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I. 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. It has been reported that lower urinary tract dysfunction occurs 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 (NARCOMS) survey of almost 10,000 patients with MS, 65% of participants reported experiencing one 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 show considerable variation 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, in addition to the serious impact of LUTS on the quality of life of MS patients, 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 over activity (NDO) (34–99%) [7].

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II. Objectives

This study was conducted to review and summarize data on neurologic lower urinary tract disorders, sexual dysfunctions and their correlation with brain and brainstem lesions in patients with MS.

III. Methods

A literature review (PubMed, Web of Science, and Scopus) was conducted for articles on urological and sexual dysfunction in MS patients and their correlation with brain and brainstem alterations.

IV. Neural Pathways of Micturition

Until the age of 3 to 5 years, the micturition occurs involuntarily in infants and in young children. After this age, the development of the system controlling the micturition is complete and mature. In CNS, there are many areas and pathways involved in this process, and they are strictly connected to tracts in the spinal cord. These circuits coordinate the activity of the smooth and striated muscle of the bladder and the tone of the sphincter, allowing the storage and the elimination of urine. The coordination is mediated by a complex neural system that is located in the brain, in the spinal cord and in the peripheral ganglia. [8]. The bladder has only two modes of operation: storage and elimination. Both modalities involve a pattern of afferent and efferent signaling in *parasympathetic* (pelvic nerves), *sympathetic* (hypogastric nerves) and *somatic* (pudendal nerves) pathways. These bring to the formation of reflexes, which can keep the bladder relaxed with a low intravesical pressure, or can initiate the contraction of the detrusor to allow bladder emptying. [9]. The parasympathetic pathways mediate the relaxation of the urinary sphincter and the contraction of the detrusor. Preganglionic neurons are located in the lateral part of the sacral (S2-S4) intermediate gray matter (also called *sacral*

parasympathetic nucleus). The postaganglionic neurons are located both in the pelvic plexus and in the detrusor wall layer. [10]. Sympathetic pathways mediate the relaxation of detrusor muscle and the contraction of the bladder outlet region and urethra. The preganglionic neurons are located in the intermediolateral nuclei of T10-L2 of the spinal cord. The axons follow a complex route through the sympathetic chain ganglia, the inferior mesenteric ganglia, ending through the hypogastric nerves to the pelvic ganglia. [11]. The motoneurons controlling the activity of external urinary sphincter (EUS) are located in the lateral border of the ventral horn, commonly names as the *Onuf nucleus*. The somatic innervation is provided by the pudendal nerve [12]. The afferent pathways moves from periphery through the pelvic nerves to the dorsal root ganglia at the lumbosacral level of the spinal cord, but some fibers travel from periphery to the spinal cord through the hypogastric nerve [13]. The most important informations come from receptors of the bladder wall, which travel along those routes and are activated when the intravesical pressure overcomes a certain threshold (5-15 mmH2O, first sensation of bladder filling). There are also smaller fibers which are "silent", but are activated following chemical irritation to the bladder mucosa. Recent evidences suggests that the urothelium itself can serve as an important signaling unit, producing a big variety of biochemical mediators [14]. Bladder filling is mediated by a *sympathetic storage reflex* and a *somatic storage reflex*, with the purpose to relax the bladder and to contract the EUS. As the bladder distends, afferent fibers travel informations through the pelvic nerves to the spinal cord, activating a sympathetic response (L1-L3) and a consequent decrease in parasympathetic activity. The predominant innervation of the human bladder from sympathetic fibers is in the outlet region, where it mediates contraction. Pelvic nerves driving impulses to the spinal cord activate also neurons in the nucleus of Onuf, activating a response through the pudendal nerve ending in the contraction of the EUS. In addition to this, there is also a supraspinal imput to the nucleus of Onuf, responsible of the voluntary control of the EUS [15]. When the bladder is very full and the impulsis from the afferent fibers arise, they are brought also to more rostral areas of the spinal cord, and to the brain. The periacqueductal gray (PAG) in the rostral brain stem integrates information from afferent fibers and from the cerebral cortex, and is strictly connected to the Pontine micturition center (PMC), which also controls the pathway of the micturition reflex. When the afferent activity overcomes a certain threshold, PMC activity increases and activates the parasympathetic pathways, determining the activation of the detrusor and the relaxation of the EUS, performing micturition [8]. Summing up, in adults, micturition depends on a long-loop spinobulbo-spinal reflex. During the filling phase, that usually occupies at least 99% of the time, afferent signals from the bladder and urethra ascend through the spinal cord to synapse in the midbrain periaqueductal gray (PAG). Their intensity increases as the bladder is filled. If the reflex operated automatically, then it would be triggered when afferent input exceeded a certain threshold; fibers descending from the PAG would then excite the pontine micturition center (PMC); PMC excitation activates descending motor efferents, which are hard-wired to cause coordinated urethral sphincter relaxation and bladder contraction; thus the system would enter the voiding phase and empty the bladder. However, automatic triggering of the reflex implies involuntary voiding (incontinence). Normally therefore the reflex is inhibited [16].

