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Lower urinary tract functions in a series of Charcot–Marie–Tooth neuropathy patients

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Objectives – To evaluate lower urinary tract (LUT), bowel, and sexual dysfunctions in a series of patients with Charcot–Marie–Tooth disease (CMT). *Materials and Methods* – A cohort of 58 patients and 54 healthy controls filled out the International Prostate Symptoms Score (IPSS) and the International Consultation on Incontinence Modular (ICIQ) Questionnaires to assess their symptoms and their impact on the patient's quality of life. *Results* – On the IPSS questionnaire, CMT patients reported a significantly higher score compared with the healthy controls in 7 of 8 questions. The ICIQ-male LUT symptoms questionnaire revealed a significantly higher score in 7 of 26 questions. In the ICIQ-female LUT questionnaire, a significantly higher score was observed in 13 of 24 questions. When assessing the bowel function in CMT patients using the ICIQ-bowel questionnaire, a significantly higher score in 30 of 40 questions was noted. No differences in sexual function were found in either group. *Conclusions* – The occurrence of the LUT symptoms and bowel dysfunctions in CMT patients was significantly higher when compared with an age-matched control group. The symptoms were more frequent in female patients. The findings suggest that autonomic dysfunction should be evaluated and included in the diagnostic approach and care of CMT patients.

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Key words: bowel dysfunction; hereditary motor and sensory neuropathy; lower urinary tract dysfunction; questionnaire survey; sexual dysfunction

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Introduction

Charcot–Marie–Tooth disease (CMT) is a motor and sensory neuropathy with a prevalence of 1:2500 people (1). CMT is genetically and clinically heterogeneous. Mutations in more than 50 different genes have been described, leading to many forms of hereditary neuropathy (www.molgen.ua.ac.be/CMTMutations/). While the condition does not shorten the mean life expectancy, it severely affects the quality of life (QoL), and causative treatment is not available (2). The disease usually occurs in the first or second decade of life, affecting both sexes equally. It manifests itself with foot deformity (pes cavus), atrophy, and weakening of the distal muscles and sensitivity disorders in the lower extremities, often followed by the same dysfunction affecting the hands. Impairment of the autonomic nervous system and organ function due to CMT has been documented in some cases, but never studied systematically and only a few reports mention lower urinary tract (LUT) dysfunction (3). Miura et al. (4) studied 12 members of single family suffering from CMT. They described impaired sensation of bladder fullness and bladder hypo-activity confirmed by urodynamic studies. Bladder dysfunction was also previously reported in CMT1B patients (5). None of those studies quantified lower urinary tract symptoms (LUTS) using validated quality of life questionnaires. Despite this evidence, CMT patients are rarely questioned about micturition, bowel, and sexual disturbances, therefore LUT, bowel, and sexual dysfunction may have been underestimated. In addition, in most cases, care of these patients does not involve an urologist or gastroenterologist. The latest Cochrane review of the therapeutic options for CMT concluded that more

properly designed clinical studies are needed (6). This study used validated questionnaires to quantify the effects of the disease on the LUT, bowel, and sexual functions and the degree to which these symptoms affected the QoL.

Methods and materials

Patients and controls

A total of 160 patients with CMT disease were contacted. The patients were selected from the membership registry of the C-M-T Association in the Czech Republic (a nationwide association of patients suffering from CMT disease, www.c-m-t.cz). The response rate was 36.25%, providing an evaluated population of a total of 58 CMT patients (22 men and 36 women). The mean age of the sample was 52.8 years ± 13.4 years. The genetic characteristics of the sample population are summarized in Table 1. Patients with diabetes, malignancies of the small pelvis, an indwelling catheter, or patients who had undergone extensive pelvic operations, or had radiotherapy in the area of pelvis, were excluded from the study. No other concomitant diseases that could significantly influence the function of the LUT were diagnosed. However, we do not have exact information about patients' list of medication. Eighty-six healthy control subjects were also contacted. The response rate was 62.79%, providing an evaluated control population of 54 subjects (24 men and 30 women). The mean age was 49.1 ± 12.5 years.

