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Autonomic dysfunction in multiple sclerosis and neuromyelitis optica spectrum disorder

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Autonomic dysfunction occurs frequently in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). Patients with either condition may present with autonomic symptoms such as bladder, sexual, cardiovascular, thermoregulatory, and gastrointestinal dysfunction, and fatigue, but autonomic symptoms that affect quality of life are underrecognized in clinical practice. The immunopathogenesis of MS has been considered to be associated with autonomic dysfunction. Applying appropriate treatment strategies for autonomic dysfunction is important to improve the quality of life of patients. Here we review autonomic dysfunction and how this is managed in patients with MS and NMOSD.

Key words: Autonomic nervous system diseases; Multiple sclerosis; Neuromyelitis optica spectrum disorder; CNS demyelinating autoimmune diseases

INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are inflammatory demyelinating disorders of the central nervous system. Neurological symptoms such as motor weakness, sensory changes, gait disturbance, and decreased visual acuity directly affect the disabilities and can be easily detected. In contrast, although autonomic dysfunction may present in the early stages of MS and NMOSD, it can be underrecognized by patients or overlooked by clinicians.[1,2] Furthermore, since autonomic dysfunction is associated with fatigue that can decrease the quality of life, it requires early detection and appropriate management.[3,4] Lesions that disrupt the anatomical pathway of the autonomic nervous system (ANS) or interactions between the ANS and an altered immune

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system in patients with MS (pwMS) can cause autonomic dysfunction.[5] Immunotherapies and drugs for symptomatic MS and NMOSD treatment can also cause or exacerbate autonomic symptoms. This review aimed to determine the epidemiological, pathophysiological, and clinical characteristics and the appropriate management of autonomic dysfunction in pwMS or NMOSD.

PATHOPHYSIOLOGY OF AUTONOMIC DYSFUNCTION IN MS AND NMOSD

There are two possible mechanisms of autonomic dysfunction in MS and NMOSD. First, the lesions in MS or NMOSD can disrupt the anatomical pathways of the ANS. Several studies have found an association between autonomic dysfunction and lesion location. Brainstem lesions in magnetic resonance imaging (MRI) are associated with autonomic dysfunction (particularly sympathetic cardiovascular dysfunction) in MS.[2,6] Cervical cord atrophy is also correlated with autonomic dysfunction, suggesting that autonomic dysfunction is related to secondary axonal loss rather than demyelination itself.[7] In NMOSD, lesions often occur in the diencephalon, brainstem surrounding the third and fourth ventricles, and spinal cord surrounding the central canal with a high aquaporin-4 channel density. Dysregulated thermoregulation and sleep-cycle disturbance have been observed in patients with hypothalamic lesions.[8,9]

Second, peripheral blood monocyte cells altering interactions between the immune system and ANS is another possible mechanism of autonomic dysfunction.[10] Peripheral blood lymphocytes, neurons, and adrenal cells can produce catecholamines (dopamine, epinephrine, and norepinephrine) that act as autocrine or paracrine mediators in the immune system and transmitters between the immune cells and nerves.[11] The adrenergic receptor is increased and impaired in the lymphocytes in MS, and the level of tyrosine hydroxylase, a rate-limiting enzyme in catecholamine synthesis, is decreased, which results in altered catecholamine production. This may explain the correlation between sympathetic dysfunction and disease activity in MS.[12]

AUTONOMIC DYSFUNCTION IN MS

Autonomic dysfunction reportedly occurs in 45-85% of pwMS,[7,13] with the frequency differing according to the clinical type of MS. Autonomic dysfunction is more frequent in progressive MS (PMS) than in relapsing-remitting MS (RRMS).[7] A prospective study of 75 patients found that autonomic symptoms appeared in 75% of primary PMS, 60% of secondary PMS, and 30% of RRMS cases, and abnormalities on the autonomic function test (AFT) occurred in 80%, 52%, and 30%, respectively, with significant differences among them. Autonomic dysfunction has also been found in clinically isolated syndrome (CIS) and has been suggested as a marker associated with its prognosis. A prospective study of 84 patients with CIS found that postural orthostatic tachycardia syndrome (POTS) was a significant predictor of conversion to MS within 6 months (odds ratio = 12.4, 95% confidence interval = 1.13-136.6; $p = 0.040$).[14] A 2-year follow-up prospective study of 94 patients with CIS found that the hazard for new relapse in patients with CIS with a high composite autonomic system score-31 (COMPASS-31; >7.32) was 2.7 times higher than that of patients with a low score (<7.32), suggesting that the burden from autonomic symptoms predicts disease activity in early MS.[1]

