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REVIEW

Neurogenic lower urinary tract dysfunction in multiple sclerosis, neuromyelitis optica, and related disorders

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Abstract

Purpose Multiple sclerosis (MS), neuromyelitis optica (NMO), and related disorders are major immune-mediated central nervous system diseases affecting the spinal cord. We reviewed the occurrence of neurogenic lower urinary tract dysfunction (NLUTD) in these categories of diseases.

Methods We systematically reviewed the literature regarding bladder dysfunction in MS, NMO spectrum disorder (NMOSD), and related disorders (acute disseminated encephalomyelitis, acute immune-mediated myelopathy, and meningitis-retention syndrome).

Results The literature, although somewhat limited for diseases other than MS, suggests that bladder dysfunction is not uncommon in these diseases, presumably reflecting lesions in the spinal descending and ascending pathways. The pattern of bladder dysfunction is a combination of overactive bladder and large post-void residuals/urinary retention. Post-void residual is measured by portable ultrasound devices.

Conclusions Because of the complexity of bladder behavior, careful consideration of bladder management is necessary in MS, NMO, and related disorders: e.g., antimuscarinics, etc., for overactive bladder and clean, intermittent self-catheterization for urinary retention. These management practices should help improve patients' quality of life.

Keywords Multiple sclerosis · Neuromyelitis optica · Spinal cord · Overactive bladder · Urinary retention

Introduction

Multiple sclerosis (MS) is a common immune-mediated disease of the central nervous system (CNS) [73]. Neurologic symptoms typically present in young adulthood and vary according to the site of inflammation, although disorders of the hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and optic nerves are common. Among these, lesions in the spinal cord can affect gait, sensation, and bladder autonomic function. Neurogenic lower urinary tract dysfunction (NLUTD) remains a clinical challenge to treat and becomes a serious disability in affected individuals, greatly impacting annual health care costs [73]. Neuromyelitis optica (NMO, Devic's disease) spectrum disorder (NMOSD) was recognized in 2004 as a novel disease entity akin to MS [6, 70] by the discovery of an NMO-IgG antibody that selectively binds aquaporin (AQP) 4. In terms of the frequency of the two diseases, MS is thought to be dominant in Europe/North America, while NMO is dominant in Asia [40, 48]. More recently, myelin oligodendrocyte glycoprotein (MOG)-IgG has been identified [18]. The clinical spectrum of MOG disease covers optic neuritis, myelitis, and acute disseminated encephalomyelitis (ADEM) [18]. Therefore, bladder dysfunction might occur in NMOSD and related disorders, but only limited literature exploring this link is available. The present article reviews NLUTD in immune-mediated CNS disorders affecting the spinal cord, e.g., MS, NMOSD, ADEM [53], acute immune-mediated myelopathy [19, 69], and a newer concept, "meningitis-retention syndrome" (MRS) [59], with particular reference to lower urinary tract symptoms (LUTS), urodynamic findings, and patient management.

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Methods

We systematically reviewed the literature regarding NLUTD in MS, NMOSD, ADEM, AM, and MRS, all of which are immune-mediated CNS disorders mainly affecting the spinal cord. The literature search keywords and phrases included, for bladder dysfunction, "bladder", "urinary", "incontinence", "micturition", "overactive", "underactive", "post-void residual", and "retention", and for neurological disease, "multiple sclerosis", "neuromyelitis optica spectrum disorder", "acute disseminated encephalomyelitis", "acute myelopathy", and "meningitis-retention syndrome". We used the current version of PubMed focusing on publications since 2000.

