Autonomic dysfunction in multiple sclerosis

Adamec, Ivan; Habek, Mario

Autonomic dysfunction in multiple sclerosis

Ivan Adamec, MD[1], Mario Habek, MD, PhD[1,2]

[1] University Hospital Center Zagreb, Department of Neurology, Refferal Center for Demyelinating Diseases of the Central Nervous System, Zagreb, Croatia

[2] School of Medicine, University of Zagreb, Department of Neurology, Zagreb, Croatia

Corresponding author:
Ivan Adamec
University Department of Neurology
University Hospital Center Zagreb
Kišpatićeva 12
HR-10000 Zagreb
Croatia
Phone: +38512376033; fax: +38512376033; e-mail: ivan.adamec@yahoo.com

Word count: 2564
Number of references: 78
Number of figures: 2

Authors' contributions
Study concept and design: Adamec, Habek. Acquisition of data: Adamec, Habek. Analysis and interpretation of data: Adamec, Habek. Drafting of the manuscript: Adamec. Critical revision of the manuscript for important intellectual content: Adamec, Habek. Administrative, technical, and material support: Adamec, Habek.

Conflict of interest statement: There is no conflict of interest.

Abstract

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults. Since the pathophysiology of MS is characterized by dissemination in space, as well as in time, the autonomic nervous system is inevitably damaged in the course of the disease in many patients and the proportion of affected patients increases with disease duration. Autonomic dysfunction (AD) in MS is explained by lesions in regions responsible for autonomic regulation such as nuclei in the periventricular region of fourth ventricle in the brainstem as well as medullar lesions. Reports about frequency of AD in MS patients vary notably between groups. Nevertheless its impact on quality of life is substantial but, unfortunately, often overlooked. The aim of this article is to present a concise review of various symptoms and signs of autonomic system dysfunction in MS.

Key words: multiple sclerosis, autonomic dysfunction, cardiovascular, bowel, bladder, sudomotor, sleep disorder, sexual dysfunction.

Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults [1]. Since the pathophysiology of MS is characterized by dissemination in space, as well as in time, the autonomic nervous system is inevitably damaged in the course of the disease in many patients and the proportion of affected patients increases with disease duration [2]. Activity of the disease seems to affect the parasympathetic and sympathetic parts of the autonomic system in different patterns. While long-term disease activity leads to sympathetic dysfunction, parasympathetic dysfunction correlates with progression of clinical disability [3]. Autonomic dysfunction (AD) in MS is explained by presence of lesions in regions responsible for autonomic regulation, such as nuclei in the periventricular region of fourth ventricle in the brainstem as well as medullar lesions [4,5]. The total MRI brain MS lesion load is another pathologic substrate related to AD incidence as demonstrated by Saari et al [6]. On the other hand, AD has been related to MRI findings of cervical spinal cord atrophy rather than the presence of demyelinating lesions in that region, postulating that AD results not solely from demyelination but from axonal loss as well [7].

Reports about frequency of AD in MS patients vary notably between groups. Nevertheless its impact on quality of life is substantial but, unfortunately, often overlooked. This is evident in scores used to assess neurological disability for clinical and research purposes such as the Kurtzke Expanded disability status scale (EDSS) where AD is underappreciated being represented with only bowel and bladder dysfunction.

The aim of this article is to present a concise review of various symptoms and signs of autonomic system dysfunction in MS.

Cardiovascular dysfunction

Cardiovascular autonomic dysfunction is reported to be present in up to two-thirds of MS patients and is known to show deterioration during the course of the disease [8, 9].