Bladder dysfunction

Bladder dysfunction or lower urinary tract symptoms frequently occur in MS: in 30-75% of cases in the early stage and in >90% in the advanced stage. Furthermore, bladder dysfunction is more common in PMS than in RRMS.[15,16] Severe disability status and long disease duration have frequently been associated with bladder dysfunction.[17] The bladder symptoms vary with the lesion location in the micturition pathway. Lesions above the pontine micturition center can cause detrusor muscle hyperactivity by inhibiting the inhibitory function of the micturition reflex, which results in urinary urgency. Spinal lesions in the cervical and thoracic cord provoke detrusor hyperactivity and detrusor-sphincter dyssynergia. However, urinary symptoms have weak correlations with lesion location in the early disease stage, which suggests that urinary symptoms in the early stage of MS can be induced by the interactions between components of an altered immune system and the ANS.[18] Urinary retention is less common than urgency, but can cause hydronephrosis,

chronic renal failure, and urinary tract infection. Incontinence without awareness may occur during the late stage. In a urodynamic study of 90 pwMS (mean age of 44.5 years, and including 64 females) with voiding complaints, detrusor hyperreflexiawith or without impaired contractility was common (63.3%) but detrusor areflexia was rare (14.4%).[19] The pattern of voiding dysfunction was not correlated with international prostate symptom scores. Furthermore, the results of that urodynamic study might not be correlated with bladder functional system scores (part of the expanded disability severity scale [EDSS]), and about 12% of pwMS have a postmicturition residual volume of >100 mL.[20] Since it is difficult to identify the type of voiding dysfunction from only the voiding-symptom complaints of patients, a urodynamic study is needed to confirm the pattern of voiding dysfunction and how to treat it appropriately.

The targets of treating urinary symptoms are to (1) inhibit bladder hyperactivity and (2) relax the sphincter.[21] Anticholinergic and alpha-adrenergic blockers can be used. To inhibit the detrusor hyperactivity, a parasympathetic suppressor such as oxybutynin can also be used. Due to the risk of residual urine accumulation, the residual urine volume should be monitored after treatment is initiated. Intranasal desmopressin can reduce frequent urination, and an onabotulinum toxin injection might be attempted if bladder hyperactivity is not well controlled by oral medications.[15] Suprapubic vibration and the Crede maneuver may also be attempted for incomplete bladder emptying. Clean intermittent catheterization or permanent suprapubic catheter insertion should be considered if the bladder dysfunction is severe.

Gastrointestinal dysfunction

Gastrointestinal dysfunction occurs in 45-68% of pwMS,[10] and is a major cause of poor quality of life and social isolation.[22] It is common in PMS similar to bladder dysfunction and has a positive correlation with urinary symptoms and the EDSS score.[21] Constipation and diarrhea are the most common gastrointestinal symptoms, of which the main pathophysiology is pelvic-floor dyssynergia due to cortical modulation dysfunction in the spinal reflex caused by spinal cord lesions.[15] Fecal incontinence often occurs as other bowel symptoms progress, but may also result from a dysfunctional external anal sphincter.[23] Upper gastrointestinal symptoms include delayed gastric emptying time, nausea, vomiting, and gastroesophageal reflux. Anorectal manometry, colonic transit time study, and external anal sphincter examination using electromyography can be performed to evaluate lower gastrointestinal function. Delayed emptying time can be observed in the gastric emptying scintigraphy for upper gastrointestinal evaluation, which is associated with perceived fullness, hiccups, vomiting, and gastroesophageal reflux disease.[24]

The aims of treating gastrointestinal symptoms are to improve the symptoms and quality of life of the patient. Medications including osmotic and stimulant laxatives, stool softeners, and bulk-forming laxatives can be used. Adequate physical activity, fiber-rich foods, and sufficient fluid intake should also be encouraged.[21] Biofeedback retraining can help control constipation or fecal incontinence by improving pelvic-floor dyssynergia. Trials with antimotility agents, rectal stimulants, transanal irrigation, and bacterial stools liquefaction may be helpful in some cases.