Questionnaires

Standardized questionnaires were used for the assessment of autonomic functions. International Prostate Symptoms Score (IPSS) was used to assess LUTS, and their impact on a patient's quality of life Table 2. In addition, the following modules of the International Consultation on Incontinence Modular Questionnaires (ICIQ) were used: ICIQ-MLUTS (13 questions, version 1/06) for the assessment of LUTS in men, ICIQ-FLUTS (12 questions, version 8/04) for the assessment of LUTS in women, ICIQ-B (21 questions, version 04/08) for the assessment of bowel symptoms in both sexes. ICIQ-MLUTSsex (4 question, version 7/05) for the assessment of sexual functions in men and ICIQ-FLUTSsex (4 question, version 8/04) for the assessment of sexual functions in women. Each ICIQ module uses a common question format. Most questions use 5-point Likert scale to assess the presence or absence of a symptom and its severity, followed by visual analog scale of 0–10 to assess associated bother (7).

Table 1 Genotype characteristic of CMT patients

Male/Female	Subtype of CMT disease	Gene mutation
6/20	CMT 1A	PMP22 duplication
3/3	CMT X1	GJB1 mutation
3/2	CMT 4C	SH3TC2 mutation
1/2	CMT 1B	MPZ mutation
0/2	HNPP	PMP22 deletion
1/0	CMT 2A	MFN-2 mutation
7/5	CMT 2	Not known
1/2	CMT 1	Not known

Statistical analysis

The difference between CMT patients and healthy controls was compared using a nonparametric Wilcoxon's two-sample test with correction for sequence alignment for the values measured in the ordinal scale. P-values ≤ 0.05 were considered statistically significant. We used the NCSS statistical software for statistical processing of the obtained results (8).

Results

Lower urinary tract assessment

The IPSS, ICIQ-MLUTS and ICIQ-FLUTS questionnaires were used to assess LUTS in CMT patients, which were then compared to age-matched controls. Male CMT patients reached significantly higher scores in 3 of 8 questions. A significant difference was recorded in both questions related to storage symptoms (urgency, frequency). When analyzing voiding symptoms, a significant difference was recorded in the question related to weak stream. In female CMT patients, a statistically significant increase was recorded in 5 of 8 questions on the IPSS questionnaire. These included 3 of 4 questions focusing on voiding symptoms, as well as number of episodes of nocturia and the quality-of-life assessment question. When scores from all CMT patients on IPSS questionnaire were analyzed together, a significantly higher score was recorded on 7 of 8 questions compared with healthy controls.

The ICIQ-MLUTS questionnaire revealed a significantly higher score in 7 of 26 questions. For storage symptoms, a significantly higher score was recorded in 3 of 6 questions, and a

Table 2 Results of IPSS (lower urinary tract dysfunctions) questionnaire in total sample (both male and female patients)

Variables	Total sample			Male			Female		
	Controls (n = 54) M*	Patients (n = 58) M*	P	Controls (n = 24) M*	Patients (n = 22) M*	P	Controls (n = 30) M*	Patients (n = 36) M*	P
IPSS1 Incomplete emptying	0 (0–3)	0 (0–5)	0.290	0 (0–3)	0 (0–5)	0.263	0 (0–3)	0 (0–4)	0.017
IPSS2 Frequency	1 (0–5)	1 (0–5)	0.043	1 (0–2)	1 (0–5)	0.013	1 (0–5)	1 (0–5)	0.675
IPSS3 Interrupted stream	0 (0–2)	0 (0–5)	0.048	0 (0–2)	0.5 (0–5)	0.086	0 (0–2)	0 (0–4)	0.713
IPSS4 Urgency	0 (0–2)	1 (0–5)	0.001	0 (0–2)	1 (0–3)	0.017	1 (0–2)	1 (0–5)	0.222
IPSS5 Weak stream	0 (0–2)	1 (0–4)	0.000	0 (0–2)	1 (0–4)	0.007	0 (0–1)	0 (0–4)	0.022
IPSS6 Straining during voiding	0 (0–4)	0 (0–4)	0.020	0 (0–4)	0.5 (0–4)	0.285	0 (0–1)	0 (0–2)	0.001
PSS7 Nocturia	1 (0–5)	1 (0–5)	0.003	1 (0–5)	1 (0–5)	0.401	0 (0–3)	1 (0–5)	0.004
IPSSQoL Quality of life	1 (0–6)	1 (0–6)	0.001	1 (0–3)	1 (0–4)	0.061	0.5 (0–6)	1 (0–6)	0.002

*M, Median (Min–Max)

significantly higher score was recorded for 3 of 12 questions related to voiding symptoms.