Orthostatic intolerance occurs in up to 50% of MS patients [10]. It is characterized by symptoms such as dizziness, nausea and palpitations when assuming upright position or prolonged standing or sitting. Head up tilt table testing is a valuable diagnostic method

used for assessment of impaired heart rate and blood pressure response to orthostatic challenge. Our group has observed a substantial number of MS patients with a variety of pathologic tilt table test results, such as orthostatic hypotension (OH) (Fig. 1) or postural orthostatic tachycardia syndrome (POTS) (Fig. 2) [11]. OH represents a significant and sustained decrease of blood pressure upon standing [12]. MS patients have a greater tendency to develop OH because of impaired sympathetic vasoconstrictory reflex responsible for maintaining adequate blood pressure after standing up from a supine position, lack of which causes subsequent pooling of blood into lower extremities [13]. POTS is characterized by sustained heart rate increase on orthostatic challenge without concomitant OH and is associated with symptoms of orthostatic intolerance [14]. POTS has been reported to occur frequently in MS and the connection of the two entities is explained by the presence of demyelinating brainstem and hemispheral lesions disrupting the physiological heart rate variability modulation [10,14]. Almost half of POTS patients complain of fatigue and the concomitant appearance of POTS and MS aggravates the dire sense of fatigue that MS patients often experience [15].

There is a battery of other clinical tests commonly used to assess cardiac autonomic dysfunction such as deep breathing test and Valsalva maneuver. Sanya et al. used baroreflex stimulation to demonstrate that MS patients have impairment of both the vagal mediated heart rate variability, as well as sympathetic control of blood vessel tone [16]. An interesting hypothesis was postulated by Keselbrener et al. who found that age-related reduction in vagal activity occurred earlier in MS patients complaining of fatigue, assuming that this form of AD may well be the pathological cause of fatigue [17].

It is important to bear in mind that de novo appearance of cardiac symptoms in MS can actually be a sign of disease exacerbation. Acute central nervous system lesions can induce an increased release of catecholamines causing necrotic changes in cardiac myocytes [18]. This, in return, can disrupt the endocardial conduction system causing arrhythmias such as sinus bradycardia or paroxysmal atrial fibrillation [19,20]. There have even been reports of cardiogenic shock and pulmonary edema caused by MS relapse [21,22]. Although the catecholamine surge in acute brain lesions can lead to myocardial damage, such as demonstrated in Takotsubo syndrome, there is, as well, an association presence of demyelinating lesions in the brainstem and the disruption of central

autonomic influence on cardiac and respiratory system [22,23]. MS therapy itself can contribute or cause cardiac pathology. Administration of high doses of corticosteroids to patients in relapse has been known to cause cardiac arrhythmias [24]. Mitoxantrone is occasionally used in patients that don't respond favorably to immunomodulating therapy. It is a drug with potential cardiotoxic effect and should therefore be administered with caution [25]. Unfortunately, some of the newer immunomodulatory drugs have cardiac side effects as well. Fingolimod treatment initiation must be accompanied with cardiac monitoring since sinus bradycardia, as well as asistoly, has ocurrred following its administration [26,27].

The initial therapy of orthostatic intolerance is consisted of patient education, reassurance and administration of counter-pressure maneuvers [28]. The next step is pharmacological intervention with volume expanders, vasoconstrictors and adrenergic antagonists. Patients with cardiac arrhythmia or ventricular dysfunction should be treated in consultation with a cardiology specialist. A novel cardiac symptom in an MS patient without a history of heart disease should always raise suspicion of MS relapse and be treated accordingly.

Bladder dysfunction

Urinary symptoms can be present as either storage phase dysfunction leading to incontinence or voiding phase dysfunction resulting in retention and incomplete bladder emptying [29]. These symptoms occur in up to 97% of MS patients during the course of the disease [30]. Incontinence often leads to social embarrassment and can have a severe impact on quality of life. The economic burden it produces is not to be depreciated [31]. Bladder dysfunction in MS results mainly from demyelinating lesions affecting the spinal cord, interrupting neural connections from the pontine micturition center to the parasympathetic sacral micturition center [32]. This leads to sensitization of the so-called silent C fibers causing detrusor hyperactivity, the most common problem in MS patients [33]. This was corroborated by urodynamic studies, which found detrusor hyperreflexia to be the main abnormality present, followed by detrusor sphincter dyssinergia and the least number of MS patients showing detrusor hyporeflexia [34]. The most common urinary symptom reported from the same group of patients was urgency followed by frequency, urge incontinence, stress incontinence and dysuria [34].

