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Review Article

Dysfunctions of the lower urinary tract in patients with multiple sclerosis. Pathogenesis, symptomatics, diagnosis

Igor V. Kuzmin
Academician I.P. Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia

Multiple sclerosis is a chronic autoimmune demyelinating disease, one of the most common symptoms of which are urinary disorders. The review article provides information on the epidemiology, pathogenesis, symptoms, clinical course and diagnostic features of neurogenic dysfunctions of the lower urinary tract in patients with multiple sclerosis. Attention is drawn to the need for early diagnosis of urinary tract dysfunctions, which predetermines the timely initiation and effectiveness of treatment.

Keywords: multiple sclerosis; neurogenic lower urinary tract dysfunction; detrusor overactivity; detrusor-sphincter dyssynergy; overactive bladder; urge incontinence.

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Обзорная статья

Дисфункции нижних мочевых путей у больных рассеянным склерозом. Патогенез, симптоматика, диагностика

И.В. Кузьмин

Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова, Санкт-Петербург, Россия

Рассеянный склероз — хроническое аутоиммунное демиелинизирующее заболевание, одними из наиболее частых симптомов которого являются нарушения мочеиспускания. В обзорной статье приведены сведения об эпидемиологии, патогенезе, симптоматике, клиническом течении и особенностях диагностики нейрогенных дисфункций нижних мочевыводящих путей у больных рассеянным склерозом. Обращено внимание на необходимость ранней диагностики дисфункций мочевых путей, что предопределяет своевременное начало и эффективность лечения.

Ключевые слова: рассеянный склероз; нейрогенная дисфункция нижних мочевыводящих путей; гиперактивность детрузора; детрузорно-сфинктерная диссинергия; гиперактивный мочевой пузырь; ургентное недержание мочи.

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BACKGROUND

Multiple sclerosis (MS) is a chronic immune neurodegenerative disease of the central nervous system and is characterized by the appearance of demyelination foci and diffuse changes in the brain and spinal cord tissues [1, 2]. According to the clinical course, MS has three types, namely, relapsing-remitting, primary progressive, and secondary progressive [1]. Relapsing-remitting MS is the most common form of the disease (up to 85% of patients) and is characterized by periods of acute neurological symptoms alternating with periods of remission. Secondary progressive MS occurs usually 10–20 years after the onset of relapsing-remitting MS. With this disease type, neurological symptoms increase, and periods of remission become rarer and shorter. Primary progressive MS (15% of patients) is manifested by steady progression and increased neurological symptoms [3, 4].

The prevalence of MS ranges from 18.6 to 265 per 100,000 people [5, 6]. The incidence of MS is approximately three times higher in women than in men. In the Russian Federation, 200,000–250,000 patients have MS, with the largest number of MS cases registered in the northern, northwestern, and western regions [7]. MS is usually diagnosed in young people aged 20–40 years. Thus, according to A.V. Zyryanov et al. [8], the average age of MS onset is 25.1 ± 3.54 years. Moreover, 15–20 years after the first clinical manifestations of MS, up to 50% of patients become disabled [7]. MS is considered the main cause of non-traumatic disability in young people, which determines the sociomedical significance of the disease [9].

NEUROGENIC DYSFUNCTIONS OF THE LOWER URINARY TRACT IN PATIENTS WITH MULTIPLE SCLEROSIS

Epidemiology

Neurogenic lower urinary tract dysfunctions (NLUTD) are disorders associated with urine accumulation and bladder voiding, which is a result of neurological diseases [10]. NLUTDs are among the most common clinical manifestations of MS. The prevalence of urination disorders in patients with MS is high and ranges from 50% to 90% [11–15]. The incidence of urination disorders is more than three times higher in patients with MS than in the general adult population [16]. Zyryanov et al. [8] indicated that NLUTD is registered in 65% of patients with MS. Al Dandan et al. detected nearly the same prevalence of NLUTD (68%) in patients with MS [17] based on the results of a meta-analysis of 12 studies involving 2507 patients [17].

