ORIGINAL COMMUNICATION

Urinary symptoms, quality of life, and patient satisfaction in genetic and sporadic hereditary spastic paraplegia

Susanne A. Schneider[1,2] · Viktoria E. Beckinger[1] · Bettina Möller[1] · Stephanie Knüpfer[3] · Moritz Hamann[3] · Günther Deuschl[1]

Abstract

Background Urinary involvement is common in hereditary spastic paraplegias (HSPs), but has rarely been assessed systematically.

Methods We characterized urinary complaints in 71 German HSP patients (mean age 55.4 ± 13.9 years; mean disease duration 20.7 ± 14.3 years; 48% SPG4-positive) using validated clinical rating scales (SCOPA-AUT, ICIQ-SF, ICIQ-LUTSqol). Treatment history and satisfaction with medical care was also assessed.

Results 74.6% of patients had one or more urological problems, most commonly nocturia and urgency. Incontinence was more severe in women, correlating with SCOPA-AUT. Female gender and SPG4 mutations were associated with higher urinary frequency and severity of urological involvement. QoL was overall reduced, more in women and in SPG4 mutation carriers. Almost 90% consulted a medical specialist; more than half were largely satisfied. 43.4% received oral medication and 5.7% received intravesical botulinum toxin. However, more than one-third of patients remained untreated.

Conclusion Urinary complaints are common in HSP and should be addressed and treated.

Keywords Hereditary spastic paraplegia · Bladder · SPG4 · Satisfaction with care · Urinary incontinence · Nocturia · Urgency · Urinary frequency · Urinary hesitancy · SCOPA-AUT · Quality of life · International Consultation on Incontinence Questionnaire

Introduction

Hereditary spastic paraplegias (HSPs) are characterized by progressive spasticity and hyperreflexia of the lower limbs, often accompanied by bladder dysfunction [1]. At least 54 genes and 74 loci have been identified. However, in the majority of patients, genetic testing remains elusive.

Neurogenic bladder symptoms are common, yet a few studies have systematically assessed or reported the spectrum of urological involvement [2, 3]. Here, we used validated questionnaires and rating scales in 71 HSP patients to characterize lower urinary tract/urological symptoms and patient satisfaction.

Methods

Patients with a diagnosis of HSP were recruited from our tertiary referral hospital database (2001–2012) and via German HSP patient organizations. Using the standardized questionnaires, the following information was retrieved: epidemiological and general disease aspects related to the diagnosis of HSP (age and symptoms at onset; course of motor, urological and other features, history of urinary tract infections, genetic subtype, treatment, and response to treatment, etc.). Autonomic, in particular, urological symptoms were assessed using the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT, 26 items, range 0–69 points, higher scores reflect higher autonomic involvement), the Short Form of the International Consultation

✉ Susanne A. Schneider
susanne.schneider@med.uni-muenchen.de

1   Department of Neurology, Christian-Albrechts-University Kiel, Kiel, Germany

2   Department of Neurology, Ludwig-Maximilians-University München, Feodor-Lynen-Straße 19, 81377 Munich, Germany

3   Department of Urology, Christian-Albrechts-University Kiel, Kiel, Germany

on Incontinence Questionnaire (ICIQ-SF, 4 items, range 0–21 points, assesses the severity of incontinence, higher scores reflect higher burden) and the International Consultation on Incontinence Questionnaire—Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol, 19 items, range 19–276 points, lower points reflect a better QoL). Finally, questions for satisfaction with medical care (using a visual analogue scale, scale range 0–10) were included. The study was approved by the local Ethics Committee; all patients gave written informed consent. Statistical analysis was conducted using SPSS 12.0 (SPSS for Windows 12.0, Chicago) applying t tests, Pearson's chi-square tests, and Spearman's tests. Significance levels were set at 0.05 and 0.01.