Sexual dysfunction

The frequency of sexual dysfunction has been found to reach 80% in pwMS.[25] Sexual dysfunction is more common in RRMS than in PMS and may also be associated with disease severity, but this is controversial.[15] Patients commonly complain of sexual hypoactivity or decreased libido. Erectile dysfunction related to parasympathetic dysfunction in male patients has been found in 26-72% of cases, and was also correlated with both bladder and bowel dysfunction. Ejaculation abnormalities due to sympathetic dysfunction have been found in 37-50% of pwMS.[26] The main complaint among female patients is the difficulty to achieve orgasm, followed by decreased lubrication and genital sensory disturbance. The frequency of sexual dysfunction in females increases with the level of disability, but no association with bladder dysfunction has been found. Decreased memory and concentration were more common in patients with sexual dysfunction, and were correlated with decreased libido/lubrication and erectile dysfunction.[27]

Multiple factors can underlie sexual dysfunction. In addition to lesions that disrupt the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, motor disability, fatigue, medications, and psychological factors can cause sexual dysfunction.[28] Although there is no specific

diagnostic procedure or AFT for sexual dysfunction, abnormal findings may identified on a sympathetic skin response test in the genital area, and abnormalities may be observed in the pudendal nerve somatosensory evoked potentials.[21]

Phosphodiesterase 5 inhibitors and apomorphine hydrochloride sublingual are commonly used to treat erectile dysfunction. The medicated urethral system for erection may be applied if the medications are contraindicated. In females, vaginal lubrication can be improved by using topical hormonal agents such as estrogen or methyltestosterone.[29]

Thermoregulatory dysfunction

Thermoregulatory dysfunction can be caused by demyelinating lesions in the spinal cord, and results in impaired preganglionic output and sudomotor ganglion neurons. Another possible mechanism is the disruption of central sudomotor pathways that involve the preoptic region of the hypothalamus and tracts to the intermediolateral column of the spinal cord.[21]

Cold sensitivity and anhidrosis are common in the lower extremities, and episodic hypothermia due to lesions in the periventricular hypothalamus and brainstem have been observed.[30,31] Neurological symptoms may also worsen with changes in body temperature, which is known as the Uhthoff phenomenon, wherein a 0.5℃ change in core body temperature affects sensory, cognitive, and autonomic symptoms.[32] This may be due to changes in axons affected by demyelination and changes in ion channels caused by changes in body temperature, which result in diminished or blocked transmission through those fibers. Heat sensitivity in exercise has also been frequently observed. During exercise, pwMS had delayed sweating onset and a more than twofold increment in the rectal temperature change compared with health subjects.[33] Heat sensitivity also affects cognitive, motor, and sensory functions. Cognitive deteriorations include the impairment of sustained attention, slow reaction times, and increased cognitive errors. Motor impairments include fatigue, balance deficits, spasticity, muscle weakness, and dysarthria.

Thermoregulatory sweat tests (TST) are used to evaluate thermoregulatory function. About 42% of pwMS have abnormal sweating responses in TST.[34] Decreased sweating in TST presents with various patterns, from a complete absence in the whole body to a reduction in the focal area.[35,36] However, decreased sweat secretion was common in the lower limbs. Sweating impairment was correlated with MS severity.

Cold-water ingestion as a treatment cannot lower deep or skin temperature during exercise in pwMS with heat sensitivity, but it can increase exercise time by 30%, and cooling before and during exercise helps to improve the exercise capacity.[37]

Cardiovascular autonomic dysfunction

Cardiovascular autonomic dysfunction (CAD) is found in two-thirds of pwMS, while orthostatic hypotension (OH) is found in half of them.[38] Lesions in the hypothalamus, midbrain, limbic structures, insula, parietal lobe, and spinal cord (cervical or cervicothoracic) may induce CAD. CAD is often only found on the AFT in patients who have not complained of symptoms, whereas the stress-induced cardiomyopathy (Takotsubo cardiomyopathy) has been indicated as the first symptom of MS.[39] The risk of arrhythmias such as atrial fibrillation increases during relapse, and neurogenic pulmonary edema may also be associated with brainstem lesions.[39,40] Cardiac symptoms may be a sign of MS progression, since elevated catecholamine levels in acute lesions can induce necrosis of cardiac myocytes and disruption of the intracardiac conduction system can lead to bradycardia or atrial fibrillation.[41,42]

