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Managing Urological Disorders in Multiple Sclerosis Patients: A Review of Available and Emerging Therapies

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Multiple sclerosis (MS) is a progressive neurological autoimmune disease with a diverse range of urological symptomatology, and most MS patients experience 1 or more moderate to severe urinary symptoms, as well as bladder and/or sexual disorders. Urologists play the director's role in evaluating and treating these patients. Therefore, identifying the proper evaluation tools and the most suitable therapeutic options for specific patients requires a thorough understanding of this disease process.

Keywords: Multiple sclerosis; Lower urinary tract symptoms; Urinary incontinence; Neurogenic detrusor overactivity

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INTRODUCTION

Multiple sclerosis (MS), which is the most frequently occurring progressive neurological autoimmune disease in young people, can affect any part of the central nervous system (CNS). The lifetime prevalence of MS is roughly 250 per 100,000 people [1]. MS is commonly diagnosed in younger adults (20–40 years) and affects females 3–4 times more often than males. Lower urinary tract dysfunction (LUTD) has been reported to occur in the first 18 years after disease onset in up to 90% of MS patients [2,3]. In the 2005 North American Research Committee on Multiple Sclerosis survey of almost 10,000 patients with MS, 65% of participants reported experiencing 1 or more moderate to severe urinary symptoms, as well as bladder and sexual disorders [4]. In MS patients, lower urinary tract symptoms (LUTS) occur on a spectrum of severity, ranging from urgency to urge urinary incontinence, potentially accompanied by incomplete bladder emptying and/or hesitancy. The severity of LUTS and their presentation may vary considerably among MS patients as a result of the multifocal and diffuse involvement of the CNS. Roughly 70% of MS patients indicated that they experienced a moderate or severe impact on their quality of life as a result of LUTS [5]. Furthermore, LUTS also pose an elevated risk for upper urinary tract integrity [6]. In diagnostic evaluations of patients with MS, the most frequently observed urological findings are urgency, frequency, and neurogenic detrusor overactivity (NDO) (34%–99%) [7].

OBJECTIVES

This study was conducted to review and summarize data on urological disorders and treatment options in patients with MS.

METHODS

A literature review (PubMed, Web of Science, and Scopus) was conducted for articles on urological dysfunction in MS patients.

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UROLOGICAL DISORDERS IN MULTIPLE SCLEROSIS

Bladder dysfunction is the most frequently encountered disturbance of the autonomic nervous system in MS, but it is often inadequately diagnosed and insufficiently treated. According to a systematic review of recent articles presenting the findings of urodynamic studies in MS patients (12 studies, 1,524 patients), 53% of MS patients had detrusor overactivity (DO), 43% had detrusor sphincter dyssynergia (DSD), and 12% had atonic bladder. Magnetic resonance imaging (MRI) studies of MS patients have suggested an association between MS lesions in the corticospinal tract with progressive lower urinary tract bother, hesitancy, and urgency or frequency [8]. Cervical lesions are often linked to the presence of DSD [9]. Furthermore, urinary incontinence and weak stream have shown associations with lesions in the cerebellum and pons [10]. Over the course of disease progression, it is necessary to reassess MS patients in order to adjust their therapies. In many patients, conservative and pharmacological therapies show diminishing effectiveness, which may be due to the cumulative impact of physiological, cognitive, and physical changes over the course of MS [10, 11]. For this reason, it is important to regularly change treatment regimens of MS patients for urological safety and to promote their quality of life. If conservative and pharmacological treatments become ineffective, it is important for both physicians and patients to understand the benefits, risks, and outcomes of secondary and tertiary treatments for LUTS related to MS.

Sexual dysfunctions (SDs) are also widespread among MS patients; although their prevalence is frequently underestimated, they may have a remarkably strong effect on patients' quality of life. SDs have been reported to be present in 50%–90% of MS patients [12,13].