Results

Seventy-one HSP patients participated [mean age 55.4 ± 13.9 years; mean disease duration 20.7 ± 14.3 years; 34 males; 48% SPG4-positive). Of these, three quarters ($n = 53$ (74.6%); $n = 28$ women (75.7%), $n = 25$ men (73.5%)] complained of at least one urological problem (Table 1). The mean onset age was 35.8 ± 15.6 years for motor involvement and 46.5 ± 22.8 years for urological involvement. While motor complaints were the presenting symptom in the majority, urological features preceded (8.7%) or co-occurred (15.9%) with the motor onset in about one quarter of patients. Notably, there was a highly significant correlation ($p < 0.01$) between the age at first motor and the first urological symptom, whereas there was no correlation with disease duration.

Table 1 Summary of the main findings of our study and previous studies

	Our study				Braschinsky et al (2010)	Fourtassi et al (2012)			Joussain et al (2016)
	All	Subgroup SPG4 mutation-positive*	Male	Female		All	Male	Female	All
Number of patients initially recruited	71	34			49 [9 patients (18%) SPG4 pos.]	n/a			33
Age	55.4 years	56.2 years			50.9 yrs				62 yrs
Gender (m:f)	34:37	14:20	34	37	30:19				23:10
Number of patients with urological involvement	53	31	25	28	38	29	16	13	33
% of pat. with urological involvement	74.6%	91.2%	67.6%	82.4%	77.6%	100%	100%	100%	100%
Mean age	57.6 yrs	56.1 yrs	56.9 yrs	58.3 yrs	n.d	48.6 yrs	n.s	n.s	62 yrs
Voiding frequency	24,5%	22.6%	16%	32.2%	55.1%	**65,5%**	43.8%	84.6%	n.s
Hesitancy	24,5%	35.5%	28%	21.4%	**59.2%**	51.7%	62.5%	38.5%	85%
Incontinence	26.4%	23.5%	16%	35.7%	**69.4%**	55.2%	37.5%	76.9%	54%
Incomplete bladder emptying	9.4%	9.7%	12%	7.1%	36.7%	41.4% *	37.5% *	46.2% *	70%
Nocturia	**81.1%**	80.6%	80%	82.1%	n.d	51.7%	37.5%	61.5%	56%
Urgency	**75.5%**	74.2%	80%	71.4%	51%	**72.4%**	68.8%	76.9%	85%
History of urinary tract infection	22.6%	22.6%	28%	17.9%	42.9%	44.8%	n.s	n.s	25%
SCOPA-AUT (mean)	$18.7 \pm 8,9$	17.6 ± 9.0	$18.7 \pm 9,4$	18.7 ± 8.7	n.d	n.d			n.d
ICIQ-SF (mean)	8.3 ± 5.3	7.4 ± 5.9	6.0 ± 5.2	10.3 ± 4.8	n.d	n.d			n.d
ICIQ-LUTSqol (mean)	88.7 ± 62.2	77.3 ± 57.4	71.9 ± 63.1	103.7 ± 58.5	n.d	n.d			n.d

Most frequent symptoms of each study are shown in bold

n/a not applicable, *n.d.* no data, *n.s.* not specified

*As determined by urodynamic investigation

The five most common urological symptoms were nocturia (81.1% of urologically affected participants; 80% of the male participants, and 82.1% of the female participants) and urgency (75.5%; 80% of the male; 71.4% of the female participants) affecting more than three quarters of patients each, followed by incontinence (26.4%), voiding frequency and hesitancy (24.5% each), and incomplete bladder emptying (9.4%). Incontinence and voiding frequency occurred twice as frequently in women compared to men (35.7% vs. 16%; 32.2% vs 16%). Incontinence was also more severe in females than males as rated on the ICIQ-SF (10.3 ± 4.8 vs 6.0 ± 5.2, $p = 0.004$). Severity of incontinence correlated with SCOPA-AUT ($p < 0.01$), but did not correlate with age at motor or urological onset or disease duration. Patients also affected by bowel symptoms (i.e., bloating and constipation as assessed by SCOPA-AUT) tended to be more severely affected urologically, i.e., higher scores on the ICIQ-SF, but numbers were too small for firm conclusions. Notably, SPG4-positive patients appeared to be more commonly (91.2% had lower urinary tract dysfunctions) and more severely affected (7.4 ± 5.9 points on the ICIQ-SF vs 5.2 ± 5.7 in SPG4-negative patients, $p = 0.204$).

