Multiple Sclerosis

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62.1 Introduction

In 1868, Jean-Martin Charcot in Paris provided the first detailed pathology of "la sclérose en plaques," characteristic periventricular white matter lesions now appreciated as a pathological hallmark of multiple sclerosis (MS), the most common immune-mediated disease of the central nervous system (CNS) [1]. MS is characterized by exacerbations of neurological dysfunction due to inflammatory demyelination. Neurologic symptoms typically present in young adulthood and vary based on the site of inflammation, although disorders from hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and vision are common. MS occurs more frequently in women and its development is complex—genetics, hormones, geography, vitamin D, and viral exposure all play roles. Neuroimaging and cerebrospinal fluid (CSF) abnormalities, particularly oligoclonal band, help diagnosing early MS. In the past decade, there has been a remarkable expansion in disease modifying therapy 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. In particular, the treatment of bladder dysfunction remains a clinical challenge while it becomes a great disability in affected individuals and annual health care cost [1].

Neuromyelitis optica (NMO) spectrum disorder (NMOSD) is now recognized a novel disease entity akin to MS [2, 3]. In 1894, Eugene Devic in Lyon first described a series of patients with optic neuritis and myelitis, a monophasic manifestation and significant disability unlike multiple sclerosis. It was once felt that NMO and MS represented one disease entity, with variable phenotypes and expression. This notion, however, was replaced by the discovery NMO-IgG antibody that selectively binds aquaporin (AQP) 4 in 2004. Not only optic neuritis and myelitis, but also white matter disease/encephalitis etc. may occur with AQP4, thus these diseases are coined NMOSD. Further evidences suggest that NMOSD is distinct with respect to immunopathogenesis and suitable treatment. Frequency of MS vs. NMO is thought to be MS dominant in European/North America, while NMO dominant in Asia [4, 5]. More recently, myelin-oligodendrocyte glycoprotein (MOG)-IgG has been identified. MOG disease is now being separated from MS and NMOSD [6]. Clinical spectrum of MOG disease also covers optic neuritis, myelitis, and acute disseminated encephalomyelitis (ADEM) [6]. Therefore, bladder dysfunction might have often occurred in NMOSD and related diseases, while only limited literature is available.

This article reviews bladder dysfunction in MS, NMOSD, ADEM (monophasic, acute onset of encephalitis and myelitis) [7]. acute immune-mediated myelopathy as a localized form of ADEM [8, 9], and a newer concept 'meningitis-retention syndrome (MRS)' as a mild form of ADEM [10] with particular reference to lower urinary tract symptoms (LUTS), urodynamic finding and sphincter electromyography (EMG), and patient management.

62.2 Multiple Sclerosis

62.2.1 Bladder Dysfunction Is Common MS

Several control studies indicated the frequency of lower urinary tract symptoms (LUTS) in MS patients being up to 70% [11, 12]. 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 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 cord lesion). Overflow incontinence secondarily occurs after large post-void

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residuals. Nocturnal frequency (nocturia) comes from not only neurogenic 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 rarely hypothalamic lesions (loss of nocturnal increase in arginin vasopressin of central origin)). Nocturnal polyuria can be assessed by bladder diary. These storage symptoms significantly affect the 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 [11, 12].

62.2.2 Both Overactive Bladder and Large Post-Void Residuals Occur in MS

Studies have shown that MS patients have both overactive bladder and large PVR, and the quality of life (QOL) index in MS patients was significantly higher (i.e., worse) for bladder dysfunction than that in controls. Many of them show large PVR urine volume > 100 mL.