Results and discussion

Multiple sclerosis

In 1868, Jean-Martin Charcot in Paris provided the first detailed pathology of "la sclérose en plaques", characteristic periventricular white matter lesions now understood as the pathological hallmark of MS [73]. MS is characterized by the onset and gradual exacerbation of neurological dysfunction due to inflammatory demyelination. Neurologic symptoms typically present in young adulthood and vary according to the site of inflammation, although disorders originating from hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and optic nerves are common. MS occurs more frequently in women and its development is complex, involving genetics, hormones, geography, vitamin D, and viral exposure. Neuroimaging and cerebrospinal fluid (CSF) abnormalities, particularly oligoclonal bands, help in diagnosing early MS. In the past decade, there has been remarkable expansion in disease-modifying therapies for MS, but treatment of progressive disease (10% at onset) is still not established. Clinical features of MS include cognitive, gait, coordination, sensation, and bladder function. Treatment of bladder dysfunction remains a particularly significant clinical challenge and can become a serious disability in affected individuals, greatly impacting annual health care costs [73].

Bladder dysfunction is common in MS

Several control studies have indicated that the frequency of LUTS in MS patients can reach 70% [49, 51]. LUTS comprise one of the most common autonomic nervous system disorders in MS, together with cardiovascular autonomic nervous system disorder. Orthostatic intolerance/postural orthostatic tachycardia syndrome occurs in up to 50% of patients [2]. Severe orthostatic hypotension also occurs in MS [57]. Amarenco and colleagues studied the correlation between bladder and cardiovascular disorders in MS but found no clear correlation, indicating separate pathophysiologies [4]. LUTS in MS patients comprise storage and voiding symptoms, or both. Storage symptoms include overactive bladder (urinary urgency, usually accompanied by urinary frequency), and in advanced cases, urinary incontinence of the urgency type. Stress urinary incontinence is rare in neurological diseases, since it derives from pelvic floor weakness or sphincter weakness (the latter occasionally occurs from sacral spinal cord lesions). Overflow incontinence secondarily occurs after large post-void residuals. Nocturnal frequency (nocturia) comes from not only neurogenic overactive bladder (OAB) but also from insomnia and nocturnal polyuria [caused by mild cardiac failure [increased brain natriuretic protein (BNP) of cardiac origin], kidney dysfunction, postural hypotension, and, on rare occasion, hypothalamic lesions (loss of nocturnal increase in arginine vasopressin of central origin)]. Nocturnal polyuria can be assessed by a bladder diary. These storage symptoms significantly affect quality of life in MS patients. Voiding symptoms include hesitation, poor stream, difficulty urinating, and urinary retention. However, post-void residual (PVR) is often not perceived by patients; therefore, objective ultrasound measurement is important. Large PVR may lead to recurrent pyelonephritis, kidney dysfunction, and morbidity [49, 51].

Both overactive bladder and large post-void residuals occur in MS

Studies have shown that MS patients have NLUTD, particularly both overactive bladder and large PVR. The quality of life (QOL) index in MS patients was significantly higher (i.e., worse) for those with bladder dysfunction than for MS controls. Many of them showed large PVR urine volume, greater than 100 ml [49, 51].

What is the underlying mechanism for both overactive bladder and large PVR in MS patients? Since MS is a progressive immune-mediated disease that affects multiple CNS regions, MS patients may have a wide range of urodynamic abnormalities that may change with progression of the illness. Videourodynamics [25] allows us to infer the site of lesions, and sphincter electromyography (EMG) enables us to assess lumbosacral cord functions. Neuroimaging and pathology studies have shown that the commonly affected regions in MS are hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and optic nerves. Among these, the medial/prefrontal/insular cortex [12] (total brain volume [65]) (basal ganglia, hypothalamus), cerebellum [12], brainstem (midbrain [12, 54], pons [12, 68]), and cervicothoracic

spinal cord [65] are all relevant to micturition function. Among these, brain lesions cause detrusor overactivity, and sacral/peripheral lesions cause detrusor underactivity; on the other hand, partial spinal cord lesions show complex bladder behavior, and the spinal cord is very often affected in MS patients. This bladder behavior due to spinal cord lesions is called DHIC, detrusor hyperactivity with impaired contraction, i.e., detrusor overactivity during bladder filling due to a novel C-fiber-mediated micturition reflex and detrusor underactivity during voiding due to a damaged bladder descending pathway. This may accompany an unrelaxing sphincter (also called DSD, detrusor–sphincter dyssynergia) (Fig. 1). Therefore, we should treat MS patients both for OAB by anticholinergic medication, etc., and for large PVR by clean, intermittent catheterization (CIC).