Twelve patients (28% of male; 17.9% of female) had a positive history of symptomatic urinary tract infections which required treatment in of 5/7 males and all females.

The majority of patients (88.7%) sought advice from a medical specialist (general practitioner, neurologist, and/or urologist) or a family member; most of them consulted an urologist (15.1%). Notably, 11.3% did not seek any help, albeit 83.3% of them would have liked advice for their urological concerns. More than half of the patients who had consulted a medical specialist were satisfied (rates ≥ 8 of 10). Consultation of a neurologist led to the highest satisfaction ratings (8.7 points) compared to urologists (7.8) or general practitioners (6.5). Oral medication (anticholinergics, muscarinic receptor antagonists, and alpha receptor antagonists such as tamsulosin) was prescribed in 43.4%. Three patients (5.7%) had received intravesicular botulinum toxin (btx) injections. This is in contrast to those who were aware of btx as treatment option for bladder symptoms (18.3%) or spasticity (22.5%) in HSP. More than three quarters of treated patients reported benefit (78.8%) of treatment including two of the three treated with btx. Patients receiving oral medication scored higher (mean 7.3 points) than untreated patients (mean 6.1 points) on satisfaction scales. Btx treatment led to highest scores (mean 7.6 points). Notably, 37.7% of HSP patients with urological involvement had never received specific treatment for their urological symptoms.

Quality of life was assessed using the ICIQ-LUTSqol (mean 88.7 ± 62.2 points) with higher scores reflecting less QoL. This demonstrated reduced QoL in females (103.7 ± 58.5 vs 71.9 ± 63.1 in males, $p = 0.046$) and in SPG-positive patients [77.3 ± 57.4 vs 62.4 ± 77.6 in SPG-negative patients ($p = 0.18$)]. This was mainly due to higher ratings in questions related to the overall impact on everyday life (81.3 ± 48.4 in females vs 55.1 ± 50.4 in males, $p = 0.036$). Amongst others, patients reported that bladder symptoms affected their social interactions to some (14%) or a large amount (5.6%). ICIQ-LUTSqol scores correlated with age at motor ($p = 0.039$; correlation coefficient $= 0.284$) and with age at urological onset ($p = 0.011$), as well as ICIQ-SF ($p < 0.01$) and SCOPA-AUT ($p < 0.01$) scores. Urological disease duration correlated with higher burden scores ($p = 0.012$).

Discussion

Only a few studies have systematically assessed the urological features of HSP reporting data from 29[3], 33[4], and 49[2] patients with mixed results. Urgency, (72.4%[3] to 85%[4]), incontinence (69.4%[2]), frequency (65.5%)[3], and hesitancy (59.2[2] to 85%[4]) were identified as the most common complaints. In our cohort, nocturia (81.1%) and urgency (75.5%) were reported most frequently using validated clinical scales; and overall, three quarters of patients (67.6% of men and 82.4% of women) were affected by at least one urological symptom. This is more common than in the general age-adjusted population (where nocturia and urgency occur in 20% and 10%, respectively) [5] and also more common than in Parkinson's disease [6] (nocturia in 60%, urgency in 33–54%, frequency in 16–36% of patients).

Our female HSP patients were more affected by increased voiding frequencies. This has been attributed to smaller bladder volumes, i.e., urethral outflow problems, compared to men [7]. Another risk factor in females are past pregnancies/deliveries which may trigger incontinence.

Braschinsky et al. [2] found no difference in the incidence of urinary dysfunction between clinical subtypes (i.e., pure or complicated HSP) and no differences in prevalence, character, or severity of neuro-urological complaints related to genetic status (SPG4 positive vs negative). However, they only included 9 SPG4 mutation-positive patients, whereas 31 of 53 of our probands with urological problems carried SPG4 mutations. We found these SPG4 mutation-positive patients to be more commonly (91.2% of SPG4 mutations positive carriers had lower urinary tract symptoms) and more severely affected than SPG4 mutation-negative participants. This was particularly true for SPG4 mutation-positive women; based on the ICQ-SF scores, SPG4-type females were more severely affected than SPG4-type males (mean score in females 10.4 vs 4.6 in males). However, the overall number of SPG4 patients remains small and large series suggested that there is clinical overlap between the genetic subforms [8].