V. Urological Disorders in Multiple Sclerosis

Bladder dysfunction is the most frequently encountered disturbance of the autonomic nervous system in MS, but in many cases, it is inadequately diagnosed and insufficiently treated. According to a systemic review of recent articles presenting the findings of urodynamic studies in MS patients (12 studies, 1524 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 [17]. Furthermore, urinary incontinence and weak stream have shown associations with lesions in the cerebellum and pons [18]. 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. 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 and 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 [19, 20].

VI. Neural Alterations in Overactive Bladder and Urinary Urge Incontinence

Urgency, frequency, and neurogenic detrusor overactivity are the most common urological symptoms in patients with neurogenic disorders like multiple sclerosis (MS), Parkinson's disease, spinal cord injuries, or ischemic stroke. Dysfunctional voiding occurs in 34% to 79% of the patients [21]. There seem to be three separate regimes. Firstly, at small bladder volumes when sensation is mild, responses show abnormal deactivation of limbic regions, perhaps to suppress unwanted emotional reaction. Secondly, at large bladder volumes with strong sensation but in the absence of DO, responses are exaggerated, representing recruitment of acces-sory pathways to maintain bladder control and/or increased bladder awareness. Finally, if bladder control is lost, signified by the onset of DO, then there seems to be a third pattern of responses, including deactivation of the prefrontal cortex, that may indicate inability to maintain voluntary control of voiding [16]. In individuals with proven urge incontinence and DO, brain responses to bladder filling at small bladder volumes (with relatively mild sensation and no DO) differ from normal. A considerable part of the limbic (emotional) system shows deactivation with bladder infusion, including hippocampus, parahippocampal gyrus and possibly amygdala, together with adjacent inferior temporal lobes, medial orbito-frontal cortex, and parts of the posterior cortex. Such extensive deactivations were not seen in normals (significant difference between groups, $P<0.01$ uncorrected), the location of deactivations in the limbic system may imply that urge-incontinent individuals suppress unwanted emotional reactions aroused by bladder infusion, even when there is no urgency and no DO. Such suppression might be a conditioned reaction to bladder filling, formed by previous negative experiences of loss of bladder control [16].

Other striking differences between brain responses in urge-incontinent and normal subjects occur at larger bladder volumes, after subjects have signaled strong desire to void orurgency (but there is no DO or incontinence). Firstly, urge-incontinent subjects show significantly stronger and more extensive activation of the brain globally, especially in the ACG, part of the limbic (emotional) nervous system. Secondly, they exhibit significantly stronger activation in accessory areas that include frontoparietal regions involved in pelvic-floor motor activity and the lateral somatomotor cortex identified by Critchley et al, a region that supports interoceptive awareness. Together, these changes suggest abnormally strong emotional arousal induced by bladder filling, and an attempt to recruit accessory pathways in order to maintain control of pelvic-floor muscles and inhibition of the PMC (and the voiding reflex) when loss of bladder control threatens. In DO patients, the presence of DO was associated with marked decrease in activation of the prefrontal cortex bilaterally andparts of the limbic system (right parahippocampal gyrus/amygdala). There was no significant change in the activation of ACG or orbitofrontal cortex. This pattern of changes suggests a lack of voluntary control of the bladder with ongoing arousal [16, 17].

Urgency is a key characteristic of urge incontinence. It is an abnormal sensation characterized by a compelling natureand pronounced emotional content, as indicated by currentand past definitions: ''a sudden compelling desire to void thatis difficult to defer'', associated with ''fear of leakage.''[16, 17]