Storage and voiding symptoms can be reduced in female patients by pelvic floor muscle training [35]. Suprapubic vibration and Crede manouever can be given a trial in patients with incomplete bladder emptying [36]. Pharmacological treatment of detrusor hyperreflexia is based on anticholinergics such as oxybutynin, which reduce detrusor activity. Intranasal desmopressin is applicated to decreases the number of voiding episodes and Botulinum toxin A injected intravesically has shown to be an efficient therapy for bladder overactivity [37,38,39]. Urinary retention and incomplete bladder emptying may lead to hydronephrosis and chronic renal failure. Therefore the residual urine volume should be always measured. If there is a raised post-micturition residual urinary volume, the most efficient, but incommodious therapy, is intermittent self-catheterization [30]. α blockers can be used if the residual volume is not substantial but their efficacy is often limited [40]. In patients with neurogenic bladder not responding to conservative therapy, uretroileostomy may be performed in order to lower urinary tract pressure, although the perioperative morbidity necessitates careful risk to benefit assessment [41].

Given the high incidence of bladder dysfunction in MS, urinary tract infections (UTI) pose a significant problem in this population. UTI, as any infection in MS patients, can cause transient neurologic worsening and can even trigger a relapse [42]. What's even more concerning, UTI have been reported as the cause of up to 10% of deaths in MS patients [43]. Antibiotics should be administered when the infection's symptomatic. As far as prevention of urinary infection is concerned, prophylactic administration of antibiotics doesn't reduce clinical evident UTI but decreases the number of asymptomatic bacteriuria [44].

Sexual dysfunction

More than 80% of MS patients report sexual dysfunction (SD) [45]. Patients should be reassured to talk freely about this intimate subject, as SD often happens to be overlooked or underestimated as a symptom and therefore denied the possibility of treatment. The pathogenesis of SD in MS might be the result of lesions disrupting the hypothalamic–pituitary–adrenal and the hypothalamic–pituitary–gonadal axis [46]. There is, as well, an association between the presence of sphinteric disorders and some symptoms of SD

[47,48]. Relapse of the disease itself doesn't seem to add to the number of SD symptoms [49]. Most of the affected patients experience sexual hypoactivitiy [50]. Beside reduced libido, men are often disabled by erectile dysfunction and premature ejaculation whereas women experience reduced libido, decreased vaginal lubrication and difficulties in reaching orgasm [45]. This all contributes to MS patients having sexual intercourse less frequently compared to patients with other chronic diseases or healthy controls [47]. This is an important factor adding to relationship dissatisfaction felt by MS patients, as well as their partners [50]. Conceivably, there seems to be an association between cognition and impaired sexuality as patients with SD more often report symptoms such as memory and concentration problems [48].

Sildenafil, an oral phosphodiesterase-5 inhibitor, is an effective agent for erectile dysfunction in men but has been of limited usefulness in women, showing only some improvement in the lubrication domain [51,52]. Another agent used for erectile dysfunction is apomorphine hydrochloride administered sublingually [53]. In women, hormonal therapy such as estrogen and methyltestosterone may be used to improve lack of libido and vaginal dryness [53]. Increased partner support has a positive effect on sexual satisfaction in MS patients stressing the importance of psychosocial interventions and couple support therapy [54].

Bowel dysfunction

Constipation is present in 43% of MS patients while fecal incontinence affects 51% of patients [55]. All together, 68% of MS population complains of bowel dysfunction symptoms [55]. Constipation is a result of not only disease exacerbation itself, but also of decreased ambulation of patients and concomitant medications that may alter bowel movement. As well, there is evidence of paradoxical puborectalis contraction in MS, corresponding to detrusor sphincter dyssinergia in patients with bladder symptoms [56]. Fecal incontinence results from impairment of external anal sphincter function [57]. Gastric emptying scintigraphy can be used to assess autonomic dysfunction of the gastrointestinal tract. MS patients tend to have slower gastric emptying rate, which is associated with symptoms such as sense of fullness, hiccups, vomiting and gastroesophageal reflux [58].