The probability of NLUTD development depends on the time elapsed since the establishment of MS diagnosis. According to Nazarie et al. [18], 6 years after the first manifestations of MS, NLUTD is detected in 40% of patients, whereas after 10 years, it occurs in more than half of patients. In addition to the increasing incidence, the severity of neurogenic urinary disorders also intensifies [18]. The significance of NLUTD in patients with MS is due not only to their high prevalence but also to a significant deterioration in the quality of life of patients, risk of severe complications, and a significant economic burden on the healthcare system [16, 19, 20].

Pathogenesis

In patients with MS, NLUTD is mainly caused by damage to the spinal cord, which is the most common localization of the demyelinating process [13–15]. Table 1 presents the main dysfunctions of the lower urinary tract, clinical manifestations, and levels of associated damage to the central nervous system. Most often, pathological changes are revealed in the cervical spinal cord, less often in the thoracic and lumbar spine, and even rarer in the sacral region [21]. Impaired conduction along the spinal pathways causes a decrease in the inhibitory effect from the overlying nerve centers on the sacral center of urination, which leads to detrusor hyperactivity. In these cases, urodynamic examination reveals involuntary detrusor contractions, and the clinical signs of this urodynamic phenomenon are storage symptoms, namely, frequent urination, urge to urinate, and urinary incontinence (UI). Owing to the deterioration of conductivity in the spinal cord, the interaction between the neurons of the pontine micturition center, which are responsible for coordinating and synchronizing the function of the detrusor and external urethral sphincter, and the neurons of the sacral micturition center, is also disrupted, resulting in detrusor-sphincter dyssynergia (DSD). The clinical manifestations of DSD are voiding symptoms, including difficulty initiating urination, difficulty urinating, and decreased micturition pressure. Detrusor overactivity and DSD are the most frequent findings in urodynamic studies in patients with MS, and they are often concomitant in one patient [22, 23]. Other disorders, such as detrusor hypoactivity and acontractility, are less common in patients with MS, and their development is associated with spinal cord lesions at the level of the sacral micturition center (S2–S4) and lower [11]. These dysfunctions are clinically represented by disorders of the evacuation function of the bladder of varying severity.

Symptoms

Owing to the multifocal and diffuse nature of the lesions in the central nervous system, patients with MS have diverse clinical manifestations of varying severity [4, 24]. The most common are storage symptoms, which are a manifestation of an overactive bladder caused by

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Table 1. Characteristics of neurogenic dysfunctions of the lower urinary tract depending on the level of damage to the central nervous system

Таблица 1. Характеристика нейрогенных дисфункций нижних мочевыводящих путей в зависимости от уровня поражения центральной нервной системы

Type of dysfunction	Clinical manifestations	Level of lesion
Detrusor overactivity without detrusor-sphincter dyssynergia	Symptoms of storage	Above the pons level
Detrusor overactivity with detrusor-sphincter dyssynergia	Storage and voiding symptoms	Between the sacral micturition center and the pons
Detrusor-sphincter dyssynergia	Voiding symptoms	Between the sacral micturition center and the pons
Detrusor underactivity	Voiding symptoms	Sacral micturition center (segments S2–S4 of the spinal cord) and below

Table 2. Clinical manifestations of neurogenic dysfunctions of the lower urinary tract in patients with multiple sclerosis

Таблица 2. Клинические проявления нейрогенных дисфункций нижних мочевыводящих путей у больных рассеянным склерозом