OVERACTIVE BLADDER AND URGENCY URINARY INCONTINENCE

The most frequently reported symptoms in MS patients involve the storage phase, and DO is the most common urodynamic finding. Anticholinergics are the first-line treatment for storage symptoms; acting on the detrusor muscle, anticholinergics can relieve muscle spasms, reduce bladder pressure, and relieve LUTS during urine storage. In patients with slight disability and overactive bladder (OAB) symptoms, pelvic floor muscle training (PFMT) may be beneficial [5]. For PFMT to be effective, the neural pathways leading to the pelvic floor must be intact, and patients must be able to contract the pelvic floor muscles. PFMT is thought to strengthen the inhibition exerted on the detrusor by pelvic floor contraction [11]. Several authors have demonstrated beneficial impacts of PFMT on the course of the disease [14]. As mentioned above, antimuscarinic agents (level of evidence: 1A) constitute the first line of treatment for neurogenic LUTS [15]. However, most findings on the efficacy and adverse effects of antimuscarinics have been obtained from patients with idiopathic DO. Only a few studies have investigated NDO, and only poor-quality data exist on patients with MS. A recent study evaluated the efficacy of 10 mg/day of solifenacin compared with 50 mg/day of mirabegron for treating DO in patients with MS. In total, 60 patients diagnosed with MS and NDO were evaluated. Patients were divided in 4 groups. In group A (n=15) patients continued to receive solifenacin (10 mg/day); in group B (n=15) patients received mirabegron (50 mg/day); in group C (n=15) patients received desmopressin (120 μg/day), and in group D (n=15) patients received mirabegron (50 mg/day) and desmopressin (120 μg/day). All patients were assessed using a 3-day bladder diary at the beginning and end of treatment. The results showed that all patients in groups A, B, and C did not demonstrate statistically significant changes at the end of the treatment period in their 3-day bladder diary and in the presence of urinary tract infections. In group D, a statistically significant improvement was noted in the mean change from baseline to end of treatment in micturition episodes, urgency episodes, and the mean number of episodes of urinary incontinence (1.0±0.2 episodes per 24 hours). The study demonstrated that treatment with mirabegron and desmopressin was both effective and safe in patients with NDO and MS [16].

Mirabegron alone (50 mg) has been also demonstrated to improve both patient-reported outcomes and urodynamic variables in NDO, without relevant side effects [17]. A recent meta-analysis [18] showed the promise of cannabinoids as a safe and effective treatment modality for neurogenic LUTD in MS patients, as cannabinoids led to a meaningful reduction in the number of incontinence episodes in all 3 studies that were included in the meta-analysis. In addition, a recent observational study used clinical tools and instrumental analyses to evaluate the effects of a tetrahydrocannabinol-cannabidiol (THC/CBD) oromucosal spray on resistant OAB in MS patients [19]. The THC/CBD spray was successful in reducing OAB symptoms (P=0.001), suggesting that it might be effective for improving

OAB symptoms in patients with MS, with beneficial effects on DO. However, the evidence base remains highly inadequate, and more high-quality, well-designed studies with suitable sample sizes and adequate power must be conducted to reach definitive conclusions.