Constipation treatment is based on laxatives and diet rich in fibers wit a high fluid intake [59]. Treatment of fecal incontinence is often unsatisfactory and relies on combining antimotility agents with rectal stimulants [32]. Transanal irrigation has mainly been used to treat symptoms in neurogenic bowel syndrome. A recent study has demonstrated its effectiveness in MS, with incontinence showing greater improvement than constipation [60]. Biofeedback behavioral therapy can lead to improvement of resistant bowel symptoms and alleviate depression associated with this type of symptoms [61].

Sleep disorders

Many MS patients report sleeping-related difficulties. In a large study of more than thousand individuals with MS, prevalence of moderate or severe sleep problems was more than 50% [62]. The most common symptoms are difficulty initiating and maintaining sleep, frequent awakenings because of leg cramps and discomfort, snoring and nocturia [63]. Lack of sleep leads to increased fatigue, daytime somnolence and respiratory dysfunction episodes [64]. Involvement of hypothalamus on MRI is associated with increased fatigue [65]. There has been a report of hypersomnia and low orexin-1 level due to a demyelinating lesion in the hypothalamus [66]. However, studies in larger groups of patients with relapsing remitting MS have found cerebrospinal fluid levels of hypocretin-1 to be normal, and they didn't observe a correlation with hypersomnolence [67]. Many of the drugs used in MS treatment, including immunomodulatory therapy, can cause dyssomnias [68]. Nocturnal polysomnography is the method of choice for analyzing the pattern of sleep and identifying the type of disorder. It is important to stress out that depression is strongly associated with sleep disorders and that their treatment should be considered concomitantly [69].
Treatment of insomnias is pharmacologically based on short-term use of agents such as antihistaminics, benzodiazepines and sedating antidepressants with education on sleep hygiene, relaxation technics and behavioral therapy [70]. Other treatable entities that contribute to sleep problems such as pain, leg cramps and nocturia should be properly managed [62,69]. Treatment of sleep disorder results in improvement not only of patient's sleepiness, but of feeling of fatigue, energy and well being [71].

Sudomotor dysfunction

Heat or increased ambient temperature is one of the most common factors known to worsen MS symptoms [72]. Sweating, the physiological response to heat is mediated by sympathetic activity. Decreased sudomotor response occurs significantly higher in MS patients than in healthy controls and is related to disease activity [73]. Thermoregulation is impaired in MS patients because of interruption in the central sudomotor pathways that originate in the preoptic region of the hypothalamus and descend to intermediolateral column of the spinal cord where they exit the central nervous system and travel to sweat glands via peripheral nerves [74]. Temperature increase can diminish the current needed for depolarization of axons [75]. Thus, hyperthermia can cause a neuro-blockade of partially demyelinated axons, which leads to neurologic deterioration known as Uhthoff's phenomenon [76]. Since there have been reports that such deterioration can be long-lasting, difficulties in thermoregulation may have a more serious influence on patients than previously suspected [77]. Head and neck cooling reduce body temperature and may provide alleviation of heat-induced symptoms in MS [78]. Avoidance of prolonged exposure to heat is recommended to all MS patients.

Conclusion

Virtually any part of the diverse autonomic system can be affected in MS, causing various symptoms and signs. Cardiovascular abnormalities compromise a group of potentially hazardous but often overlooked symptoms in MS patients. Their treatment does not differ from treatment in individuals without MS, but their abrupt appearance in patients with an established MS diagnosis must be viewed in the context of a possible disease relapse. The most frequent and often embarrassing manifestations of AD in MS are bladder and bowel symptoms. Their therapy is often unsatisfactory and can be strenuous to manage for the patient and their caregivers. Since UTI are known to contribute to mortality in MS, their management is of great importance, especially in patients with decreased mobility. Sexual dysfunction can be surrounded by an aura of taboo and is often omitted in the patient-doctor conversation. However, it must be actively sought for by the physician and appropriately treated as it greatly affects patients' quality of life, as well as their social functioning. Sleep disorders cause

significant aggravation to patients and may attribute to fatigue and deteriorate their perception of well-being. Sudomotor dysfunction is an under-investigated area in MS, showing potential as an auspicious part of AD research.

