had a bladder disorder, 31% had bowel dysfunction and 23% had disturbed sexual function [5]. These symptoms are known to have a significant negative impact on patients' quality of life [4, 5]. Moreover, these intimate symptoms can be difficult for patients to talk about [19]. Unfortunately, these complaints are not systematically sought out by medical teams, therefore we recommend a systematic clinical visit dedicated specifically to continence disorders. This dedicated consultation could be held at the stage when running becomes impossible (disability stage = 3), indicating the pathological degeneration process of the motor system. As a marker, absence of complete bladder emptying during ultrasound scans of the urinary tract (presence of post-voiding residue) was positively correlated to the degree of leg spasticity and negatively correlated to gait speed in a previous report [7].

Neurogenic detrusor overactivity and detrusor-sphincter-dyssynergia is the most frequently reported urodynamic pattern in other pathologies such as multiple sclerosis [20–22], amyotrophic lateral sclerosis [23], and spinal cord injuries [24, 25]. The principles of management for this type of neurological bladder dysfunction (neurogenic detrusor overactivity and detrusor-sphincter-dyssynergia) are well-known and have been recommended for many years. The main objective of management is to obtain a low-pressure reservoir, using therapies such as anticholinergics or injections of intra-detrusor botulinum toxin [26] and to allow for complete and regular emptying of the bladder at low pressure, in accordance with the Lapides principle [27], using a clean intermittent urinary catheter 5 times a day. Management of these non-motor symptoms could potentially improve walking in these patients. It is a raised irritative process that is known by clinical teams to reduce spasticity but has not been proved in the literature yet.

This study has limitations. It is a retrospective study with some missing data (clinical and genetic) and as such, it was difficult to determine the degree of walking independence at the onset of symptoms. An ongoing prospective study is currently being led to improve upon this evaluation (Walk-Up: ClinicalTrials.gov ID NCT05373082). Urological and gynecological histories are not recorded and could present confounding factors in this cohort, as has been the case with other studies with a similar population.

This study shows that the urodynamic pattern of HSP is predictable, and that treatment is possible. Due to the potential complications of neurogenic bladder and the high impact of bladder, bowel, and sexual disorders on quality of life, a systematic consultation with patients regarding these symptoms is fundamental, especially when walking impairment occurs: usually preceding bladder dysfunction. These disorders appear to be part of the natural course of the disease, depending on genotype and occurring later for the SPG4/*SPAST* group.

AUTHOR CONTRIBUTIONS

Pauline Lallemant-Dudek: Conceptualization; investigation; writing – original draft; writing – review and editing; methodology. **Marine Guillaud-Bataille:** Data curation. **Claire Hentzen:** Validation; methodology; writing – review and editing. **Charles Joussain:** Writing – review and editing; validation; methodology. **Bertrand Pichon:** Writing – review and editing; data curation. **Gilberte Robain:** Writing – review and editing; data curation. **Rebecca Haddad:** Writing – review and editing; data curation. **Giulia Coarelli:** Writing – review and editing; data curation. **Anna Heinzmann:** Writing – review and editing; data curation. **Pierre Denys:** Writing – review and editing; validation; data curation. **Gérard Amarenco:** Writing – review and editing; validation; methodology. **Alexandra Durr:** Methodology; validation; writing – review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

No conflict of interest for any author.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Lallemant-Dudek P, Guillaud-Bataille M, Hentzen C, et al. Hereditary spastic paraplegias: When to expect bladder dysfunction a genetic and urodynamic study. *Eur J Neurol*. 2025;32:e70003. doi:10.1111/ene.70003