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 allows us to assume the site of lesions, and sphincter EMG enable us to assess particularly the lumbosacral cord functions. Neuroimaging and pathology studies showed that the commonly affected regions in MS are: hemispherical motor/sensory, cerebellar, brainstem, spinal cord, and optic nerves. Among these, medial/prefrontal/insular cortex [13] (total brain volume [14]) (basal ganglia, hypothalamus), cerebellum [13] brainstem (midbrain [13, 15] pons [13, 16, 17]) and cervicothoracic spinal cord [14, 17] are all relevant to micturition function. Among these, brain lesions cause detrusor overactivity; sacral/peripheral lesions cause detrusor underactivity; and partial spinal cord lesions show a complex bladder behavior, and the spinal cord is very often affected in MS patients. This bladder behavior in spinal cord lesion is called DHIC, detrusor hyperactivity with impaired contraction, i.e., detrusor overactivity during bladder filling due to a novel C-fiber mediated micturition reflex, while detrusor underactivity during voiding due to damaged bladder descending pathway. This may accompany unrelaxing sphincter (also called DSD, detrusor-sphincter dyssynergia) (Fig. 62.1). Therefore, we should treat MS patients for not only OAB by anticholinergic medication etc., but also for large PVR by clean, intermittent catheterization (CIC) together. Sphincter electromyography (EMG) allows us to see whether sacral plaques are present in MS patients. Koutsis and colleagues studied relationship between LUTS (particularly OAB) with serum and cerebrospinal fluid (CSF) in MS patients [18]. They found low CSF 5-hydroxyindole acetic acid (5-HIAA, serotonin metabolite), and low

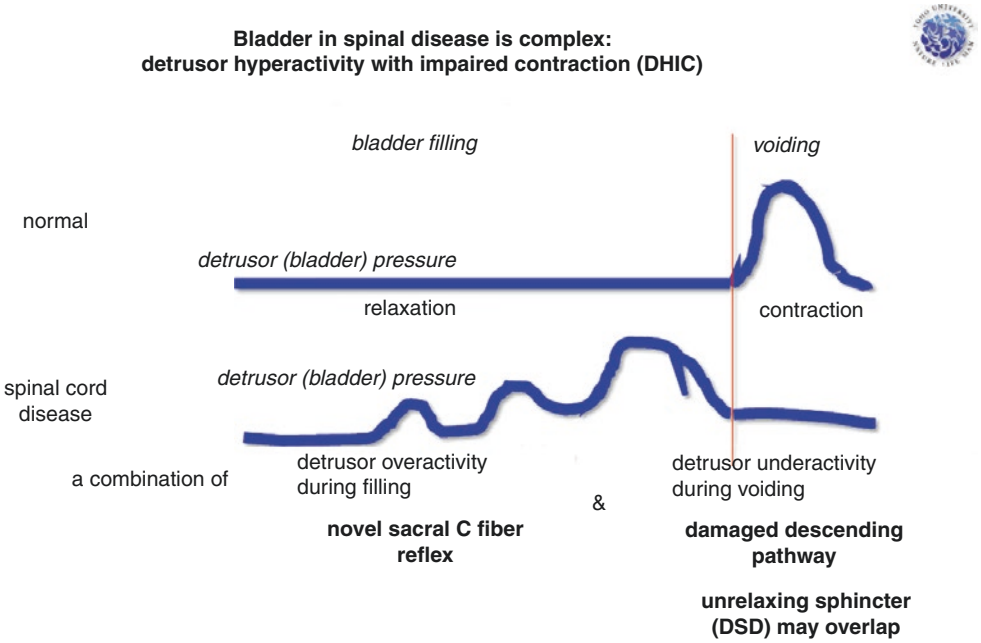

Fig. 62.1 Bladder in partial spinal cord disease is complex: a common cause of urinary symptoms in patients with MS. Both storage and voiding symptoms in patients with MSA were significantly worse than age matched controls. Particularly they had a significantly higher prevalence of voiding symptoms, particularly retardation in initiating urination (hesitancy) than the controls

serum cortisol. What do these findings mean is a debate, but it is postulated that brainstem raphe nucleus (source of serotonin, which suppresses the micturition reflex) might be affected in MS patients [18]. Hypothalamo-pituitary-adrenal axis (HPA axis) is a major source of serum cortisol (cortisol increased in depressive/stress patients). Since HPA axis receive input from the raphe, it may change in those patients.

There are experimental studies that simulate bladder dysfunction in MS, i.e., experimental autoimmune encephalomyelitis (EAE). Some studies showed peripheral bladder changes [19], whether or not they are secondary to CNS lesions. There seem some limitations in these studies, because EAE may produce severe bladder inflammation that is not seen in clinical MS [20]. EAE studies have shown that bladder correlated with motor [21–23]; and increased descending inhibitory (via glycine and GABA)/excitatory control for detrusor under/over-activity [22]. These findings implicated future bladder treatment/prevention in MS patients.