Study	Number of patients	Urgency, %	Increased urination, %	Urge urinary incontinence, %	Urinary difficulty, %
H. Miller et al. [25]	321	60	50	36	33
W.E. Bradley et al. [26]	90	86	60	–	28
A. Hennessey et al. [27]	191	71	76	19	48
D. Borello-France et al. [28]	133	61	71	83	–
M. Ukkonen et al. [29]	24	83	54	75	58
G. Quarto et al. [30]	61	83	32	32	–
A.V. Ziryanov et al. [8]	160	98	98	84	63

detrusor overactivity (Table 2). Thus, the urgency to urinate is registered in 60%–98% of patients, increased urination in 50%–98%, and urge UI in 19%–84% [8, 25–30]. Results of a meta-analysis of 12 studies by Al Dandan et al. [17] confirm that storage symptoms remain the predominant clinical manifestations of NLUTD in MS. Increased urination was recorded in 73% of patients, urgency in 64%, and urge UI in 43%.

Less common voiding symptoms include difficulty urinating, difficulty initiating it, weakening the urine flow, and stuttering urination, due to DSD or detrusor underactivity. Thus, difficulty urinating was detected in 28%–63% of patients with MS and NLUTD [8, 25–27, 29] (Table 2). According to Al Dandan et al. [17], voiding symptoms were reported by 61% of patients with MS and urination disorders. Zyryanov et al. [8] indicated the presence of voiding symptoms in more than half of patients with MS and NLUTD, and even 76% of patients noted the need to strain during urination [8].

The subjective assessment of urination in patients with MS does not always coincide with the results of an objective examination. Significant dysfunction of the lower urinary tract is found in certain asymptomatic patients. Most patients with MS are diagnosed with NLUTD only at their first visit to an urologist, although they may have had these disorders for many years [31]. Thus, when collecting complaints from patients with MS, an active survey regarding the presence of storage and voiding symptoms in them is necessary; however, even in the absence of corresponding complaints, an instrumental examination must be performed. This was confirmed by Betts et al. [23] who demonstrated that 63% of 170 patients with MS had a residual urine volume (RUV) exceeding 100 mL; however, less than half of them complained of incomplete voiding of the bladder. Moreover, 83% of patients who believed that they completely voided the bladder had impaired evacuation function. The authors concluded that since RUV is one of the main indicators that determine the treatment approach to patients with NLUTD, relying only on patient complaints in these cases is inappropriate. These conclusions confirmed the data by Jaekel et al. [32], who revealed urodynamic study abnormalities in 73.7% of patients with MS without any urological complaints, where 21.1% of patients had detrusor overactivity, 13.2% of patients had detrusor underactivity, and 13.2% of patients had a combination of detrusor overactivity and DSD.

Clinical course

NLUTD is rarely present on MS onset, only in approximately 3%–10% of patients [1, 33–35]. However, after 10 years from disease onset, NLUTD is already established in approximately 80% of patients [36]. de Sèze et al. indicated a correlation between the frequency of detection of DSD-associated voiding symptoms and MS duration [12]. Accordingly, DSD is detected in 13% of patients with MS duration of 48 months and in already 50% with a duration of 109 months. NLUTDs in patients with MS usually develop 5–8 years (on average, approximately 6 years) after the onset of neurological symptoms; as most often, first storage symptoms occur, and then voiding symptoms become concomitant to them [35]. Interestingly, the correlation of the severity of storage symptoms with the score on the Expanded Disability Status Scale (EDSS) is higher than that of voiding symptoms [35].

The clinical manifestations of NLUTD in MS and other disease symptoms vary [24]. In the early disease stages, the patient may experience only imperative urges and increased urination, while later, urge UI may also occur and subsequently voiding symptoms up to the impossibility of unassisted urination. According to Krupin and Belova [24], such variability in the clinical presentation of NLUTD in patients with MS is due to the presence of a close pathogenetic relationship between urological disorders and the demyelinating process that damages the white matter of the brain and spinal cord. Demyelination processes can slow down or accelerate; therefore, clinical manifestations are characterized by significant fluctuations. However, over time, the symptoms stabilize relatively, more often with a tendency to progress [24].