Pathology studies have shown that the sacral spinal cord is affected in MS [62]. Although MRI scans cannot easily visualize sacral spinal cord lesions, sphincter EMG allows us to see whether sacral plaques are present in MS patients [52]. Koutsis and colleagues studied the relationship between LUTS (particularly OAB) and serum cortisol and CSF in MS patients [41]. They found low CSF 5-hydroxyindole acetic acid (5-HIAA, serotonin metabolite) and low serum cortisol. What these findings mean is still under debate, but it is postulated that the brainstem raphe nucleus (source of serotonin, which suppresses the micturition reflex) might be affected in MS patients [60]. The hypothalamus–pituitary–adrenal axis (HPA axis) is a major source of serum cortisol (e.g., cortisol is increased in depressive/stress patients). Since the HPA axis receives input from the raphe, it may change in those patients.

There are several experimental studies that have tried to simulate bladder dysfunction in MS, i.e., experimental autoimmune encephalomyelitis (EAE). Jin and colleagues reported peripheral bladder changes (interstitial cells of Cajal in the bladder wall) in EAE rats [36]. In contrast to clinical MS, where the central nervous system is the main target, EAE is known to produce severe bladder inflammation [44]. Therefore, bladder changes in EAE rats cannot simply be considered a model of the MS bladder. Studies have also shown that the bladder in EAE is correlated with motor dysfunction [3, 22] and increased descending inhibitory (via glycine and GABA)/excitatory control for detrusor under/overactivity [66]. These findings implicate future bladder treatment/prevention in MS patients.

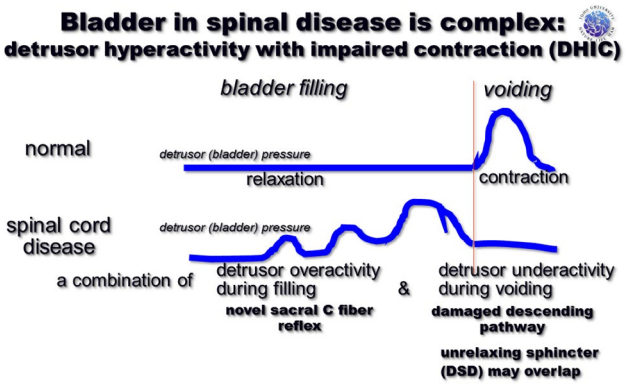

Fig. 1 Bladder in partial spinal cord disease is complex: common causes of urinary symptoms in patients with MS

Management of bladder dysfunction in MS

There are several consensus guidelines for the management of the bladder in MS [14, 16, 21, 26] (Fig. 2). These consensus recommendations can basically be applied to the majority of MS patients. It was agreed that successful management could be based on a simple algorithm which includes using reagent sticks to test for urine infection and ultrasound measurement of the PVR urine volume. This is in contrast with published guidelines which recommend cystometry. If treatment for OAB and large PVR fails, there is a possible role for cystometry. Throughout the course of their disease, patients should be offered appropriate management options for treatment of incontinence, the mainstay of which is antimuscarinics or selective beta-3 adrenergic receptor agonists [72], in combination, if necessary, with clean intermittent self-catheterization (CIC). The treatment options offered to a patient should reflect the severity of bladder dysfunction, which generally parallels the extent of neurologic disease (Fig. 3) [21, 49, 51]. Physiotherapy [8, 20, 63], desmopressin administration (desmopressin acetate nasal spray, low dose desmopressin orally disintegrated tablet) [72], tibial nerve stimulation [8], and detrusor injections of botulinum toxin A [61] can also be options.