62.2.3 Management of Bladder Dysfunction in MS

There is a United Kingdom (UK) consensus on the management of the bladder in MS as edited by Clare Fowler [24] (Fig. 62.2). This 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 post-void residual (PVR) urine volume. This is in contrast with published guidelines which recommend cystometry. If treatment fails for OAB and large PVR, there seems to be a place to perform 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, 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. 62.3) [11, 12, 24]. Physiotherapy [25–27] desmopression [28], tibial nerve stimulation [27] detrusor injections of botulinum toxin A [29] can also be options. 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 the patients [30]. Future treatments may include sacral neuromodulation [31, 32] and medical cannabis [33].

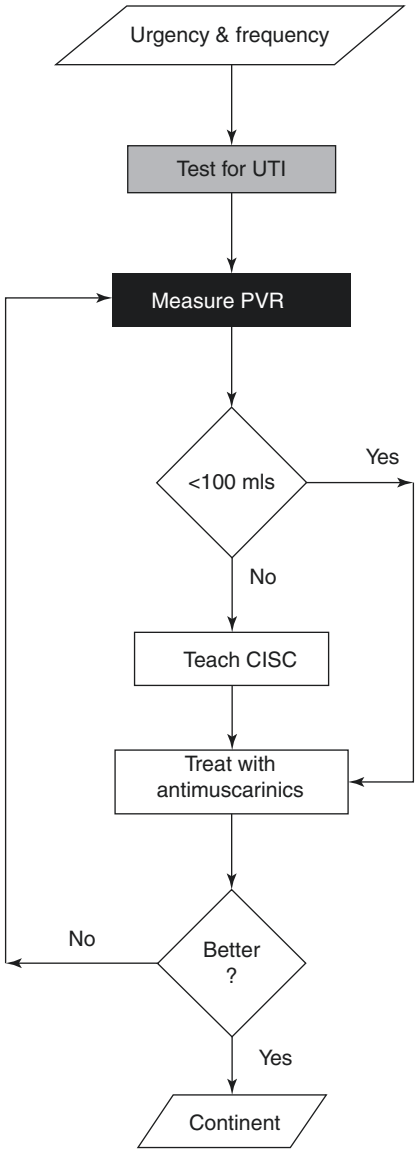

Fig. 62.2 Management algorithm for patients with multiple sclerosis presenting with urinary tract symptoms. *CISC* clean intermittent self catheterisation, *PVR* post void residual volume, *UTI* urinary tract infection. Reprint with permission from Franken et al. [23]

62.3 Neuomyelitis Optica Spectrum Disorder (NMOSD)

62.3.1 Bladder Dysfunction Is Not Uncommon in Neuromyelitis Optica (NMO)

Since spinal cord is the major site of lesions in NMOSD, bladder dysfunction might have often occurred in this disease, while only limited literature is available. Yamamoto et al. [34] 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 disabili-