As second- and third-line therapeutic strategies, catheterization, botulinum toxin (BTX) injections, and reconstructive surgery may also contribute to improvements in quality of life and safety for patients with MS. As more data on efficacy and safety are gathered, new emerging device-assisted modalities (e.g., neuromodulation) may play an increasingly salient role. Neuromodulation is a secondary or tertiary therapeutic strategy that can be used to treat refractory urinary incontinence and urinary retention. Although neuromodulation is best studied in individuals without neurological disorders, researchers are increasingly interested in the outcomes that might be achieved by using neuromodulation in MS patients to treat urinary symptoms. Peripheral tibial nerve stimulation (PTNS) is a minimally invasive technique that consists of electrically stimulating the posterior tibial nerve — a mixed sensory-motor nerve — through a small-gauge needle inserted close to the medial malleolus. Stimulation of this nerve potentiates the afferent branches of somatic nerves that pass through the L4–S3 spinal roots. Theoretically, stimulation of this pathway inhibits the central reflex pathways that cause uninhibited detrusor contractions. Some prospective studies have investigated PTNS in MS patients with LUTS refractory to medical therapy [20], with outcomes including a decreased frequency of daytime voiding (from 9 to 6 voids) and nocturia (from 3 to 1 void). Another study of 21 MS patients showed that extending maintenance PTNS treatments led to a reduction in daily voiding by 5.4 voids; furthermore, urinary incontinence decreased by 3.4 episodes daily, urgency episodes were reduced by 7.4 daily, nocturia decreased by 2.6 voids per night, and voided volume improved by 72.1 mL on average [21]. In a recent retrospective case series on the use of PTNS to treat neurogenic and idiopathic OAB [22], significant improvements were found after 12 weeks for quality of life ($P=0.004$), OAB symptoms ($P=0.01$), incontinence severity according to a bladder diary ($P=0.007$), the number of episodes of incontinence according to a bladder diary, and 24-hour frequency according to a bladder diary ($P=0.002$). That study indicated that PTNS could be a promising potential alternative for patients with neurological disorders, especially MS, who report OAB symptoms, and in whom first-line treatments are either ineffective or cannot be tolerated. Nonetheless, there is still a need for suitably designed studies to investigate the efficacy and safety of PTNS. Sacral nerve stimulation (SNS; InterStim, Medtronic, Fridley, MN, USA) is indicated for refractory OAB, nonobstructive urinary retention, and fecal incontinence. Similarly to PTNS, quite limited data are available on the outcomes of SNS in patients with progressive neurological diseases, such as MS. However, significant improvements have been shown to result from SNS in well-selected MS patients in studies with a limited sample size [23]. Concerns about the frequent need for whole-body MRI scans in MS patients have contributed to the limited adoption of neuromodulation devices as a treatment for MS. For this reason, and given the unknown long-term efficacy of neuromodulation, limiting SNS to MS patients with a clinically isolated syndrome or stable relapsing and remitting disease may be prudent.

DETRUSOR SPHINCTER DYSSYNERGIA

Voiding dysfunction (VD) is a common consequence of MS that may be debilitating. More severe MS is associated with a higher prevalence and severity of VD, but voiding LUTS can occur even in patients with the mildest forms of the disease, as shown by the fact that voiding LUTS have been reported in 30% of MS patients [2,3]. MS can cause a broad range of urinary symptoms and urological complications because the voiding phase is regulated by each component of the CNS. The effects of MS on voiding can be categorized based on the function of the bladder and the urethral sphincter during urine storage and emptying. Urodynamic parameters are currently the most effective method for identifying the type of VD in patients with MS (DSD or acontractile bladder). DSD is defined as the loss of coordination between the detrusor and external sphincter in patients with neurological pathology. According to a systematic review of recent articles presenting the findings of urodynamic studies in MS patients (12 studies, 1,524 patients), 53% of MS patients had DO, 43% had DSD, and 12% had atonic bladder [2]. Despite the lack of a standard definition of MS-related urinary retention, it has been proposed that a postvoiding residual volume greater than 300 mL should be used as a threshold based on a review of the literature. Patients with DSD have an elevated risk for upper tract impairment, autonomic dysreflexia, and recurrent urinary tract infections unless they receive appropriate follow-up and treatment. The basis of treatment should be risk stratification for morbidity from retention and the symptoms caused by retention. Regarding risk stratification,

in 1981 Blaivas et al. [24] proposed a classification of DSD into 3 types, where type 1 is characterized by a crescendo increase in electromyographic (EMG) activity, type 2 by clonic sphincter contractions throughout the detrusor contraction, and type 3 by a sustained increase in activity. Approximately 20 years later, Weld et al. [25] classified DSD as continuous or intermittent on the basis of EMG patterns. Despite being conceptually intriguing, these systems are not generally used in everyday clinical practice because they have failed to demonstrate ongoing prognostic value in clinical settings. For this reason, in routine clinical practice, risk stratification is based on the intensity and frequency of LUTS due to MS. Before initiating any therapy, clinicians should first identify the goals of treatment. In general, a first step is to determine whether the primary treatment goal is to improve quality of life, safety, or both. Once this is established, target outcomes should reflect the goals of treatment, and patients should receive frequent follow-up clinical evaluations to assess whether the treatment is effective. Repeated urodynamic studies should be performed to determine the stability of postintervention improvements in DSD. The guidelines of the European Association of Urology (EAU) [26] suggest that the primary aims when treating neurogenic disorders are to protect the upper urinary tract, to improve urinary continence, to restore (at least partially) lower urinary tract function, and to improve the patient's quality of life. Further considerations include potential complications, the technical complexity of the intervention, its cost-effectiveness, and the patient's disability status [27].