According to the German register of patients with MS, >56% of patients with impaired lower urinary tract function do not receive any treatment because of insufficient NLUTD detection [37]. If left untreated, NLUTD can induce complications, such as vesicoureteral reflux, recurrent urinary tract infection, lithogenesis, and further worsen the quality of life of patients [12, 38]. Moreover, most authors indicate that upper urinary tract lesions with the development of hydronephrotic transformation and renal failure are non-typical for MS-related NLUTD and are registered much less frequently than in patients with traumatic spinal cord injuries and *spina bifida* [11, 12, 39, 40]. This phenomenon may be due to a decrease in the detrusor contractile activity in patients with MS, which determines the absence of a significant increase in intravesical pressure [11, 39]. However, this does not exclude the possibility of developing upper urinary tract complications in patients with MS. Patients with indwelling catheters and a combination of detrusor overactivity and DSD, in which intravesical pressure can reach high values, are considered at high risk of kidney damage in MS. Other risk factors are chronic MS, increased RUV, advanced age, and male sex [35]. Upper urinary tract complications usually occur no earlier than 6–8 years after NLUTD onset. The risk of kidney damage with the development of renal failure with MS duration of >10 years is 2%–3% [35].

Diagnostics

Diagnostics of NLUTD in patients with MS is based on anamnesis and complaints of the patients and the results of laboratory and instrumental research methods [24].

Urination diaries are an important tool for an objective assessment of NLUTD severity in patients with MS. Patients are advised to fill them out within 3 days, recording each urination, urgency, UI episode, and amount of urine excreted during urination.

To assess the presence and severity of urinary disorders and quality of life, special questionnaires that enable to objectify and formalize the procedure for collecting information are recommended [41]. The most common questionnaires for use in patients with MS and NLUTD include the Neurogenic Bladder Symptom Score (NBSS), Multiple Sclerosis Quality of Life 54-item scale, Qualiveen, Incontinence Quality of Life, Multiple Sclerosis Impact Scale 29-item, Functional Assessment of Multiple Sclerosis, Hamburg Quality of Life Questionnaire in MS, Multiple Sclerosis Quality of Life Index, Actionable Bladder Symptom Screening Tool, and Bladder Control Self-Assessment Questionnaire. Of these, the Russian versions of the Qualiveen [42] and NBSS [43] questionnaires have been validated. The validated Russian version of the Questionnaire on Pelvic Organ Function [44] is also noteworthy. Adapted and validated Russian versions of these questionnaires can be recommended for widespread use in clinical practice and scientific research.

Laboratory studies include general urinalysis and, according to indications, microbiological examination of urine, and assessment of the functional state of the kidneys (creatinine and serum urea, if necessary, assessment of the glomerular filtration rate). As a laboratory marker of NLUTD, determining the blood level of nerve growth factor is recommended [45].

Instrumental examination methods included ultrasonography and urodynamic examination. Ultrasonography is used to assess the condition of the kidneys and bladder, and RUV is also determined. Urodynamic studies include uroflowmetry, filling cystometry, pressure-flow studies, and electromyography of the pelvic floor and external urethral sphincter. Uroflowmetry, a non-invasive research method, is used to evaluate the evacuation function of the bladder. Owing to its availability, uroflowmetry is recommended as a screening diagnostic method. A specific type of dysfunction of the lower urinary tract (hyper- and hypoactivity of the detrusor, DSD) is determined only through cystometry and electromyography. The frequency of the detection of certain disorders

of urodynamics in patients with MS is high and reaches 78% [46], 86% [47], and 86.5% [48]. However, the results of a meta-analysis performed by Al Dandan et al. [17] showed a slightly lower incidence of urodynamic disorders in patients with MS (64%), whereas detrusor hyperactivity (42.9%) and DDM (35.4% of patients) are most often detected [17]. According to Averbeck et al. [15], for patients with MS, a combination of detrusor hyperactivity in the filling phase and impaired contractile activity in the voiding phase with/without DSD is a characteristic urodynamic finding. In patients with MS and neurogenic detrusor overactivity, the amplitude of involuntary contractions is significantly higher than in patients with idiopathic detrusor overactivity [49]. Even in the absence of urination disorders in patients with MS, a significant number of them have urodynamic abnormalities. Domurath et al. [47] revealed urodynamic disorders of the lower urinary tract in 52.2% of patients with "asymptomatic" MS [47].

