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ORIGINAL ARTICLE

Management of Urinary Dysfunction in Patients with Multiple Sclerosis

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Abstract: *Besides the motor and sensory dysfunction that characterizes multiple sclerosis, during the disease evolution and with the accumulation of new demyelinating lesions in specific areas of the central nervous system, autonomic dysfunction be-comes more prevalent among patients suffering from multiple sclerosis. Although not usually addressed, the complex spectrum of autonomic dysfunction manifestations has the potential of a negative impact on the daily activities of multiple sclerosis patients, needing specific investigations and therapeutic measures destined to alleviate symptoms and increase the quality of life. Since urinary dysfunction is evident from the early stages of multiple sclerosis on urodynamic studies even in patients without urinary complaints, it is indicated to thoroughly screen for urinary tract dysfunction as well as other autonomic dysfunctions in all the multiple sclerosis patients.*

Keywords: *autonomic dysfunction, urinary dysfunction, multiple sclerosis*

INTRODUCTION

Multiple sclerosis (MS) is one of the most common causes of disability in young patients. Clinically it does manifest uniquely for every patient, but depending on the site of the demyelinating lesions, some symptoms have a higher frequency in different combinations, particularly sensory symptoms, motor weakness, and bladder dysfunction. Most commonly, patients will present with numbness, tingling, diplopia, Lhermitte sign, and motor weakness, that last for at least 24 hours and may or may not resolve completely. Many patients may have residual symptoms, heat sensitivity with worsening of symptoms in case of increased body temperature, known as Uhthoff's symptom [1–3].

AUTONOMIC DYSFUNCTION IN MULTIPLE SCLEROSIS

As the disease follows its course over the years, inevitably patients will also experience damage to the autonomic nervous system with the involvement of both sympathetic and parasympathetic parts in different proportions. The promoters of the autonomic dysfunction appear to be lesions located in the nuclei of the periventricular regions of the fourth ventricle, medulla, but it was also seen in patients who presented cervical spinal cord atrophy with or without demyelinating lesions, suggesting that autonomic dysfunction may also result from axonal depletion [4].

Although severely overlooked, autonomic dysfunction has a great impact on the quality of life of patients suffering from multiple sclerosis, the most commonly addressed issues being bowel and bladder disturbances, which tend to be more bothersome in the case of longer disease, greater disability, or recent relapses [5].

Approximately 50% of patients experience orthostatic intolerance manifested by dizziness, loss of postural tonus, and tachycardia while transitioning from a supine to an upright position or in case of prolonged standing. The impaired sympathetic vasoconstrictor reflex responsible for maintaining

normal blood pressure leads to an increased frequency of orthostatic hypotension among those patients[4].

Sleep disturbances in patients with multiple sclerosis are not very well studied, the most common symptom being difficulty initiating and maintaining sleep. There are several factors like muscle spasms, trigeminal neuralgia, restless legs syndrome, anxiety, depression, and side effects of medication used to treat fatigue, that contribute to insomnia, which can be searched for and addressed [2,4].

Another common but less addressed pathological aspect of multiple sclerosis is the sexual dysfunction that can be a consequence of multiple lesions including spinal cord lesions of the motor and sensory pathways and can be aggravated by the urinary incontinence and the spasticity accompanying upper motor lesions. About 50% of MS patients tend to become sexually inactive during the disease, with consequences like decreased libido, impotence, and infertility [2,5,6].

Bowel dysfunction is present in up to 50% of MS patients, about 43 % of them will complain of constipation partially due to disease exacerbations, and partially to decreased ambulation and certain medications that may alter bowel movement. A great proportion of patients with bowel dysfunction will present fecal incontinence as a consequence of impaired external anal sphincter function [2,4,7].