In the ICIQ-FLUTS questionnaire, a significantly higher score was observed in 13 of 24 questions. The score for questions regarding storage symptoms was significantly higher in 4 of 6 instances, and questions about voiding symptoms had a significantly higher score in 3 of 6 questions. The results are presented in Tables 3 and 4.

Sexual function assessment

Patients, which indicated that they do not have an active sexual life, were excluded from this assessment (Tables 5 and 6). We did not observe any statistically significant differences between the groups of male patients, however, the ICIQ-FLUTSsex questionnaire showed a significant difference in the question related to urine leak during intercourse (1 of 8) (Tables 5 and 6).

Bowel function assessment

When assessing the entire CMT patient population using the ICIQ-B questionnaire, a significantly higher score in 30 of 40 questions was noted. The subgroup of questions focusing on the symptoms of constipation documented a significantly higher score in 4 of 4 questions. Responses to questions aimed at fecal incontinence showed a significantly higher score in 12 of 20 instances. A significantly higher score for the CMT patient group was recorded in 8 of 40 questions in males. Questions addressing constipation symptoms revealed a significant difference between patients and healthy controls in 1 of 4 instances. Questions inquiring about symptoms related to fecal incontinence showed a difference in 4 of 20 questions. The female subgroup reached a significantly higher score in 30 of 40 questions. The questions regarding constipation showed a difference in 2 of 4 instances. Questions about incontinence showed a difference in 13 of 20 questions.

Discussion

The clinical phenotype of CMT is caused by a mutation in many different genes involved in the coding of multiple proteins (myelin and gap junction-forming proteins, various enzymes etc.) leading to demyelination and axonal degeneration. The classic clinical phenotype is characterized by motor impairment and loss of sensation to touch, pain, and vibration distally in lower, later, and less frequently, upper limbs. Gradual progression of both motor and sensory deficit leads to the impairment of locomotion and balance. In the last two decades, studies have documented autonomic nervous system (ANS) dysfunction being associated with later stages of CMT disease (9). The pupilary abnormalities related to late onset axonal neuropathy caused by *MPZ* gene mutation (Glu97Val) and most frequently in CMT type 2 caused by different gene mutations were reported (10, 11). Another *MPZ* gene mutation (Thr124Met) causing late onset axonal neuropathy is related to bladder dysfunction, sudomotor dysfunction, pupilary abnormalities and in

Table 3 Results of ICIQ-MLUTS questionnaire in males

Variables	Controls (n = 24) M*	Patients (n = 22) M*	P
MLUTS2A Micturition start delay	1 (0–3)	1 (0–2)	0.2728
MLUTS2B Quality of life	0 (0–5)	2 (0–8)	0.0172
MLUTS3A Straining during voiding	0 (0–3)	1 (0–3)	0.2232
MLUTS3B Quality of life	0 (0–5)	0.5 (0–8)	0.0555
MLUTS4A Stream strength	0 (0–3)	1 (0–3)	0.0568
MLUTS4B Quality of life	0 (0–5)	0.5 (0–8)	0.1204
MLUTS5A Interrupted stream	1 (0–3)	1 (0–4)	0.4426
MLUTS5B Quality of life	0 (0–2)	0 (0–9)	0.1904
MLUTS6A Incomplete emptying	0 (0–1)	1 (0–3)	0.0111
MLUTS6B Quality of life	0 (0–5)	1.5 (0–10)	0.0068
MLUTS7A Urgency	0 (0–2)	1 (0–3)	0.0936
MLUTS7B Quality of life	0 (0–10)	2 (0–10)	0.0926
MLUTS8A Urge incontinence	0 (0–1)	0.5 (0–2)	0.0013
MLUTS8B Quality of life	0 (0–8)	0.5 (0–10)	0.0021
MLUTS9A Stress incontinence	0 (0–0)	0 (0–1)	0.3169
MLUTS9B Quality of life	0 (0–0)	0 (0–3)	0.0681
MLUTS10A Incontinence for no obvious reason	0 (0–1)	0 (0–1)	0.1366
MLUTS10B Quality of life	0 (0–0)	0 (0–10)	0.0326
MLUTS11A Incontinence during sleep	0 (0–1)	0 (0–3)	0.2605
MLUTS11B Quality of life	0 (0–1)	0 (0–9)	0.0577
MLUTS12A Post-micturition incontinence	0 (0–1)	0 (0–10)	0.0177
MLUTS12B Quality of life	0 (0–10)	0 (0–10)	0.0509
MLUTS13A Voiding frequency	0 (0–2)	1 (0–7)	0.0743
MLUTS13B Quality of life	0 (0–5)	0.5 (0–9)	0.0786
MLUTS14A Nocturia	1 (0–2)	1 (0–5)	0.533
MLUTS14B Quality of life	0.5 (0–6)	0 (0–9)	0.943

*M, Median (Min–Max).