Sympathetic dysfunction is the most common dysfunction in CIS (43%), followed by sudomotor (33%) and parasympathetic (5%) dysfunction. More than 50% of patients with RRMS and more than 90% of patients with PMS present cardiovascular autonomic dysfunction, and the latter patients have a higher composite autonomic severity score (CASS) and lower heart rate variability (HRV).[43] As in CIS, sympathetic dysfunction is common in the early stage of RRMS due to decreased norepinephrine synthesis in brainstem (especially in the locus coeruleus), which results in reduced exercise capacity due to blunted blood pressure response to exercise. Moreover, sympathetic nervous system dysfunction is related to immune system dysregulation, but parasympathetic dysfunction is caused by the lesion itself.[12] Parasympathetic dysfunction is therefore more common in the advanced stages and is correlated with the EDSS score.

The hand grip test, blood pressure response to the Valsalva maneuver, and tilt-table test can be used to evaluate the sympathetic nervous system. The deep breathing test and

the Valsalva maneuver are used to evaluate HRV as a measure of parasympathetic function. Significant differences have been found between active and inactive MS.[21] Spectral analysis of HRV is a valuable noninvasive measurement that reflects vagal and sympathetic activity, sympathovagal balance, and sympathetic reactivity.[44] Disease duration is associated with altered sympathovagal balance. Sympathovagal balance was more disrupted in PMS than in healthy controls and patients with RRMS, indicating high basal sympathetic activity and sympathetic reactivity failure during orthostatic stress. Impaired pressor response was also observed in isometric exercise due to impaired sympathetic control for blood-vessel tone.[45] Reduced HRV in 24-hour Holter monitoring compared with healthy controls was found regardless of the lesion location in MRI, the EDSS score, or the number of attacks.[46]

Severe disease-modifying drugs used in pwMS can influence autonomic cardiovascular function. Interferon-β may affect sympathetic regulation depending on the disease stage and the age, sex, and hormonal status of the patient, but fingolimod, mitoxantrone, and high doses of steroids adversely affect cardiovascular function.[10] OH management includes increasing blood volume and peripheral vessel tone through adequate fluid intake, wearing elastic stockings, the counterpressure maneuver, and medications such as fludrocortisone or a sympathomimetic agent.

Fatigue

Fatigue can occur from the early stage of MS, and can be caused by various factors including neurological, immunological, and neuroendocrine ones; autonomic disturbance may also contribute to fatigue.[47] However, no correlation was found between fatigue and disease severity or duration. Previous studies suggest that decreased vagal function and normal-to-low sympathetic activity are related to perceived fatigue.[10] According to a study that used self-reports of the COMPASS-31 score, the pupillomotor, orthostatic intolerance, and bladder dysfunction domains are associated with fatigue.[47] Lesions in the amygdala, hypothalamus, insular cortex, and anterior cingulate cortex were related to perceived fatigue in pwMS.

Physical conditioning, avoiding smoking cigarettes, and improving sleep hygiene should be recommended to improve fatigue. Medications that can be used for treatment include amantadine, modafinil, and interleukin-1β antagonist that can reduce vagus nerve signaling.[21]

Sleep disorder

Moderate or severe sleep disturbances are present in more than 50% of pwMS, with females having a higher risk than males.[48] The main complaint is difficulty in initiating and maintaining sleep. The main causes of insomnia include nocturnal muscle spasms, periodic limb movements (PLMD), restless leg syndrome (RLS), nocturia, medication effect, and psychiatric illnesses such as depression. The exact prevalence rates of PLMD and RLS in pwMS are unknown, but both have been indicated to be more common than in the general population. Treatments include medications that are conventionally used to treat RLS and PLMD.

Medications for MS can aggravate the sleep disturbance.[49] Interferon β1-b reportedly causes insomnia in 3-17% of pwMS. High-dose methylprednisolone may affect the sleep architecture by decreasing rapid eye movement sleep latency and density, and decreasing slow-wave sleep. The prevalence of obstructive sleep apnea in pwMS does not differ from that in the general population, but demyelinating lesions in the medullary reticular formation have the potential to affect nocturnal respiratory effort, which leads to sleep-disordered breathing and even nocturnal death (Ondine's curse).[50]

An association has also been found between narcolepsy and MS, both of which are strongly linked to similar human leukocyte antigen expression. Hypocretin-1 in the cerebrospinal fluid may decrease in patients with hypothalamic lesions, which results in somnolence. Modafinil can significantly improve excessive daytime somnolence associated with narcolepsy.