Many data suggest that there may be a dysfunction of the prefrontal cortex in urge-incontinent subjects, either weaker activation of orbitofrontal cortex or deactivation of medial frontal cortex. Because the prefrontal cortex is associated with decision-making in a social context and is involved in voiding, it is plausible that dysfunction of this region could be a cause of incontinence. The dysfunction could be caused either by a regional defect or by disruption of connecting pathways. In urge-incontinent subjects, brain responses to bladder filling differ from normal at both small and large bladder volumes, even in the absence of DO. Weak response or deactivation observed in the prefrontal cortex or the limbic system may represent intrinsic defects of supraspinal bladder control that cause urge incontinence. Exaggerated ACG response at large bladder volumes apparently represents a learned reaction to imminent loss of control that originates elsewhere in the brain or is due to abnormal bladder afferents. It may be the neural correlate of the abnormal sensation called urgency. If actual DO develops then the prefrontal cortex seems to become deactivated, consistent with the loss of voluntary bladder control. Different causes or combinations of causes may be responsible for urge incontinence in different individuals, implying that there are different phenotypes that may require different treatments. Understanding of these differences and their causes, based on functional brain imaging, promises to bring about the next great advance in diagnosis and therapy of this difficult problem [16, 17].

VII. Neural Alterations in Detrusor-Sphincter Dyssynergia

Detrusor sphincter dyssynergia (DSD) is a very frequently found problem in patients with neurological diseases. In fact, it is commonly seen in patients with SCI and MS but there seem not to be clear relationship to type of DSD and severity of the neurological condition. Residual urine volume and thus secondary

UTIs onset with the risk of kidney damage is currently a problem. DSD is defined as a rise of muscle activity in the pelvic floor electromyography during relaxation of the pelvic floor, showing that the urethral sphincter muscle contracts, instead of relaxing completely during initiation of voiding. Khavari et al [22] have demonstrated in subjects with MS and DSD that the patients show lower, more diffuse activation than the healthy volunteers. Furthermore, patients who demonstrated NDO tended to have more activation in the areas associated with executive function (bilateral middle and right inferior frontal gyrus) and the brainstem than the group without NDO. Additionally, the right inferior frontal gyrus, which is implicated in risk aversion, is more activated in patients with NDO, which could be explained as an inhibition signal to accept a risky option of urinary incontinence [23]. About patients with DSD, this small subgroup expressed a trend toward greater activation in areas of executive function, emotional processing, movement (right caudate) and the brainstem (each $p < 0.01$) [22]. Interestingly, the caudate nucleus, one of the structures in the basal ganglia that has been long associated with motor processes because of its role in Parkinson's disease, is also significantly activated in this group at the time of DSD. This reaction could possibly be explained by the learned behavior that these patients may require to initiate more abdominal straining and Valsalva maneuvers to begin to void due to higher bladder outlet resistance.

A recent study from Sandra Seseke et al [24] demonstrated some differences between DSD patients and healthy controls in fMRI. Surprisingly, the pontine region showed a completely different activation site in the group activation map of the patients. The activation was detected in the more rostral/dorsal part in the DSD group. It could be explained by a stronger activation of the pontine L-region as the patients have to try harder to initiate the micturition and the urethral sphincter is inhibited as functional brain studies of Blok et al [25] and Nour et al [26] elucidated. In a recent study of Keller et al [27] using an animal model, neurons in the PMC expressing estrogen receptor 1 were identified, which are responsible for bladder contraction and relaxation of the urethral sphincter, whereas the other subset of neurons found, expressing corticotropin-releasing hormone, only increased the bladder pressure. The study could show that molecularly and functionally distinct cell groups may play a role in the subcortical regulation of micturition. In human, further studies with larger samples have to clarify the location differences in functional mapping of the pontine regions.

VIII. Neural Alterations in IPO- and Acontractile Bladder

A wide range of neurologic injures or neurologic diseases can lead to detrusor under activity (DUA). This dysfunctions may involve the brain, the spinal cord or the peripheral nerves, in both their afferent and efferent component [28]. In the brain, the pontine micturition center (PMC) receives many imputs from the cerebral cortex, in particular from the limbic system. Many areas, like the insula, hypothalamus and the periaqueductal gray help integrating all the stimuli, resulting in the activation of micturition pathways. Any lesion in one of those regions, for example, secondary to MS plaques, may potentially lead to DUA, even if there is not always a direct correlation between the neurologic lesion in the brain and the urological dysfunction [29]. Overall, DUA may occur in up to 20% of patients affected by MS, but in particular if neurological lesions affect the lumbosacral cord instead of the brain [30]. In Parkinson's disease or after a cerebrovascular accident overactive bladder is the most common sequela, but in the acute period about 50% of the patients may develop acute urinary retention, due to the "cerebral shock" [31]. About peripheral innervation, injures at the level of lumbosacral cord, the cauda equina and the sacral and pelvic nerves can lead to DUA. This may occur as the result of a trauma, a disease of the vertebral column or after radical pelvic surgery. An interruption or impairment of efferent signaling in the sacral cord (segments S2-S4), sacral roots or pelvic nerves can present with reduced or absent detrusor contraction [32]. In a systematic review [33], the overall incidence of LUT dysfunctions after radical hysterectomy was 72%, and high incidences of DUA were reported also in older series of patients undergoing radical rectal surgery. An impairment in afferent function (from the bladder or the urethra) can potentially reduce or delete the micturition reflex, leading to partial or total loss of voiding efficiency. Also normal aging is associated with a decline in sensory function in the lower urinary tract [34]. Without intact bladder sensation, correct functioning of the efferent limb of the micturition reflex is compromised. Also urethral afferents have an important role in the perception of the detrusor contraction and the flow through the urethra [35].