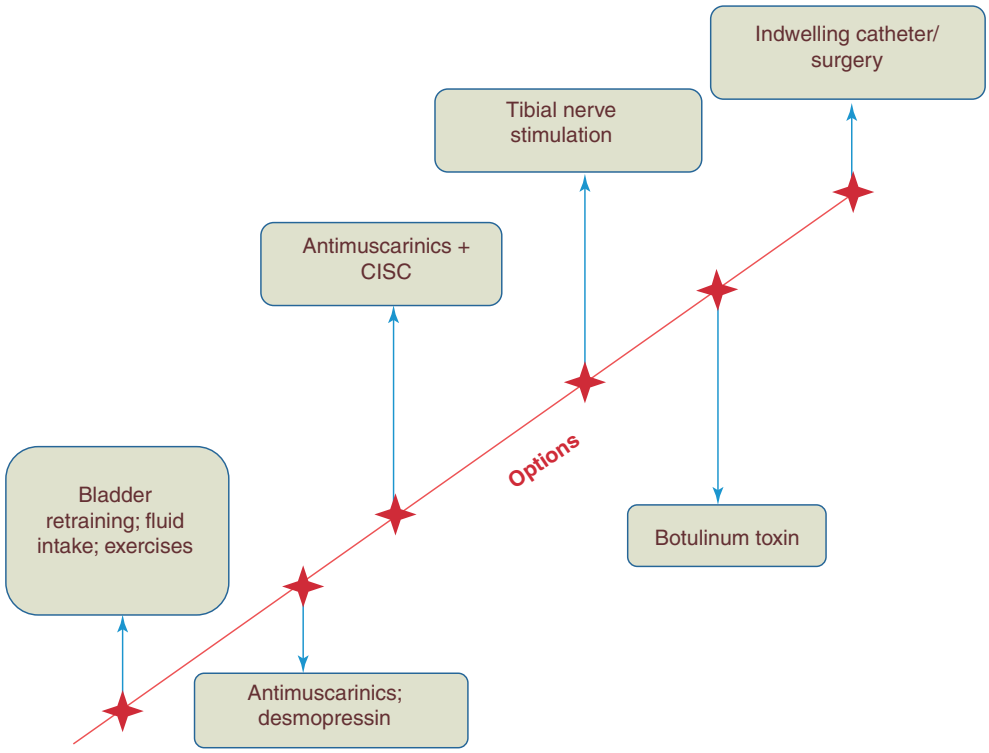

Fig. 62.3 Management algorithm for patients with multiple sclerosis presenting with urinary tract symptoms. *CISC* clean intermittent self catheterisation, *PVR* post void residual volume, *UTI* urinary tract infection. Reprint with permission from Phé et al. [11]

ties. Mutch et al. [35] studied 60 NMO by a LUTS questionnaire; and 78% had LUTS, 35% of them disappeared but in the remaining 65%, they persisted after resolution of first myelitis episode. De Carvalho et al. [36] urodynamically studied 30 NMOSD. They found detrusor overactivity (DO) alone in six (20.0%), DO and detrusor-sphincter dyssynergia (DSD) in 11 (36.6%), and DSD alone in seven (23.3%), while storage and voiding phases are not clearly separated. These findings seemed almost the same with those with MS. Furlana [37] and Dimitrijevic [38] 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.

62.4 Acute Disseminated Encephalomyelitis (ADEM)

ADEM is an immune-mediated demyelinating central nervous system (CNS) disorder with predilection to childhood [7]. ADEM is akin to MS; occurrence often postinfectious, but the differences include mostly monophasic, acute onset, and distinct pathologies. MRI of ADEM typically demonstrates white matter lesions of the brain and the spinal cord, and involvement of thalamus and basal ganglia may occur. However, in some cases ADEM presents with aseptic meningitis alone [39]. CSF analysis reveals a mild pleocytosis and elevated protein, but is often negative for oligoclonal band. The role of biomarkers, e.g., autoantibodies like anti myelin oligodendrocyte glycoprotein (MOG) is currently under debate. After immunotherapy such as steroid pulse therapy, outcome of ADEM is generally favorable, but cognitive deficits may persist in younger patients.

Patients with ADEM commonly have LUTS, which varies from urinary retention to urgency incontinence [40–42]. 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; and detrusor underactivity often with detrusor-sphincter dyssynergia (DSD) (reflecting a suprasacral spinal cord lesion); and neurogenic motor unit potentials in sphincter EMG in some patients (reflecting a conus 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 [41, 43]. In some cases, abnormal F-waves were recorded, suggesting conus or a radicular lesion. Jayakrishnan [44] also showed that ADEM can cause autonomic dysreflexia due to neurogenic bladder dysfunction.

Management of bladder dysfunction in ADEM can be applied according to that of MS, since the spinal cord is one of the major sites of lesions in this disease as well.

62.5 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 [8, 9]. Most patients share common disabilities, e.g., motor, sensory, and bladder dysfunction. Of these, bladder dysfunction 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 lesion, and loss of bladder sensation and urinary retention. MRI of such cases demonstrates 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 [45]. MRI of such cases shows localized lesions in the lateral funiculus, where the spinal descending pathway for micturition exists [46, 47]. Urodynamics commonly show detrusor overactivity in the storage phase; and detrusor underactivity often with detrusor-sphincter dyssynergia (DSD) (reflecting a suprasacral spinal cord lesion) [48–50]. Canon [51] 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.

62.6 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) [10, 52]. 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 also in other countries. Recently, frequency of MRS among AM is reported to be 8% [53]. The duration of total illness and hospitalization in MRS was longer than that in AM without urinary retention. Average latencies from the onset of meningeal irritation to urinary symptoms were 0–8 days. Therefore physicians should aware that urinary retention can follow after admission in AM patients. The duration of urinary retention in MRS was mostly 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 cerebrospinal fluid (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. The CSF examination of the patients showed a mononuclear pleocytosis of 38–370/mm[3], 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). Recently, elevated CSF adenosine deaminase (ADA) levels or decreased CSF/serum glucose ratio may be predictive factors for MRS development [53] (Fig. 62.4).