An ileal conduit has been shown to improve quality of life in patients with advanced MS [43]. A suprapubic cystostomy (tube placement) is also a choice. However, beyond a certain point, incontinence may become refractory to all treatment options and it is at this stage that a long-term indwelling catheter should be offered. These treatments may prevent recurrent pyelonephritis and kidney dysfunction in patients [11]. However, we should keep in mind that high rates of potentially high-risk complications (e.g., infection, bladder cancer) associated with long-term indwelling catheters have been well demonstrated [33]. Future treatments may include sacral neuromodulation [1, 67] and medical cannabis [47].

Neuromyelitis optica spectrum disorder (NMOSD)

Neuromyelitis optica (NMO, Devic's disease) spectrum disorder (NMOSD) is now recognized as a novel disease entity akin to MS [6, 70]. In 1894, Eugene Devic in Lyon first described a series of patients with optic neuritis and myelitis, a monophasic manifestation and significant disability:

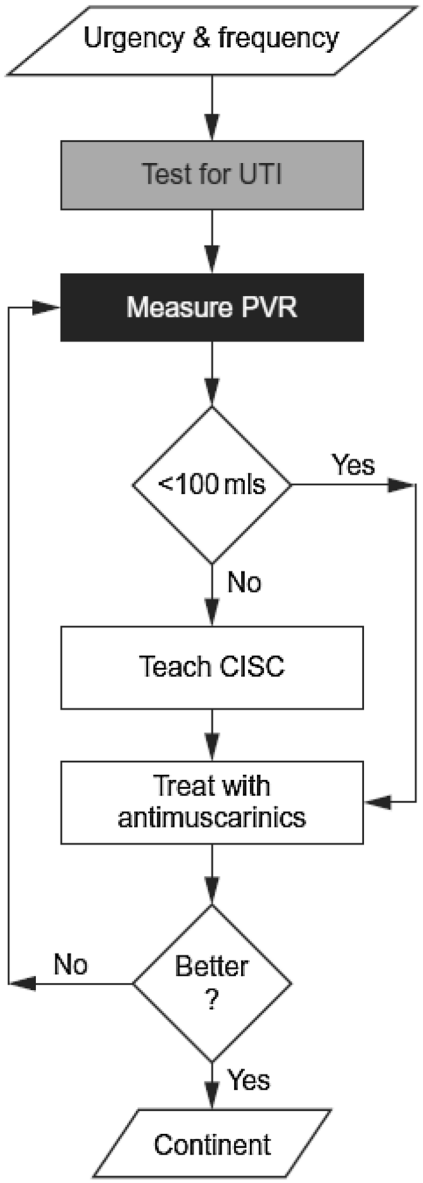

Fig. 2 Management algorithm for patients with multiple sclerosis presenting with urinary tract symptoms. CISC clean intermittent self-catheterization, PVR post-void residual volume, UTI urinary tract infection (cited from Ref. 36)

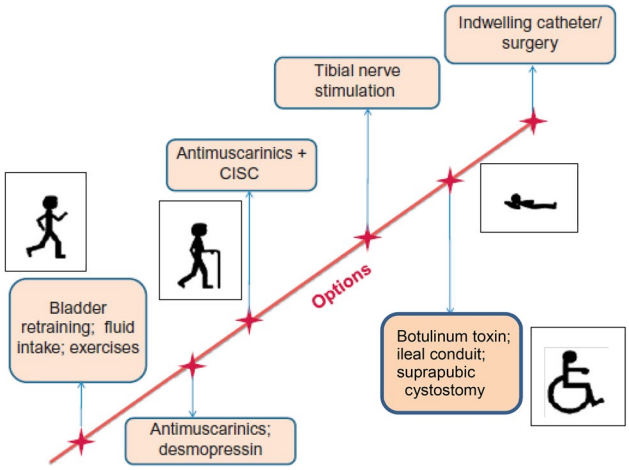

Fig. 3 Stepwise approach to managing lower urinary tract symptoms in multiple sclerosis, which often relates to the progression of disabilities (see text for details). CISC clean intermittent self-catheterization (cited and modified from Refs. 36, 51)

symptoms that were distinct from those of MS. After the association with AQP4 was discovered in 2004, white matter disease/encephalitis, etc., were included in NMOSD, which is distinct from MS with respect to immunopathogenesis and suitable treatment.