Alpha-blockers are considered to be the first-line pharmacological treatment for DSD (level of evidence: 1B), with the aim of reducing bladder outlet resistance. The efficacy of tamsulosin was evaluated by Abrams et al. [28] in 263 patients with neurogenic LUTD secondary to supra-sacral spinal cord lesions. A 4-week trial (with a placebo control group) yielded no statistically significant reduction in maximal urethral pressure, the primary endpoint of the study. Nonetheless, an increase in mean voided volume (assessed through a bladder diary) and improvements in quality of life (evaluated using the International Prostate Symptom Score [IPSS]) and the severity of symptoms of autonomic dysreflexia were reported in a 1-year, open-label extension study. Data on the use of alpha-blockers in MS patients remain poor, particularly in women. Nonetheless, several European consensus statements recommend this class of drugs for voiding symptoms, especially in men in whom benign prostatic obstruction is expected to contribute to the symptoms [28-31]. The efficacy of alpha-blockers in treating DSD was also tested by Chancellor et al. [32]; in that study, 5 mg of terazosin was given to 15 normotensive DSD patients with spinal cord injuries, and urodynamic findings showed no reduction in voiding pressure. Contrastingly, Stankovich et al. [33] used 0.4 mg of tamsulosin in MS patients with DSD, and reported significant improvements in postvoid residual measurements and the mean volume of voided urine. Since data supporting efficacy are still lacking, alpha-blockers are still not a recommended therapy for symptomatic DSD.

Similarly, baclofen has also been tested with the objective of reducing DSD severity in patients suffering from neurogenic bladder. Despite the value of oral baclofen in treating skeletal muscle spasticity, its permeability across the blood-brain barrier is low, which limits its potential usefulness for the treatment of DSD. Nonetheless, intrathecal baclofen delivery may directly inhibit interneurons in Onuf's nucleus, thereby inhibiting the external sphincter [34]. Several small trials and case reports have provided support for the efficacy of baclofen in mitigating DSD [35,36], but no randomized trials have been reported and its long-term benefits remain poorly understood.

Intrasphincteric injections of BTX are an option for treating DSD, with the dosage depending on the specific preparation. BTX-A can be injected transurethrally, directly into the external sphincter, or through a transperineal approach under ultrasound guidance. Injections are usually made into the sphincter at 2–3 points between the 9-o'clock and 3-o'clock positions. Despite a lack of standardization of the injection technique into the external sphincter, most studies have suggested a total BTX-A dose of 100 U. If the procedure is performed via cystoscopy, the injection must be at least 1 cm deep in the submucosa in order to treat the sphincter muscle and to avoid injecting BTX-A into the submucosal space. After treatment, DSD resolves for only a few months, making repeated injections necessary. This treatment has high efficacy and few adverse effects [37,38], for which reason it received a grade A recommendation in the EAU guidelines.

Intermittent catheterization (IC) is a primary treatment for managing DSD-related symptoms. In order to preserve upper urinary tract integrity, when treating progressive hydronephrosis due to low bladder compliance or chronic urinary tract infections, it is necessary for the patient to empty the bladder only by catheterization, and to avoid making attempts to void until the situation stabilizes. The schedule of IC should be daily, with a sufficient frequency to reduce the standing volume. Patients

should be instructed to pass the catheter to the level of the sphincter, and then to wait for spasms to reduce before continuing to pass the catheter. During follow-up, the effectiveness of the treatment in resolving hydronephrosis should be evaluated by renal ultrasound exams, which also help to avoid complications. In cases where DSD has caused urinary retention, and thus LUTS, it is possible to perform IC postvoiding to completely empty the bladder. In patients suffering from overflow incontinence, especially at night, this strategy is a very good option for preserving quality of life. Screening urine cultures in asymptomatic patients performing IC is not recommended because of the risk of overtreating bacterial colonization. Finally, in patients in poor physical condition who cannot perform IC, indwelling catheters can be considered [39].