UROLOGICAL DYSFUNCTIONS

The most frequent autonomic dysfunction present in patients suffering from multiple sclerosis is bladder dysfunction, the prevalence of neurologic lower urinary tract dysfunction varies between 65 to 92% [8]. Approximately 75% of patients report bladder dysfunction secondary to a storage phase dysfunction leading to incontinence, or the voiding phase dysfunction leading to urinary retention and incomplete bladder emptying [2,4]. Bladder control requires complex coordinated functions of the cerebral cortex, pontine and sacral micturition centers, and the integrity of the peripheral nervous system [6]. The demyelinating lesions localized at the spinal cord level disrupt the fiber connections from the pontine micturition center to the parasympathetic sacral micturition center causing the silent C fibers, usually insensitive to bladder filling in normal conditions, to be hypersensitive leading to detrusor hyperactivity [9,10]. Spinal cord centers activate storage reflexes in the filling phase of the bladder, while the brain centers of micturition are responsible for the act of urine output [4,11]. Detrusor overactivity, which translates in clinical terms to symptoms like urgency to void that occurs at a lower bladder volume than normal, frequency or urge and incontinence are the leading complaints. On the opposite side lies detrusor sphincter dyssynergia described as detrusor contraction without urethral sphincter relaxation, which is responsible for the impossibility of bladder emptying causing symptoms like hesitancy, or interrupted stream. While the former urologic abnormality is caused by demyelinating lesions of the frontal cortex, the second one is a consequence of lesions of the pontine centers of micturition or lesions above the sacral parasympathetic centers [2,6,12]. Unlike spinal cord lesions due to multiple sclerosis, spinal cord injuries, even in patients with relatively preserved neurological function, are characterized by universal bladder dysfunction, meaning that there is an impairment of both sensation of bladder fullness as well as the motor control of bladder and sphincter [6,11].

For many patients, urological symptoms arise only in the later stages of disease progression with a proportion of over 50% of patients with severe MS presenting severe bladder symptoms, whereas only 5-10% of MS patients have mild bladder abnormalities at the beginning. Nevertheless, a retrospective study conducted in Ankara, Turkey demonstrated that 52% of their multiple sclerosis patients without urological complaints had altered urodynamic results which could be explained by a subclinical impairment [13,14].

Patients with overactive bladder syndrome usually complain of urinary urgency, increased daytime frequency or nocturia, and sometimes incontinence in the absence of urinary tract infections or other associated pathology that could explain the symptoms. Obstructive symptoms are also an important point of complaint especially when leading to urinary tract infections. These manifestations can be associated and can have a huge impact on patients' quality of life in terms of decreased quality of sleep, decreased work productivity, and depressive symptoms [15,16].

Urine retention is a consequence either of neurogenic underactive bladder or of detrusor sphincter dyssynergia causing bladder obstruction of urine flow, leading to frequent lower urinary tract infections that can be another cause of disease relapse through the autoimmune process which it sets off [9,17,18]. Regarding the complications of the upper urinary tract there have also been mentioned vesica-urethral reflux, hydronephrosis, and end-stage kidney disease have as consequences of the morphological changes in the bladder wall caused by high intravesical pressures [16,17,19–21].

EVALUATION OF LOWER URINARY TRACT SYMPTOMS

Urological evaluation should be specifically made for every patient considering their disease type and duration, the level of disability on the EDSS scale, comorbidities, and current medications especially opiates, antipsychotics, and

antidepressants, starting with a complete history taking. The clinical dialogue should be directed towards describing urinary symptoms like frequency, urgency, hesitancy, retention, incontinence, and nocturia and the impact these symptoms have on the quality of the patient's life [16,22]. A bladder diary can provide additional information about the patient's habits of fluid ingestion and the exact frequency of bladder emptying [9].

Regarding physical examination, besides local inspection and examination of pelvic and genital organs including sacral cord mediated reflexes (bulbocavernosus, anal reflex), the neurologist should look for pontine, cerebellar as well as pyramidal signs which are indicative of lower urinary tract symptom severity [16,22]. For an initial evaluation of patients with multiple sclerosis, a bladder and renal ultrasound and a questionnaire for assessing overactive bladder and voiding dysfunction are in order, while for patients with red flags (recurring urinary tract infections, immunosuppressive treatment, EDSS >6, male patients, age >55) should be referred to a neuro-urology clinic or specialist [23].