Table 4 Results of ICIQ-FLUTS questionnaire in females

Variables	Controls (n = 30) M*	Patients (n = 36) M*	P
FLUTS2A Nocturia	0 (0–2)	1 (0–3)	0.0228
FLUTS2B Quality of life	0 (0–10)	0.5 (0–10)	0.1744
FLUTS3A Urgency	1 (0–2)	2 (0–4)	0.0001
FLUTS3B Quality of life	0 (0–10)	3 (0–10)	0.0093
FLUTS4A Pain in the bladder	0 (0–1)	0 (0–2)	0.0417
FLUTS4B Quality of life	0 (0–3)	0 (0–6)	0.04
FLUTS5A Voiding frequency	1 (0–3)	1 (0–3)	0.1455
FLUTS5B Quality of life	0 (0–6)	2 (0–10)	0.0056
FLUTS6A Micturition start delay	0 (0–3)	0 (0–3)	0.0387
FLUTS6B Quality of life	0 (0–8)	0 (0–9)	0.127
FLUTS7A Straining	0 (0–1)	0 (0–2)	0.0399
FLUTS7B Quality of life	0 (0–3)	0 (0–10)	0.0158
FLUTS8A Interrupted stream	0 (0–2)	1 (0–4)	0.0205
FLUTS8B Quality of life	0 (0–7)	1.5 (0–8)	0.0092
FLUTS9A Urge incontinence	0.5 (0–2)	1 (0–4)	0.0591
FLUTS9B Quality of life	0 (0–10)	3.5 (0–10)	0.007
FLUTS10A Frequency of urine leakage	0 (0–4)	1 (0–4)	0.0638
FLUTS10B Quality of life	0 (0–8)	3.5 (0–10)	0.0163
FLUTS11A Stress incontinence	0 (0–3)	1 (0–4)	0.0743
FLUTS11B Quality of life	0 (0–10)	2 (0–10)	0.1268
FLUTS12A Incontinence for no obvious reason	0 (0–2)	0 (0–2)	0.2383
FLUTS12B Quality of life	0 (0–7)	0 (0–10)	0.1763
FLUTS13A Incontinence during sleep	0 (0–1)	0 (0–2)	0.1407
FLUTS13B Quality of life	0 (0–5)	0 (0–10)	0.141

*M, Median (Min–Max).

exceptional cases respiratory insufficiency (12). Multiple clinical and experimental studies documented interactions between the LUT and lower gastrointestinal activity. Clinically, LUT dysfunctions often coincide with gastrointestinal dysfunctions and *vice versa*. Animal studies described cross-excitatory reflexes between the bladder, colon, and rectum, associated with various pathological conditions (13). ANS dysfunction (papilary anomalies, hearing loss, dysphagia, gastrointestinal, and urinary disturbances) has frequently been described in individual patients suffering from CMT, but studies determining the

Table 5 Results of ICIQ-MLUTS sex questionnaire in males

Variables	Controls (n = 24) M*	Patients (n = 19) M*	P
MLUTSSEX2A Erection	0 (0–2)	0 (0–2)	0.8643
MLUTSSEX2B Quality of life	0 (0–10)	0 (0–10)	0.6617
MLUTSSEX3A Ejaculation	0 (0–3)	0 (0–2)	0.6908
MLUTSSEX3B Quality of life	0 (0–5)	0 (0–10)	0.3425
MLUTSSEX4A Discomfort during ejaculation	0 (0–1)	0 (0–3)	0.2302
MLUTSSEX4B Quality of life	0 (0–3)	0 (0–10)	0.2637
MLUTSSEX5A Sex life is spoilt by urinary symptoms	0 (0–1)	0 (0–2)	0.0865
MLUTSSEX5B Quality of life	0 (0–1)	0 (0–10)	0.0789

*M, Median (Min–Max).