AUTONOMIC DYSFUNCTION IN NMOSD

Autonomic dysfunction in NMOSD has been studied less than MS, but several case reports and case series have been conducted. Life-threatening autonomic dysreflexia during relapse with cervical myelitis, severe hypertension due to the hypothalamic lesion resulting in posterior reversible encephalopathy syndrome, and disturbances of sleep-wake cycles, bradycardia, POTS, and anhidrosis have been ob-

served.[8,9,51-53]

Two prospective studies of autonomic dysfunction in patients with NMOSD (pwNMOSD) were recently published. A study of 20 pwNMOSD in Serbia and Croatia presented the characteristics of autonomic dysfunction in NMOSD compared with those in pwMS, with matching performed for age, sex, and disease duration.[54] All pwNMOSD complained of at least one of the autonomic symptoms in the COMPASS-31 assessment. In particular, all patients presented with symptoms in the pupillomotor domain, followed by the gastrointestinal (90%), bladder (60%), orthostatic intolerance (50%), secretomotor (50%), and vasomotor (45%) domains. The median total COMPASS-31 score did not differ significantly between NMOSD and MS (12.2 and 12.9, respectively; $p = 0.813$), but pwNMOSD were found to have a greater burden in the pupillomotor domain (median pupillomotor domain score of 1.3 in NMOSD vs. 0.7 in MS; $p = 0.033$). As for the possible underlying mechanisms, the authors suggested the direct involvement of the pupillomotor system by NMOSD itself and the differences in the clinical manifestations of optic neuritis between MS and NMOSD (e.g., pwNMOSD have worse final visual acuity).

In the AFT, 40% of pwNMOSD exhibited abnormality in the adrenergic CASS subscore (adrenergic index [AI]), and 50% in the cardiovagal subscore (cardiovagal index [CI]).[54] It was particularly interesting that although the frequency of CAD was lower in pwNMOSD, if CAD is present in pwNMOSD, it is more severe and is characterized by OH and parasympathetic dysfunction. pwNMOSD with only optic neuritis tend to present normal or mild CAD compared with pwNMOSD with brainstem lesions or transverse myelitis, and OH is rarely present.

In a recent prospective study of 27 South Korean pwNMOSD, 74% had an autonomic dysfunction according to the AFT (CASS >0), suggesting that autonomic dysfunction is common in pwNMOSD.[55] Sudomotor dysfunction occurred in 35% of pwNMOSD (sudomotor CASS subscore [sudomotor index] >0), by followed adrenergic dysfunction (AI >0) in 33% and cardiovagal dysfunction (CI >0) in 30%. The total CASS and the subscore for each domain did not differ between the remission and relapse groups, but this was thought to be due to the small sample size. The involvement of the brain and/or spinal cord indicated the association with the total CASS. These results were attributed to the lesions involving structures that control the ANS. Cervical cord lesion was especially associated with CI. Delayed pressure recovery time (PRT) during the Valsalva maneuver, which is a valuable index for adrenergic failure,[56] was also significantly positively associated with the EDSS score. This indicates that PRT is a useful biomarker for predicting disability in pwNMOSD. Further research is needed to elucidate the characteristics and pathophysiology of autonomic dysfunction in NMOSD.

CONCLUSION

Autonomic dysfunction in MS and NMOSD can easily be overlooked, but it is a very important factor in the quality of life of the patients and in treatment decisions. Since symptoms can vary from asymptomatic, to being observed on close inspection, to loss of consciousness, they can cause social isolation. Clinicians should ensure that they assess and interrogate autonomic symptoms to ensure appropriate management. Autonomic dysfunction may be related to both the lesion itself and the pathological mechanism of the disease. Autonomic dysfunction may also be related to the disease severity or prognosis. Further large-scale clinical and pathophysiological studies will help to improve the understanding and treatment of autonomic dysfunction in MS and NMOSD.

Conflicts of Interest

The authors declare that they have no conflicts of interest relevant to this article.

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