Furthermore, some investigations can help us better understand the nature of the urological dysfunction. Firstly, all patients complaining of urinary symptoms should undergo a urinalysis and urine culture to assess the presence of a possible urinary tract infection as well as serum creatinine. Ultrasonography can allow us to measure the post-void residual volume, and it can be done at different times a day for better quantification of the bladder emptying pattern. Patients with a known high risk of upper urinary tract disease should benefit from periodical ultrasonography examinations for early detection of upper urinary tract dilation. Since a high post-void residual volume is not enough to distinguish between detrusor contractility problems and obstruction, urodynamic studies are required. Urodynamic studies represent a combination of cystometry and pressure flow study, useful in evaluating the outlet function and compliance of the detrusor and bladder. It can be used as a prognostic tool as well as for guiding the best treatment approach. In the case of hematuria, a urethrocystoscopy evaluation is required to rule out bladder tumors, bladder stones, and urethral stricture [16,20].

TREATMENT APPROACHES IN MULTIPLE SCLEROSIS-ASSOCIATED URINARY DYSFUNCTION

Physical therapy

One of the areas worth addressing is physical therapy, which in this case refers to physical exercises like pelvic floor exercises alone or combined with intravaginal electrical stimulation. Cognitive behavioral therapies may be helpful in some patients in trying to develop a bladder voiding schedule according to each patient's natural voiding pattern which combined with restricted water intake before bedtime can improve sleep quality and reduce complaints like fatigue [16].

Medical treatment

Regarding the drugs efficient for urinary dysfunction, there are several options depending on the main cause of dysfunction, that can be assessed by urodynamic studies. The first treatment line for neurogenic bladder is antimuscarinic drugs (oxybutin, tolterodine). Anticholinergics can alleviate complaints of neurogenic bladder as well as phosphodiesterase inhibitors and desmopressin which can be used as an alternative to antimuscarinics or as an adjuvant [6,20]. In an observational prospective study on the bladder and urodynamic alterations in patients with multiple sclerosis, the degree of urinary symptom severity decreased following symptomatic urological medication by lowering the bladder pressure, improving muscle spasms, and reducing pain caused by urine storage [24].

In case of bladder outlet resistance, autonomic dysreflexia, and postvoid residual volume, alpha-blockers (prazosin, terazosin) can help sphincter relaxation by lowering bladder pressure during contraction, but administered with caution because they can aggravate hypotension [6,20,25].

In patients with hypotonic bladders, cholinergic medications (bethanechol) may help empty the bladder, while in patients with pathologic relaxation of the vesical sphincter, alpha-adrenergic medication may increase bladder storage [6,17].

Minimally invasive treatment

Catheterization, self-catheterization, or third-party catheterization is the preferred method for patients who cannot otherwise empty their bladder. Patient medical education in managing a sterile intermittent catheterization can help reduce complications like urinary tract infections or bacteriuria. The habit of keeping a bladder diary can also help choose the frequency of catheterization so that the volume of the bladder at catheterization does not exceed 400-500 ml. As short-term methods, patients can dispose of condom catheters and adult diapers.

Botulinum toxin injections in the detrusor cause reversible chemical denervation with effects lasting for approximately 9 months, but also with known side effects like urinary tract infections, elevated postvoid residual volume, and increasing need for intermittent catheterization. In the case of bladder neck and urethral obstruction, to reduce the outlet resistance and to protect the upper urinary tract, patients may benefit from chemical denervation of the detrusor sphincter using botulinum toxin [6,17,20].

Surgical treatment

Sphincterotomy for reducing the bladder outlet resistance without completely losing the closure of the urethra comports the risk of secondary narrowing of the bladder neck and needs to be repeated at regular intervals. Bladder augmentation is indicated in patients with overactive or low compliance bladder when conservative methods have not been beneficial [20]. Urethral stents, sphincterotomy, and electrical implantation devices can be taken into account in selected cases, but with limited evidence of efficacy [6,26].