When planning a urological examination in patients with MS, the high variability of NLUTD must be considered [24]. Any studies during MS exacerbation are not recommended, and the clinical course must be stabilized [38].

Many studies have focused on the diagnostics of NLUTD in patients with MS; many national and supranational professional communities have issued clinical guidelines for the examination of this category of patients. However, many aspects of diagnosing NLUTD need to be discussed, and the recommended algorithms for examining patients with MS are largely contradictory. Table 3 compares clinical guidelines for the examination of patients with MS, compiled by experts from different countries, namely, Germany [50], Spain [38], Great Britain [51], France [52], Italy [53], Belgium [13], Turkey [54], and Canada [55].

As shown in Table 3, the recommendations for the examination of patients with MS and the diagnostics of NLUTD, compiled by different expert groups, largely do not coincide. When reviewing the clinical guidelines, some controversial issues must receive attention. (1) Which patients with MS need a urological examination? (2) What are the risk factors for upper urinary tract lesions in patients with MS and NLUTD? (3) What screening results indicate the presence of NLUTD in patients in MS? (4) Which patients with MS should undergo urodynamic testing?

Which patients with MS need a urological examination?

Most researchers agree that examination by a urologist must be performed as early as possible in all patients with MS, even in the absence of specific urological complaints [32, 38, 47]. Moreover, certain clinical guidelines indicate the need for urological examination of patients with MS only in the presence of urological symptoms [50, 51], and Kavanagh et al. [55] recommend it only for patients at risk of upper urinary tract diseases.

What are the risk factors for upper urinary tract lesions in patients with MS-related NLUTD?

No consensus has been established regarding risk factors for upper urinary tract lesions in patients with MS. Medina-Polo et al. [38] reported UI with RUV of ⩾150 mL with or without asymptomatic bacteriuria, recurrent urinary tract infection, and EDSS score >3 as such risk factors. de Sèze et al. [12] consider age >50 years, male sex, duration of MS of >15 years, severe MS, and EDSS >3 as risk factors. According to De Ridder et al. [13], risk factors for upper urinary tract lesions are age ⩾50 years, male sex, EDSS score >6, MS duration of >15 years, RUV >100 mL, incidence of urinary tract infections >3 times per year, and presence of storage or voiding symptoms.

What screening results indicate the presence of NLUTD in patients with MS?

Beck et al. [56] studied the clinical parameters in patients with MS that could confirm the presence of NLUTD. Moreover, 207 patients with MS and NLUTD were followed up. A significant correlation was found between RUV and the incidence of urinary tract infections, frequency of urination, and urodynamic data indicating the presence of NLUTD. The authors concluded that increased frequency of urination and RUV and presence of urinary tract infections can be considered NLUTD predictors, and these patients require a urodynamic study. Jaekel et al. [32] suggest using only urination diaries and urinary tract infection as NLUTD predictors. According to Domurath et al. [47], NLUTD predictors include increased urination (>13 per day), UI, urinary tract infections in the previous 6 months (>0), and RUV (⩾70 mL). Parameters such as age, sex, duration of MS, and EDSS score are not NLUTD predictors.

Which patients with MS should undergo urodynamic testing?