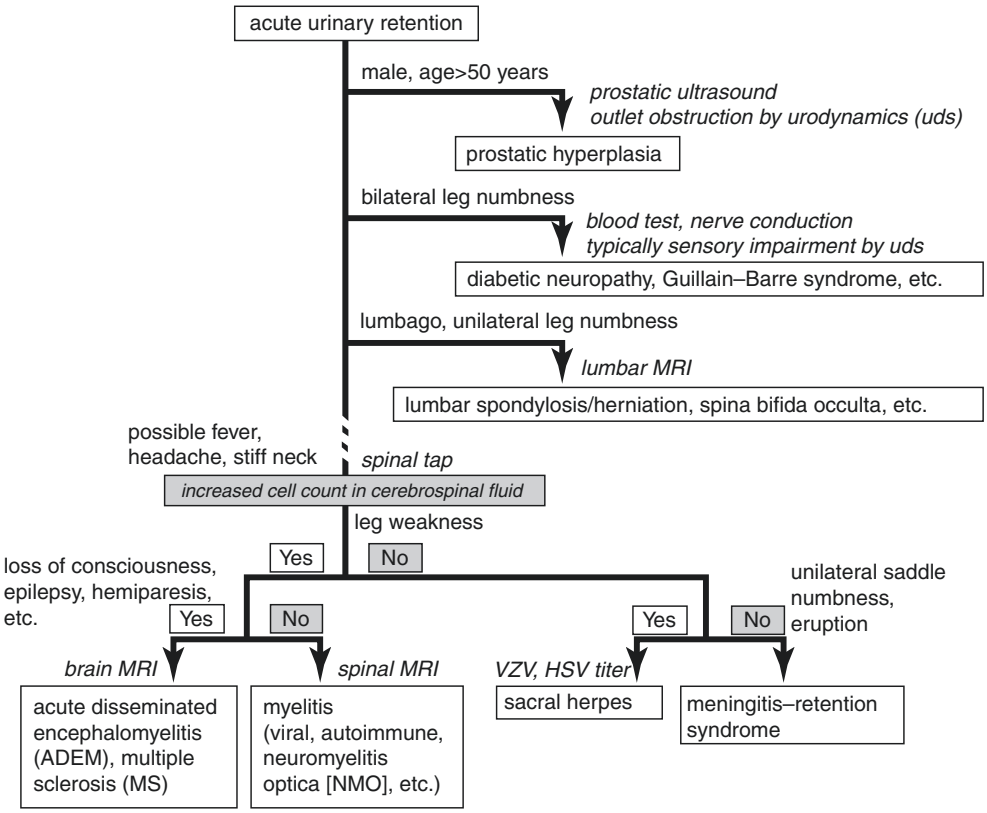

Fig. 62.4 Algorithm to diagnose meningitis–retention syndrome and related conditions. *yo* years old, *MRI* magnetic resonance imaging, *HSV* herpes simplex virus, *VZV* varicella zoster virus. Reprint with permission from Sakakibara et al. [10]

Urodynamics show that all patients examined had detrusor underactivity when on retention, and two patients had an unrelaxing sphincter together [51, 53–60]. Detrusor underactivity originates from various lesion sites along the neural axis; most commonly, PNS lesions are observed. 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 a 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 [61].

The term "Elsberg syndrome" is occasionally assigned to urinary retention of diverse etiologies. In contrast, Kennedy, Elsberg, and Lambert (1913) reported five cases of pathology-demonstrated cauda equina radiculitis [62]. 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 are uncertain. However, they resemble paraneoplastic/autoimmune lumbosacral radiculoplexus neuropathy.

While MS, NMOSD, ADEM and AM need 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, and do not miss such MRS patients.

62.7 Summary

Urinary dysfunction is common in NMOSD, ADEM, AM and MRS, immune-mediated CNS disorders particularly affecting the spinal cord. Spinal cord lesion typically leads to motor, sensory, and bladder autonomic dysfunction, and urodynamic study may reveal DHIC (detrusor overactivity [overactive bladder with/without incontinence] during bladder filling, while 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; e.g., the former antimuscarinics etc., and the latter clean, intermittent self-catheterization. In MS, consensus guideline is also available. These management may allow maximizing the quality of life in the patients.

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