Bladder dysfunction is not uncommon in neuromyelitis optica (NMO)

Since the spinal cord is the major site of lesions in NMOSD, NLUTD might often occur in this disease, while only limited literature is available. Yamamoto et al. [71] studied 14 NMO and 34 MS patients by a lower urinary tract symptom (LUTS) questionnaire and found that LUTS were more severe in NMO than MS, and LUTS might occur independently from motor/other neurological disabilities. Mutch et al. [46] studied 60 NMO patients by a LUTS questionnaire; among them, 47 (78%) had LUTS, 35% of whom had symptoms that disappeared after resolution of their first myelitis episode, but 65% of whom had persistent symptoms. De Carvalho et al. [13] urodynamically studied 30 NMOSD. They found detrusor overactivity (DO) alone in six (20.0%), DO and DSD in 11 (36.6%), and DSD alone in seven (23.3%), while storage and voiding phases were not clearly separated. These percentages seemed almost the same as those in MS. Furlana [24] and Dimitrijevic et al. [17] showed that NMO can cause autonomic dysreflexia due to neurogenic bladder dysfunction.

Management of bladder dysfunction in NMO can be done according to that of MS, since the spinal cord is the major site of lesions in this disease as well.

Acute disseminated encephalomyelitis (ADEM)

ADEM is an immune-mediated demyelinating CNS disorder, frequently occurring during childhood [53]. ADEM is akin to MS, but it differs in being mostly monophasic, with acute onset, and distinct pathologies; in addition, occurrence is often post-infectious while the infectious etiology of MS is still under debate. MRI of ADEM typically demonstrates white matter lesions of the brain and the spinal cord, and involvement of the thalamus and basal ganglia may occur. However, in some cases ADEM presents with aseptic meningitis alone [23]. CSF analysis reveals a mild pleocytosis and

elevated protein but is often negative for oligoclonal bands. The role of biomarkers, e.g., autoantibodies like anti-myelin oligodendrocyte glycoprotein (MOG), is currently under debate. The outcome of ADEM after immunotherapy such as steroid pulse therapy is generally favorable, but cognitive deficits may persist in younger patients.

Patients with ADEM commonly have LUTS, ranging from urinary retention to urgency incontinence [7, 15, 50, 55]. LUTS appears to be related to pyramidal tract involvement, and most probably reflects the severity of the spinal cord lesion. Urodynamics commonly show detrusor overactivity in the storage phase, detrusor underactivity often with DSD (reflecting a suprasacral spinal cord lesion), and abnormal neurogenic motor unit potentials in sphincter EMG in some patients (reflecting a conus medullaris lesion). Some cases of ADEM presented with LUT dysfunction alone, either initially or as the only remaining consequence of the disease, thus suggesting that LUT innervation was selectively vulnerable in these cases [7, 55]. In some cases, abnormal F waves were recorded, suggesting conus medullaris or a radicular lesion. Jayakrishnan et al. [35] also showed that ADEM can cause autonomic dysreflexia due to neurogenic bladder dysfunction.

Management of bladder dysfunction in ADEM can be performed in the same way as in MS, since the spinal cord is one of the major sites of lesions in this disease as well.