The need for a comprehensive urodynamic study in all patients with MS and NLUTD is debatable. Tadayyon et al. [36] recommended performing urodynamic studies in all patients with MS during the initial diagnostics, and their view is supported by the finding that in more than half of these patients, even in the absence of urological complaints, urodynamic disorders are detected. Medina-Polo et al. [38] believed that urodynamic studies should be performed in all patients with MS, except for those without complaints of urination disorders, with normal uroflowmetry and normal RUV [38]. However, most experts emphasize the need to perform a urodynamic study only in the case of NLUTD predictors [32, 47, 55].

Table 3. Comparison of national clinical guidelines for the examination of patients with MS and neurogenic dysfunctions of the lower urinary tract ([47], with modifications)

Таблица 3. Сравнение национальных клинических рекомендаций по обследованию больных рассеянным склерозом и нейрогенными дисфункциями нижних мочевыводящих путей ([47], с изменениями)

Question	[50]	[38]	[51]	[52]	[53]	[13]	[54]	[55]
Which patients with MS should be examined?								
Asymptomatic	–	×	–	×	×	×	×	–
Presence of symptoms	×	×	×	×	×	×	×	–
Upper urinary tract risk group	–	–	–	–	–	–	–	×
Screening studies								
Urination diary	×	×	–	×	×	×	×	×
Residual urine volume	×	×	×	×	×	×	×	×
Clinical urine test	×	×	×	×	×	×	×	×
Urine culture	O	×	–	×	×	–	×	–
Quality of life questionnaire	–	×	–	×	×	×	–	O
Ultrasound of the bladder and kidneys	–	–	–	×	×	×	×	×
Uroflowmetry	O	×	–	–	–	–	×	–
Complex urodynamic study	O	×	–	×	×	×	–	×
Risk factors for upper urinary tract lesions								
Age, years	–	–	–	⩾55	⩾55	⩾50	×	×
Sex	–	–	–	B	B	B	–	–
EDSS, score	–	>3	>6	⩾6	⩾3	>6	–	–
Multiple sclerosis duration, years	–	–	–	–	>10	>15	–	–
Residual urine volume, mL	–	⩾150	>100	⩾100	⩾100 or 1/3 bladder capacity	>100	–	–
Incidence of urinary tract infection, per year	–	⩾3	–	⩾3	⩾3	⩾3	–	⩾3
Urinary incontinence	×	×	×	–	×	×	–	–
Frequent urination	×	×	×	–	×	×	–	–
Urgency	×	×	×	–	×	×	–	–
Urinary difficulty	×	×	–	–	×	×	–	–

Note. O, optional; ×, presence of a parameter; a dash indicates the parameter absence; B, bladder.

When examining patients with MS, urinary disorders may not be associated with NLUTD, but with comorbidities. Bladder evacuation may be impaired in men with BPH or other non-neurogenic causes of infravesical obstruction, and in women, urinary obstruction may be caused by pelvic organ prolapse. When conducting a urological examination of patients with MS and urination disorders, a differential diagnostics between NLUTD and other possible causes of these disorders is necessary.

CONCLUSION

The correct interpretation of the patient's complaints and timely and complete urological examination are crucial for diagnosing NLUTD in patients with MS, which guarantee the successful treatment of patients and improvement of their quality of life.

ADDITIONAL INFORMATION

Author contribution. The author made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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AUTHOR'S INFO

Igor V. Kuzmin, MD, Dr. Sci. (Med.),
professor of the Department of Urology; address: 6–8, L'va Tolstogo st., Saint Petersburg, 197022, Russia;
ORCID: https://orcid.org/0000-0002-7724-7832;
Scopus: 56878681300; eLibrary SPIN: 2684-4070;
e-mail: kuzminigor@mail.ru

ОБ АВТОРЕ

Игорь Валентинович Кузьмин, д-р мед. наук,
профессор кафедры урологии; адрес: Россия, 197022, Санкт-Петербург, ул. Льва Толстого, д. 6–8;
ORCID: https://orcid.org/0000-0002-7724-7832;
Scopus: 56878681300; eLibrary SPIN: 2684-4070;
e-mail: kuzminigor@mail.ru