Table 6 Results of ICIQ-FLUTSsex questionnaire in female

Variables	Controls (n = 28) M*	Patients (n = 32) M*	P
FLUTSSEX2A Dry vagina	0 (0–2)	0 (0–2)	0.981
FLUTSSEX2B Quality of life	0 (0–7)	1 (0–10)	0.4928
FLUTSSEX3A Sex life is spoilt by urinary symptoms	0 (0–2)	0 (0–2)	0.6199
FLUTSSEX3B Quality of life	0 (0–10)	0 (0–10)	0.3547
FLUTSSEX4A Pain during intercourse	0 (0–4)	0 (0–4)	0.8608
FLUTSSEX4B Quality of life	0 (0–10)	0 (0–10)	0.5849
FLUTSSEX5A Urine leakage during intercourse	0 (0–1)	0 (0–4)	0.0404
FLUTSSEX5B Quality of life	0 (0–5)	0 (0–10)	0.1498

*M, Median (Min–Max).

true prevalence of symptoms affecting the ANS in these patients are lacking (12).

Since 1998, the International Consultation on Incontinence has been developing and validating universally applicable questionnaires for clinical practice and research of conditions affecting the lower urinary and intestinal tracts. In this study, we used validated ICI-recommended questionnaires to evaluate LUT, bowel, and sexual dysfunctions in patients diagnosed with CMT (14). IPSS is the most frequently used questionnaire for the assessment of LUTS and the LUTS-related quality of life in males (15). This questionnaire has also been previously utilized for the assessment of LUTS in female patients (16). The ICIQ has been developed as a universal tool for specifically assessing LUTS, bowel, and sexual functions (14). Similar to the IPSS, the questions in the individual ICIQ quantify frequency and severity of individual symptoms and their influence on the QoL. The data recorded with the IPSS, ICIQ-MLUTS, ICIQ-FLUTS, ICIQ-B, and ICIQsex questionnaires enabled us to evaluate the entire patient population and compare them to age-matched controls. The analysis was performed for both sexes combined, as well as for each sex separately.

The results show that LUTS are common among CMT patients. Storage, as well as voiding symptoms, was present in both sexes. The most prevalent form of peripheral neuropathy is caused by diabetes. Diabetic cystopathy is a condition that has been well studied and characterized (17). Majority of bladder dysfunction seen in diabetics is associated with frequency and urgency. Peripheral neuropathy could lead to disruption of normal reflex mechanisms which control the LUT function. Among those, sympathetic-to-hypogastric storage reflex responsible for keeping detrusor relaxed during filling could be disrupted in both diabetic and CMT patients due to peripheral neuropathy. Only a subgroup of diabetic patients suffers from detrusor hypo-activity. Our results showing increased prevalence of irritative LUT symptoms are in accordance with the evidence clearly documented in diabetic patients.

We recorded a similar situation in the case of bowel symptoms and showed that CMT patients suffered from these symptoms significantly more frequently than healthy volunteers. Contrary to Bird et al. (18) we did not notice a significantly higher occurrence of erectile dysfunction among male patients in the CMT group. The patient reporting of erectile dysfunction is complicated by the fact that this is a sensitive private subject. In addition, erectile dysfunction is often considered by natural part of aging. We would therefore propose a possibility that negative finding is associated with insufficient sensitivity of the questionnaire, rather than the fact that erectile function was completely unaffected.

This is a preliminary exploratory survey based on questionnaires filled on the voluntary basis by a population of patients with different types of CMT disease.

The limitation of this study such as potential selection bias, heterogeneity of the study group,

low response rate, missing information correlating individual LUT, bowel, and sexual symptoms with genotype need to be acknowledge. As this is the first comprehensive evaluation of correlation between CMT and lower urinary tract symptoms, the study has been designed without stratifying the patients according individual genotypes and fenotypes. Despite of low response rate, we believe that our data are reliable in showing that the prevalence of autonomic dysfunction in CMT patients is higher than that seen in normal population.

Conclusion

This study suggests that prevalence of autonomic dysfunction in CMT patients is higher than that seen in normal population.

Females are affected more frequently and to a greater degree than their male cohort, and these symptoms significantly affect the quality of life of a significant proportion of CMT patients. Therefore, we suggest that these patients should be evaluated for these symptoms and treated using a multidisciplinary approach.

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Conflict of interest

Authors declare no potential conflict of interest.

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