Acute immune-mediated myelopathy

Acute myelopathy is common in both general and neurologic practice. The differential diagnosis includes compressive, structural, infectious, vascular, neoplastic, metabolic, toxic, genetic, and traumatic etiologies. Among these, noninfectious inflammatory (immune-mediated) myelopathies represent a localized form of ADEM, which is a treatable group of disorders [19, 69]. Most patients share common disabilities, e.g., motor, sensory, and bladder dysfunction. Of these, NLUTD needs particular care at the acute phase. In the most extensive cases, acute immune-mediated myelopathy simulates spinal cord injury, i.e., paraplegia, sensory loss below the level of the lesion, and loss of bladder sensation and urinary retention. MRIs of such cases typically reveal a transverse lesion. In contrast, some cases of acute myelopathy presented with LUT dysfunction alone, either initially or as the only remaining consequence of the disease [31]. MRIs of those cases show localized lesions in the lateral funiculus, where the descending spinal pathway for micturition exists [30, 37]. Urodynamics commonly show detrusor overactivity in the storage phase and detrusor underactivity, often with DSD, in the voiding phase (reflecting a suprasacral spinal cord lesion) [27, 28, 56]. Canon et al. [9] showed that acute myelopathy can cause autonomic dysreflexia due to neurogenic bladder dysfunction. Management of bladder dysfunction in acute myelopathy can be applied according to that of MS.

Meningitis-retention syndrome (MRS)

In 2005, three adult patients who developed acute co-occurrences of aseptic meningitis (AM) with urinary retention that lasted for several weeks were reported; this syndrome was named "meningitis-retention syndrome" (MRS) [58, 59]. Although one of these three patients had a mild disturbance of consciousness, the other two had no other neurological abnormalities except for slightly brisk lower extremity deep tendon reflexes. MRS has been reported mostly in Japan. However, it has been recently reported in other countries. The frequency of MRS among AM is reported to be 8% [29]. The duration of total illness and hospitalization in MRS is longer than that in AM without urinary retention. The average latencies from the onset of meningeal irritation to urinary symptoms have been reported as 0–8 days. Therefore, physicians should aware that urinary retention can follow after admission in AM patients. The duration of urinary retention in MRS is typically 7–14 days, lasting up to 10 weeks.

Mild ADEM is considered an underlying mechanism of MRS because some patients show elevated myelin basic protein in the CSF and a reversible splenial lesion on brain MRI. As it is observed in ADEM, antecedent/comorbid infections or conditions with MRS include Epstein−Barr virus, HSV2, West Nile virus, listeria, *Angiostrongylus cantonensis*, Vogt–Koyanagi–Harada disease, and herbal medicine use. In one study, CSF examination of patients showed mononuclear pleocytosis (38−370/mm) [70], normal to increased protein content (up to 260 mg/dl), and normal to mildly decreased glucose content (up to 33% of that in the serum). It was recently reported that elevated CSF adenosine deaminase (ADA) levels or a decreased CSF/serum glucose ratio may be predictive factors for MRS development [29] (Fig. 4).

Urodynamics consistently show that patients affected with MRS have detrusor underactivity during retention; two patients had an unrelaxing sphincter as well [5, 9, 10, 29, 32, 34, 39, 42, 45, 58]. Detrusor underactivity originates from various lesion sites along the neural axis, most commonly peripheral nervous system (PNS) lesions. However, CNS lesions that affect the spinal cord or the brain can also cause detrusor underactivity, which is seen in the acute-shock phase of patients. Tateno et al. encountered a man with MRS in whom urodynamics was performed twice. In that case, an initially underactive detrusor became overactive after a 4-month period, suggesting an upper motor neuron bladder dysfunction [64].

The term "Elsberg syndrome" is occasionally assigned to urinary retention of diverse etiologies. In contrast, Kennedy,