CONCLUSIONS

Multiple sclerosis is a central nervous system inflammatory demyelinating disease with multiple clinical manifestations, including autonomic dysfunctions. The most common and the most addressed is bladder dysfunction, but it is only a small part of the many bothersome effects of multiple sclerosis lesions, hence the need to evaluate and treat accordingly to ensure a higher quality of life for patients.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, C.G.L., C.A.S. and D.M.; methodology, V.I.V., R.A.A., F.A.A. and A.M.R..; resources, D.M., C.A.S., and F.A.A..; data curation, C.G.L., V.I.V., and A.M.R.; writing—original draft preparation, C.G.L., C.A.S., F.A.A., and A.M.R..; writing—review and editing, V.I.V., and R.A.A. All authors have read and agreed to the published version of the manuscript.

References:

1. Baert AL, Knauth LM. Inflammatory Diseases of the Brain. 2009. https://doi.org/10.1007/978-3-540-76660-5.

2. Olek J Michael DHJ. Clinical presentation, course, and prognosis of multiple sclerosis in adults. 2023.

3. Adamec I, Habek M. Autonomic dysfunction in multiple sclerosis. Clin Neurol Neurosurg 2013;115. https://doi.org/10.1016/j.clineuro.2013.09.026.

4. Gelfand JM. Multiple sclerosis: Diagnosis, differential diagnosis, and clinical presentation. Handb Clin Neurol, vol. 122, Elsevier B.V.; 2014, p. 269–90. https://doi.org/10.1016/B978-0-444-52001-2.00011-X.

5. Wang G, Marrie RA, Fox RJ, Tyry T, Cofield SS, Cutter GR, et al. Treatment satisfaction and bothersome bladder, bowel, sexual symptoms in multiple sclerosis. Mult Scler Relat Disord 2018;20:16–21. https://doi.org/10.1016/j.msard.2017.12.006.

6. Cotterill N, Madersbacher H, Wyndaele JJ, Apostolidis A, Drake MJ, Gajewski J, et al. Neurogenic bowel dysfunction: Clinical management recommendations of the Neurologic Incontinence Committee of the Fifth International Consultation on Incontinence 2013. Neu-rourol Urodyn. 2018 Jan;37(1):46-53. doi: 10.1002/nau.23289.

7. Waldron DJ, Horgan PG, Patel FR, Maguire R, Given HF. Multiple sclerosis: assessment of colonic and anorectal function in the presence of faecal incontinence. Int J Colorectal Dis. 1993 Dec;8(4):220-4. doi: 10.1007/BF00290311.

8. Domurath B, Kurze I, Kirschner-Hermanns R, Kaufmann A, Feneberg W, Schmidt P, et al. Neurourological assessment in people with multiple sclerosis (MS): a new evaluated algorithm. Mult Scler Relat Disord 2020;44. https://doi.org/10.1016/j.msard.2020.102248.

9. Sungur U, Akkoc Y, Yuceyar N, Ekmekcİ O. Urinary Symptoms in Multiple Sclerosis: Relation with Urodynamic Findings and Impact on Patient's Quality of Life. Clin Exp Health Sci 2019;9:143–50. https://doi.org/10.33808/clinexphealthsci.564239.

10. McCombe PA, Gordon TP, Jackson MW. Bladder dysfunction in multiple sclerosis. Expert Rev Neurother 2009;9:331–40. https://doi.org/10.1586/14737175.9.3.331.

11. Fowler CJ, Griffiths D, De Groat WC. The neural control of micturition. Nat Rev Neurosci 2008;9:453–66. https://doi.org/10.1038/nrn2401.

12. Wintner A, Kim MM, Bechis SK, Kreydin EI. Voiding Dysfunction in Multiple Sclerosis. Semin Neurol 2016;36:34–40. https://doi.org/10.1055/s-0035-1571212.