IX. Neural Alterations in Sexual Dysfunctions

Sexual dysfunctions (SDs) are often found, but frequently underestimated, in patients with MS, and may have a remarkably high impact on patients' quality of life (QoL) [36]. In the past, MS-associated ED was thought to be the result mainly from MS lesions in the spinal cord [36]. More recently, functional neuroimaging in healthy men identified a network of brain areas, such as

the insula, visual and somatosensory association areas, cingulate gyrus, prefrontal cortex, as well as subcortical regions, contributing to erectyle function (EF). Basing on these assumptions, Winder and coll. conduced a retrospective study [37] assessing the cerebral lesion pattern of male MS patients and correlating them with clinical scores of EF with the MS-associated lesion sites using voxel-based lesion symptom mapping (VLSM) [38, 39]. Study results demonstrated, in summary, how decreasing DeltaIIEF5 scores correlated with a large cluster of MS lesions in the insular region including the adjacent juxtacortical white matter, most prominently in the left-hemispheric insular region. Authors hypothesized that MS lesions in the left insular region could compromise parasympathetic modulation and thereby contribute to ED. Similar results were found in a study by Winder and coll. [39]; in this study, designed in order to determine associations between alterations of female sexual arousal as well as vaginal lubrication and the site of cerebral MS lesions, authors found that, in 44 MS women, decreased lubrication scores were associated with bladder or urinary symptoms and, as shown by multivariate VLSM analysis (including arousal and lubrication scores as covariables of interest) right occipital lesions were associated with impaired arousal and left insular lesions were associated with decreased lubrication. Moreover, impaired lubrication remained associated with left insular lesions after adjustment for bladder or urinary dysfunction. Surprisingly, in this MS patients series, dysfunction of sexual arousability or lubrication was not associated with patient age, disease duration or severity, spinal cord involvement, or depression.

In contrast with previous evidences, Zorzon et al. in their study did not find any association between SDs and MS lesions in the aforementioned regions [40]; on the other hand, Zivadinov and coll. applied a multivariate regression analysis, finding associations between SDs and pontine MS lesions [41]. Furthermore, Barak et al. found correlations between male and female anorgasmia and the total volume of cerebral MS lesions, and more specifically of brainstem and corticospinal tract lesions [42].

In a recent study investigating the frequency of SD in female MS patients and exploring its association with the location and number of demyelinating lesions, Solmaz and coll. [43] evaluated 42 female patients compared with 41 healthy subjects. All patients underwent neurological examination and 1.5 T brain and full spinal MRI. Results showed as MS patients had a statistically significantly lower FSFI and SF-36 scores and higher BDI and BAI scores compared with healthy subjects, but SDs seemed to be unrelated to the location and number of demyelinating lesions. These findings highlight the importance of the assessment and treatment of psychiatric comorbidities, such as depression and anxiety, in MS patients reporting SD, as reported in previous studies [44].

Finally, in 32 female and 9 male MS patients, Barak et al reported that anorgasmia correlated with the total volume of MS lesions throughout the brain and, more specifically, with MS lesions in the brainstem and corticospinal tract [42].

X. Conclusions

Lower urinary tract symptoms are very common in multiple sclerosis patients and adversely affect this patient's quality of life. Many neural pathways are involved in the pathogenesys of these symptoms and, due to the heterogeneity of neurologic lesions, symptoms are different from patient to patient. To face better this urological dysfunctions, the urologist needs to have a deep knowledge of their pathogenesis, allowing an improved management and a long-term follow-up of the patient, that often requires also a multidisciplinary approach. In addition, urologists must have consciousness of sexual dysfunctions in this patients, to investigate and treat this conditions in the best way possible.

XI. Disclosures

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Research did not involve Human Participants and/or Animals and therefore there is no informed consent.

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