SEXUAL DYSFUNCTIONS

SDs occur frequently in patients with MS, but they are frequently underestimated, even though they may have a remarkably strong impact on quality of life. SDs have been reported to be present in 50%–90% of MS patients, depending on patients' clinical characteristics and the length of follow-up [12,13]. In MS patients, SDs comprise diverse conditions, associated with anatomical, physiological, biological, medical, and psychological factors [40]. They are more common in MS patients than in those with other neurological diseases, and are almost 5 times more frequently encountered in MS patients than in the general population [41]. Erectile dysfunction (ED) is the most common sexuality-related complaint in men with MS. A recent observational, cross-sectional study of a cohort of male MS patients [42] evaluated the prevalence of ED and its relationships with urodynamic findings, LUTS, depression, and neurological disabilities, and showed a high prevalence of ED (74.2%). A significant relationship between depression and SDs was also found (57.4%); in MS patients, depression was the most common psychiatric disorder and had a higher prevalence than other chronic diseases [43]. In a recent prospective, single-blind study, men with MS were administered 5 mg of tadalafil daily using a no-treatment group as a control. The results showed improved International Index of Erectile Function ($P<0.001$), IPSS ($P<0.001$), and OAB questionnaire ($P<0.001$) scores in the treatment group. Furthermore, an increase in maximal flow rate ($P<0.01$) and the testosterone-to-estradiol ratio [44] ($P<0.01$) were found, accompanied by reduced postvoid residual volume ($P<0.001$) and no changes in the H-reflex [44]. In a cross-sectional study, 41 men affected by MS were evaluated. Orgasmic dysfunction was graded as severe in 14 patients (35.9%) and as moderate in 5 (12.8%), while only 8 patients (20.5%) reported normal orgasmic function. The reduction in sexual desire was categorized as severe in 2 patients (5.1%) and moderate in 11 patients (28.2%), and only 12 patients (30.8%) reported normal sexual desire. Twenty-three patients (59%) stated that they experienced moderate or severe dissatisfaction during sexual intercourse (23.1% and 35.9%, respectively), while 3 patients (7.7%) described themselves as satisfied. In terms of their overall satisfaction with sexual life, 11 patients (28.2%) considered themselves to be severely dissatisfied, 10 (25.6%) reported being moderately dissatisfied, and only 6 patients (15.4%) were satisfied [45]. A recent prospective, monocentric, noninterventional study investigated the prevalence of ejaculation disorders in MS patients, and showed that dysejaculation was present in 64% of MS patients, including a decrease in the volume of the ejaculation, the strength of ejaculation, and delay in ejaculation [46].

Phosphodiesterase-5 inhibitors (PDE5i) are deemed to be the first line of treatment for patients with neurological disorders suffering from ED [47]. To date, only 3 studies investigating the effects of PDE5i in patients with MS have been published; 2 of these were double-blind, placebo-controlled, randomized trials of sildenafil [48,49], and the other was a case series on tadalafil [50]. These studies reported significantly improved erectile function and ability to engage in satisfactory sexual activity for the majority of the patients (73%–95%). It has been also seen that the restoration of erectile function seems to improve orgasmic sensations.

Intracavernous injection (ICI) of papaverine has emerged as a major step forward in managing ED in patients with neurological conditions. Excellent results of this treatment — with success rates as high as 92% — have been reported for patients with MS [51]. However, to achieve these results, patients either received a considerable dosage of papaverine (up to 80 mg) or also received phentolamine, placing these patients at an elevated risk of priapism. For these reasons, papaverine was withdrawn from the market, making prostaglandin E1 (alprostadil) the only vasoactive drug that can be administered through ICI. Alprostadil has shown high levels of efficacy, both in men with spinal cord injuries and in those with MS [52,53]. Intraurethral alprostadil (Muse) and oral apomorphine have rarely been used in MS patients, as they showed disappointing results in men with spinal cord injuries. In some patients — mainly older men in long-term, stable relationships — vacuum constriction devic-

es may be an alternative [54]. Surgical implantation of a penile prosthesis is only considered in rare cases.