13. Erden E, Ersöz M, Tiftik T, Erden E. The neurogenic bladder characteristics and treatment approaches in the patients with multiple sclerosis. Mult Scler Relat Disord 2022;58:103439. https://doi.org/10.1016/J.MSARD.2021.103439.

14. Bragadin MM, Motta R, Uccelli MM, Tacchino A, Ponzio M, Podda J, et al. Lower urinary tract dysfunction in patients with multiple sclerosis: A post-void residual analysis of 501 cases. Mult Scler Relat Disord 2020;45. https://doi.org/10.1016/j.msard.2020.102378.

15. Tadayyon F, Etemadifar M, Bzeih H, Zargham M, Nouri-Mahdavi K, Akbari M, et al. Association of urodynamic findings in new onset multiple sclerosis with subsequent occurrence of urinary symptoms and acute episode of disease in females. J Res Med Sci. 2012 Apr;17(4):382-5. PMID: 23267402; PMCID: PMC3526134.

16. Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. Lancet Neurol 2015;14:720–32. https://doi.org/10.1016/S1474-4422(15)00070-8.

17. Stoffel JT. Chronic Urinary Retention in Multiple Sclerosis Patients: Physiology, Systematic Review of Urodynamic Data, and Recommendations for Care. Urologic Clinics of North America 2017;44:429–39. https://doi.org/10.1016/j.ucl.2017.04.009.

18. Salinas-Casado J, Vírseda-Chamorro M, Matías Guiu-Antem J. Importance of Urodynamic Dysfunctions as Risk Factors for Recurrent Urinary Tract Infections in Patients with Multiple Sclerosis 2022. https://doi.org/10.35248/2168-9857.22.11.296.

19. de Sèze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B. The neurogenic bladder in multiple sclerosis: Review of the literature and proposal of management guidelines. Multiple Sclerosis 2007;13:915–28. https://doi.org/10.1177/1352458506075651.

20. Groen J, Pannek J, Castro Diaz D, Del Popolo G, Gross T, Hamid R, et al. Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol 2016;69:324–33. https://doi.org/10.1016/j.eururo.2015.07.071.

21. Hamid R, Averbeck MA, Chiang H, Garcia A, Al Mousa RT, Oh SJ, Patel A, Plata M, Del Popolo G. Epidemiology and pathophysiology of neurogenic bladder after spinal cord injury. World J Urol. 2018 Oct;36(10):1517-1527. doi: 10.1007/s00345-018-2301-z.

22. Aharony SM, Lam O, Corcos J. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines. Journal of the Canadian Urological Association 2017;11:61–4. https://doi.org/10.5489/cuaj.4058.

23. Ineichen B V., Schneider MP, Hlavica M, Hagenbuch N, Linnebank M, Kessler TM. High EDSS can predict risk for upper urinary tract damage in patients with multiple sclerosis. Multiple Sclerosis Journal 2018;24:529–34. https://doi.org/10.1177/1352458517703801.

24. Torad H, Shalaby N, Hussein HA, Sadek SZ, Abdelazim MS, Yehia A, et al. Bladder and urodynamic changes in multiple sclerosis. Egypt J Neurol Psychiat Neurosurg 2020;56. https://doi.org/10.1186/s41983-020-00178-z.

25. Schneider MP, Tornic J, Sýkora R, Abo Youssef N, Mordasini L, Krhut J, et al. Alpha-blockers for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: A systematic review and meta-analysis. A report from the Neuro-Urology Promotion Committee of the International Continence Society (ICS). Neurourol Urodyn 2019;38:1482–91. https://doi.org/10.1002/nau.24039.

26. Groen J, Pannek J, Castro Diaz D, Del Popolo G, Gross T, Hamid R, Karsenty G, Kessler TM, Schneider M, 't Hoen L, Blok B. Summary of European Association of Urology (EAU) Guidelines on Neu-ro-Urology. Eur Urol. 2016 Feb;69(2):324-33. doi: 10.1016/j.eururo.2015.07.071. Epub 2015 Aug 22. PMID: 26304502.