An interdisciplinary approach is necessary for optimal management of autonomic symptoms in MS patients. As more and more studies are performed regarding AD in MS, the importance of autonomic evaluation of this group of patients continues to be emphasized. All physicians involved in the treatment and rehabilitation of MS patients should be familiar with this field of neurology.

References

1. Edmonds P, Hart S, Gao W, et al. Palliative care for people severely affected by multiple sclerosis: evaluation of a novel palliative care service. Mult Scler. 2010;16:627–36.
2. Gunal DI, Afsar N, Tanridag T, Aktan S. Autonomic Dysfunction in Multiple Sclerosis: Correlation with Disease-Related Parameters. Eur Neurol 2002;48:1–5.
3. Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult Scler. 2001;7:327-34.
4. Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. J Neurol Sci. 1993;120:82–86.
5. Stenager E, Asbeth NS. Sexual aspect of multiple sclerosis. Sem Neurol 1992;12:120-24.
6. Saari A, Tolonen U, Pääkkö E, et al. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. Clin Neurophysiol. 2004;115:1473-78.
7. De Seze J, Stojkovic T, Gauvrit JY, et al. Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. J Neurol. 2001;248:297–303.
8. Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. Acta Neurol Scand. 2000;101:85-8.

9. Nasseri K, TenVoorde BJ, Adèr HJ, Uitdehaag BM, Polman CH. Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. J Neurol Sci. 1998;155:50-4.
10. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic Dysfunction Presenting as Postural Orthostatic Tachycardia Syndrome in Patients with Multiple Sclerosis. Int J Med Sci. 2010;7:62-67.
11. Adamec I, Bach I, Barušić AK, Mišmaš A, Habek M. Assessment of prevalence and pathological response to orthostatic provocation in patients with multiple sclerosis. J Neurol Sci. 2013;324:80-3.
12. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21:69-72.
13. Flachenecker P, Wolf A, Krauser M, Hartung HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. J Neurol. 1999;246:578-86.
14. Adamec I, Lovrić M, Zaper D, et al. Postural orthostatic tachycardia syndrome associated with multiple sclerosis. Auton Neurosci. 2013;173:65-8.
15. Carew S, Connor MO, Cooke J, et al. A review of postural orthostatic tachycardia syndrome. Europace. 2009;11:18-25.
16. Sanya EO, Tutaj M, Brown CM, Goel N, Neundörfer B, Hilz MJ. Abnormal heart rate and blood pressure responses to baroreflex stimulation in multiple sclerosis patients. Clin Auton Res. 2005;15:213-8.
17. Keselbrener L, Akselrod S, Ahiron A, Eldar M, Barak Y, Rotstein Z. Is fatigue in patients with multiple sclerosis related to autonomic dysfunction? Clin Auton Res. 2000;10:169-75.
18. Sörös P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. Lancet Neurol. 2012;11:179-88.
19. Juric S, Mismas A, Mihic N, Barac AM, Habek M. Newly onset sinus bradycardia in context of multiple sclerosis relapse. InternMed. 2012;51:1121-24.