Incomplete bladder emptying is a risk factor for urinary tract infections. A positive correlation of post-void residual volumes > 100 ml with the degree of leg spasticity has been suggested [2]. In our cohort, 12 probands had a history of urinary tract infections which required treatment in 5/7 males and all females. Other urologic–nephrologic complications may include urolithiasis (21%), hydronephrosis (8%), and renal failure (17%) [4]. Other features reported by our cohort were pain (11.3%), depression (9.9%), and restless legs (7%). This is slightly lower than in the previous studies assessing their frequencies in patients with HSP compared to healthy individuals [9–11].

Various questionnaires are available to assess the symptoms of incontinence and their impact on quality of life [12]. These measures provide useful information for screening and monitoring patients to care provides. We applied the ICIQ. Notably, an ICIQ-Neuro for assessment of neurological patients is under development [13]. Our patients scored in the lower range on the ICIQ-LUTSqol (mean score 88.7 ± 62.3; maximum possible score 276) with higher scores in females and SPG4-positive patients reflecting a reduced QoL. ICIQ-LUTSqol scores highly correlated with the ages at motor and urological onset, as well as ICIQ-SF and SCOPA-AUT scores. Urological disease duration was highly significantly associated with higher burden scores, i.e., the higher the incontinence, the higher the impact on the QoL. Our results add to the findings of a reduced health-related quality of life (HRQoL) in HSP compared to the general healthy population assessed by the RAND 36-Item Health Survey 1.0 questionnaire [14] which measures mental and general health, physical, social functioning, pain, and vitality. Questions on bladder function are not included.

With regards to management, it is important to exclude or treat urinary tract infections in patients with lower urinary tract symptoms. Storage symptoms, e.g., frequency and urgency, may respond to anticholinergics; however, these are associated with side effects and there are no randomized-controlled trials for HSP. Recently, intravesicular botulinum toxin was found equally effective compared to solfenacin for urgency urinary incontinence in a large double-blind randomized trial [15] and the growing evidence of the positive effects of intravesical botulinum toxin for neurogenic detrusor overactivity was shown in a recent meta-analysis [16]. Indeed, there are positive reports of its use in Parkinson's disease, multiple sclerosis, spinal cord injury, and idiopathic neurogenic bladder dysfunction [17–19]. To our knowledge, there are yet no detailed reports of the use of intravesicular botulinum toxin in HSP. Of our cohort of 53 HSP patients with bladder dysfunction, only three (5.7%) had received intravesicular injections, two of whom reported benefit. Finally, sacral neuromodulation [20] and transcutaneous electrical nerve stimulation may also come into consideration to treat storage symptoms. Nocturia and incomplete bladder emptying may be addressed by a trial of an alpha blocker and/or 5-alpha reductase inhibitors. It is remarkable that 37.7% of our HSP patients with urological involvement had never received any specific treatment for their urological symptoms. We encourage that when confronted with an HSP patient potential, urinary complaints should be addressed and treatment offered if appropriate. Our data show that more than half of the patients who had consulted a medical specialist were satisfied (rates ≥ 8 of 10), mostly so after consulting a neurologist (8.7 points) compared to urologists (7.8) or general practitioners (6.5).

Our study has some limitations. First, despite this being the largest series characterizing urinary features in HSP to date, some subgroups are too small for firm conclusions. Second, the findings are based on the self-reports and validated questionnaires. Furthermore, there may be a bias in patient recruitment, because patients with bladder problems may be more likely to participate and the frequency may thus be overestimated. Finally, we did not perform urinalysis or urodynamic investigations to measure sphincter tonus or residual volume of urine, or investigations reflecting upper urinary tract function (creatinine, etc.). Nevertheless, we believe that our data add to the understanding of bladder dysfunction in HSP and we support further work to shed light on this topic.