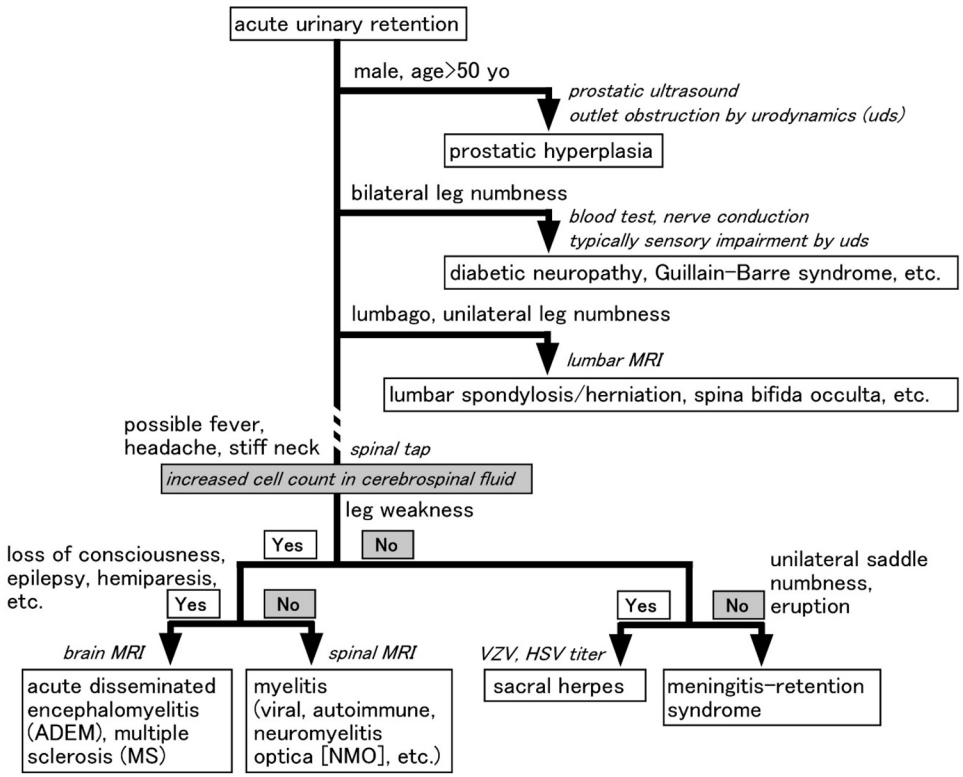

Fig. 4 Algorithm to diagnose meningitis-retention syndrome and related conditions. MRI magnetic resonance imaging, yo years old, HSV herpes simplex virus, VZV varicella zoster virus (cited from Ref. 59)

Elsberg, and Lambert (1913) reported five cases of pathology-demonstrated cauda equina radiculitis [38]. Their clinical/pathological features were rare CSF abnormalities, no clinical meningitis, a subacute/chronic course, presentation with typical cauda equina motor sensory autonomic syndrome, Wallerian degeneration of the spinal afferent tracts, and mild upper motor neuron signs. All these are different from those of MRS. The exact cause of these cases is uncertain. However, they resemble paraneoplastic/autoimmune lumbosacral radiculoplexus neuropathy.

While MS, NMOSD, ADEM, and AM all require steroid pulse or extensive immune therapy, MRS has a benign and self-remitting course, and the effectiveness of immune treatments (e.g., steroid pulse therapy) remains unclear, although such treatments may shorten the duration of the disease. Management of acute urinary retention is necessary to avoid bladder injury due to overdistension. Since AM is common in general/neurological practice, MRS is more common than was previously believed; hence, it is important for physicians to be on the lookout for such patients.

Conclusion

Bladder dysfunction is common in MS, NMOSD, ADEM, AM, and MRS, all of which are immune-mediated CNS disorders affecting the spinal cord. Spinal cord lesions typically lead to motor, sensory, and bladder autonomic dysfunction, and a urodynamic study may reveal DHIC—namely, detrusor overactivity [overactive bladder with/without incontinence] during bladder filling and detrusor underactivity [large post-void residuals/urinary retention] during voiding—with DSD (unrelaxing sphincter on voiding). Because of this, we should care for both overactive bladder and post-void residuals; i.e., treat the formerwith antimuscarinics, etc., and the latter with clean, intermittent self-catheterization. A consensus guideline for treatment of LUTS in MS is also available. These management practices may improve quality of life in affected patients.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

Ethical approval This article conforms to the ethical standards of the declaration of Helsinki.

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