For ejaculatory dysfunction, penile vibratory stimulation is considered to be the first-line treatment in men with spinal cord injuries who do not ejaculate during sexual intercourse. This method has been widely used, with a success rate of 52% in this population [55]. Oral midodrine can enhance this result [56]. Only limited data exist on penile vibratory stimulation in patients with MS, but some data show that it can be effective. Oral midodrine restored ejaculation in some patients with MS, without requiring vibratory stimulation [57]. Electroejaculation [58] and surgical sperm retrieval [59] constitute other effective options.

Hypoactive sexual desire has been reported in 31.4%–74.4% of women with MS [60], decreased lubrication in 35.7%–48.4% [61], and orgasmic dysfunction in 37%–44.9% [62]. Dyspareunia has been reported in 31%–72% of women with MS [63], and other complaints relating to the consequences (indirect or direct) of MS for sexual function have also been described. Due to the complexity of sexual function in women, treatment of both the physical and psychosocial aspects of SD has been frequently recommended for these patients [64]. Studies of sildenafil have shown that it is safe for treating SD in women with MS [65]. Dasgupta et al. [66] reported that sildenafil yielded significant improvements in lubrication, but not in the ability to reach orgasm or quality of life. In combination with PDE5i, it is possible that alpha-blockers may further facilitate vascular smooth muscle relaxation, but their real effects have yet to be demonstrated [67]. Estrogen replacement therapy and/or the use of lubricants can mitigate symptoms related to dyspareunia, vaginal dryness, and burning. It has been reported that topical estrogen improved clitoral sensitivity and reduced pain during intercourse [67]. Since changes in interpersonal relationships, depression, and reduced self-image may damage sexual function as much as disruptions to nerve circuits — or even more so — therapeutic interventions for treating SDs should include sexual and relationship therapy, behavioral approaches, psychotherapy, and general counseling [68].

Natalizumab has been approved as a disease-modifying therapy used to treat relapsing forms of MS. Patients using natalizumab have also shown improvements in health-related quality of life parameters, including cognition and fatigue [69]. In 2018, Robertson et al. [70] performed a single-center, open-label, single-arm, 24-week study that evaluated perceived changes in SDs in MS patients who received natalizumab treatment. In patients on natalizumab therapy, the primary subscale of the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 showed a statistically significant decrease over time in the mean score for SDs (-0.6976, $P=0.02$). However, the study had multiple limitations — including a relatively small sample size and the lack of a placebo group or active comparator arm — that prevented definitive conclusions about the effects of natalizumab on SD from being drawn.

In conclusion, we can assert that MS is a complex, progressive disease with primary, secondary, and tertiary consequences for sexual function. Early professional support should be offered to women and men with MS to encourage them to express their sexual needs and verbalize their sexual concerns; furthermore, they should receive suitable information, counseling, and treatment in order to overcome their difficulties. Ongoing assessments should be conducted, and treatments should be regularly adjusted as appropriate given patients' neurological condition and sexual deficits.

CONCLUSIONS

MS is a neurological autoimmune disease with a diverse variety of urological presentations. Urologists play the director's role in evaluating and treating these patients. To choose the most suitable evaluation tools and the most proper management options for specific patients, it is vital to have a thorough knowledge of the disease process. In MS patients, LUTS should be evaluated and managed with the goal of identifying those who are at an elevated risk for upper urinary tract deterioration and/or impaired quality of life. Anticholinergics — with or without IC — are the first-line treatment for symptoms of OAB. If conservative therapy does not succeed in reducing the risk of upper urinary tract deterioration or fails to improve patients' symptoms because of limited efficacy or adverse events, second-line therapies are needed. The introduction of intradetrusor injections of BTX-A has radically changed the available options for treating refractory cases. However, further research in patients with MS is required to determine more conclusively the real-world effects of sacral neuromodulation, BTX, and anticholinergic agents. Moreover, both male and female MS patients experience diminished sexual function, which appears to be associated with more severe disability, pain, and accompanying depression. For this reason, MS patients should also receive evaluations for sexual function and disability during follow-up.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *RB*
· Formal Analysis: *RB, CG*
· Investigation: *RB, CG*
· Methodology: *RB, PFB*
· Project Administration: *RB*
· Writing – Original Draft: *RB, CG*
· Writing – Review & Editing: *RB*

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