Author contributions SAS: research project: conception, organization, execution; statistical analysis: review and critique; manuscript: writing of the first draft. VB: research project: organization ad execution; statistical analysis: execution; manuscript: review and critique. BM: statistical analysis: design, execution, review and critique; manuscript: review and critique. SK: manuscript: review and critique. GD: manuscript: review and critique.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB (2017) Hereditary spastic paraplegia: clinical and genetic hallmarks. Cerebellum 16:525–551

2. Braschinsky M, Zopp I, Kals M, Haldre S, Gross-Paju K (2010) Bladder dysfunction in hereditary spastic paraplegia: what to expect? J Neurol Neurosurg Psychiatry 81:263–266

3. Fourtassi M, Jacquin-Courtois S, Scheiber-Nogueira MC et al (2012) Bladder dysfunction in hereditary spastic paraplegia: a clinical and urodynamic evaluation. Spinal Cord 50:558–562

4. Joussain CL, Charlanes J, Even A, Falcou A, Chartier-Kastler L, Denys EP (2016) Neurogenic detrusor overactivity in patients with hereditary spastic paraplegias. Ann Phys Rehabil Med 59S:e104

5. Irwin DE, Milsom I, Hunskaar S et al (2006) Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. European urology 50:1306–1314 **(discussion 1314-1305)**

6. Yeo L, Singh R, Gundeti M, Barua JM, Masood J (2012) Urinary tract dysfunction in Parkinson's disease: a review. Int Urol Nephrol 44:415–424

7. Wyndaele JJ (1999) Normality in urodynamics studied in healthy adults. J Urol 161:899–902

8. Schule R, Wiethoff S, Martus P et al (2016) Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. Ann Neurol 79:646–658

9. Fjermestad KW, Kanavin OJ, Naess EE, Hoxmark LB, Hummelvoll G (2016) Health survey of adults with hereditary spastic paraparesis compared to population study controls. Orphanet J Rare Dis 11:98

10. Vahter L, Braschinsky M, Haldre S, Gross-Paju K (2009) The prevalence of depression in hereditary spastic paraplegia. Clin Rehabil 23:857–861

11. Sperfeld AD, Unrath A, Kassubek J (2007) Restless legs syndrome in hereditary spastic paraparesis. Eur Neurol 57:31–35

12. Martin JL, Williams KS, Abrams KR et al (2006) Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess 10:1–132, iii-iv

13. http://www.iciq.net/structure.html sos

14. Braschinsky M, Rannikmae K, Krikmann U et al (2011) Health-related quality of life in patients with hereditary spastic paraplegia in Estonia. Spinal Cord 49:175–181

15. Visco AG, Brubaker L, Jelovsek JE et al (2016) Adherence to oral therapy for urgency urinary incontinence: results from the anticholinergic versus Botox comparison (ABC) trial. Female Pelvic Med Reconstr Surg 22:24–28

16. Ni J, Wang X, Cao N, Si J, Gu B (2017) Is repeat botulinum toxin a injection valuable for neurogenic detrusor overactivity—a systematic review and meta-analysis. Neurourol Urodyn 37:542–553

17. Kaviani A, Khavari R (2017) Disease-specific outcomes of botulinum toxin injections for neurogenic detrusor overactivity. Urol Clin North Am 44:463–474

18. Mehta S, Hill D, McIntyre A et al (2013) Meta-analysis of botulinum toxin A detrusor injections in the treatment of neurogenic detrusor overactivity after spinal cord injury. Arch Phys Med Rehabil 94:1473–1481

19. Knupfer SC, Schneider SA, Averhoff MM et al (2016) Preserved micturition after intradetrusor onabotulinumtoxinA injection for treatment of neurogenic bladder dysfunction in Parkinson's disease. BMC Urol 16:55

20. Niu HL, Ma YH, Zhang CJ (2018) Comparison of OnabotulinumtoxinA versus sacral neuromodulation for refractory urinary urge incontinence: a systematic review and meta-analysis of randomized controlled trials. Int J Surg. https://doi.org/10.1016/j.ijsu.2018.10.041