20. Chagnac Y, Martinovits G, Tadmor R, Goldhammer Y. Paroxysmal atrial fibrillation associated with an attack of multiple sclerosis. Postgrad Med J. 1986 May;62:385-7.
21. Uriel N, Kaluski E, Hendler A, Leitman M, Vered Z. Cardiogenic shock in a young female with multiple sclerosis. Resuscitation. 2006;70:153-7.
22. Padley JR, Feneley MP, Hayward CS, Markus R. Neurocardiogenic pulmonary oedema: initial presentation of multiple sclerosis. Heart Lung Circ. 2012;21:853-5.
23. Bramow S, Faber-Rod JC, Jacobsen C, et al. Fatal neurogenic pulmonary edema in a patient with progressive multiple sclerosis. Mult Scler. 2008;14:711-5.
24. Vasheghani-Farahani A, Sahraian MA, Darabi L, Aghsaie A, Minagar A. Incidence of various cardiac arrhythmias and conduction disturbances due to high dose intravenous methylprednisolone in patients with multiple sclerosis. J Neurol Sci. 201;309:75-8.
25. Murray TJ. The cardiac effects of mitoxantrone: do the benefits in multiple sclerosis outweigh the risks? Expert Opin Drug Saf. 2006;5:265-74.
26. Jeffery DR, Markowitz CE, Reder AT, Weinstock-Guttman B, Tobias K. Fingolimod for the treatment of relapsing multiple sclerosis. Expert Rev Neurother. 2011;11:165-83.
27. Espinosa PS, Berger JR. Delayed fingolimod-associated asystole. Mult Scler. 2011;17:1387-9.
28. Benditt DG, Nguyen JT. Syncope: therapeutic approaches. J Am Coll Cardiol. 2009;53:1741-51.
29. Panicker JN, Fowler CJ. The bare essentials: uro-neurology. Pract Neurol. 2010;10:178-85.
30. Haensch CA, Jörg J . Autonomic dysfunction in multiple sclerosis. J Neurol. 2006;253 Suppl 1:I3-9.
31. Tapia CI, Khalaf K, Berenson K, Globe D, Chancellor M, Carr LK. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: a systematic review. Health Qual Life Outcomes. 2013;11:13.

32. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. Lancet Neurol. 2010;9:1182-99.
33. Kalsi V, Fowler CJ. Therapy Insight: bladder dysfunction associated with multiple sclerosis. Nat Clin Pract Urol. 2005;2:492-501.
34. Nakipoglu GF, Kaya AZ, Orhan G, et al. Urinary dysfunction in multiple sclerosis. J Clin Neurosci. 2009;16:1321-4.
35. Lúcio AC, Perissinoto MC, Natalin RA, Prudente A, Damasceno BP, D'ancona CA. A comparative study of pelvic floor muscle training in women with multiple sclerosis: its impact on lower urinary tract symptoms and quality of life. Clinics (Sao Paulo). 2011;66:1563-8.
36. Fowler CJ, Panicker JN, Drake M, et al. A UK consensus on the management of the bladder in multiple sclerosis. Postgrad Med J. 2009;85:552-9.
37. Bosma R, Wynia K, Havlikova E, De Keyser J, Middel B. Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: a meta-analysis. Acta Neurol Scand. 2005;112:1–5.
38. Kalsi V, Gonzales G, Popat R, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. Ann Neurol 2007; 62: 452–57.
39. Habek M, Karni A, Balash Y, Gurevich T. The place of the botulinum toxin in the management of multiple sclerosis. Clin Neurol Neurosurg. 2010;112:592-6.
40. O'Riordan JI, Doherty C, Javed M, Brophy D, Hutchinson M, Quinlan D. Do alpha-blockers have a role in lower urinary tract dysfunction in multiple sclerosis? J Urol. 1995;153:1114–16.
41. Legrand G, Rouprêt M, Comperat E, Even-Schneider A, Denys P, Chartier-Kastler E. Functional outcomes after management of end-stage neurological bladder dysfunction with ileal conduit in a multiple sclerosis population: a monocentric experience. Urology. 2011;78:937-41.
42. Metz LM, McGuinness SD, Harris C. Urinary tract infections may trigger relapse in multiple sclerosis. Axone. 1998;19:67-70.

43. Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. Neuroepidemiology. 2006;26:102-7.
44. Morton SC, Shekelle PG, Adams JL, et al. Antimicrobial prophylaxis for urinary tract infection in persons with spinal cord dysfunction. Arch Phys Med Rehabil. 2002;83:129–38.
45. Tepavcevic DK, Kostic J, Basuroski ID, Stojsavljevic N, Pekmezovic T, Drulovic J. The impact of sexual dysfunction on the quality of life measured by MSQoL-54 in patients with multiple sclerosis. Mult Scler. 2008;14:1131–36.
46. Guo ZN, He SY, Zhang HL, Wu J, Yang Y. Multiple sclerosis and sexual dysfunction. Asian J Androl. 2012;14:530-5.
47. Zorzon M, Zivadinov R, Bosco A, et al. Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. Mult Scler. 1999;5:418-27.
48. Demirkiran M, Sarica Y, Uguz S, Yerdelen D, Aslan K. Multiple sclerosis patients with and without sexual dysfunction: are there any differences? Mult Scler. 2006;12:209-14.
49. Zorzon M, Zivadinov R, Monti Bragadin L, et al. Sexual dysfunction in multiple sclerosis: a 2-year follow-up study. J Neurol Sci. 2001;187:1-5.
50. Schmidt EZ, Hofmann P, Niederwieser G, Kapfhammer HP, Bonelli RM. Sexuality in multiple sclerosis. J Neural Transm. 2005;112:1201-11.
51. Fowler CJ, Miller JR, Sharief MK, Hussain IF, Stecher VJ, Sweeney M. A double blind, randomised study of sildenafi l citrate for erectile dysfunction in men with multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;76:700–05.
52. DasGupta R, Wiseman OJ, Kanabar G, Fowler CJ, Mikol DD. Efficacy of sildenafil in the treatment of female sexual dysfunction due to multiple sclerosis. J Urol 2004;171:1189–93.
53. DasGupta R, Fowler CJ. Bladder, bowel and sexual dysfunction in multiple sclerosis: management strategies. Drugs. 2003;63:153-66.

54. Blackmore DE, Hart SL, Albiani JJ, Mohr DC. Improvements in partner support predict sexual satisfaction among individuals with multiple sclerosis. Rehabil Psychol. 2011;56:117-22.
55. Hinds JP, Eidelman BH, Wald A Prevalence of bowel dysfunction in multiple sclerosis. A population survey. Gastroenterology 1990;98:1538–42.
56. Chia YW, Gill KP, Jameson JS, et al. Paradoxical puborectalis contraction is a feature of constipation in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 1996;60:31-5.
57. Waldron DJ, Horgan PG, Patel FR, Maguire R, Given HF. Multiple sclerosis: assessment of colonic and anorectal function in the presence of faecal incontinence. Int J Colorectal Dis 1993;8:220–224
58. El-Maghraby TA, Shalaby NM, Al-Tawdy MH, Salem SS. Gastric motility dysfunction in patients with multiple sclerosis assessed by gastric emptying scintigraphy. Can J Gastroenterol 2005;9:141–145, Gupta YK. Gastroparesis with multiple sclerosis. JAMA. 1984;252:42.
59. Wiesel PH, Norton C, Glickman S, Kamm MA. Pathophysiology and management of bowel dysfunction in multiple sclerosis. Eur J Gastroenterol Hepatol. 2001;13:441-8.
60. Preziosi G, Gosling J, Raeburn A, Storrie J, Panicker J, Emmanuel A. Transanal irrigation for bowel symptoms in patients with multiple sclerosis. Dis Colon Rectum. 2012;55:1066-73.
61. Preziosi G, Raptis DA, Storrie J, Raeburn A, Fowler CJ, Emmanuel A. Bowel biofeedback treatment in patients with multiple sclerosis and bowel symptoms. Dis Colon Rectum. 2011;54:1114-21.
62. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. Mult Scler. 2008;14:1127-30.
63. Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol. 1994;34:320-3.
64. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. Semin Neurol. 2005;25:64-8.

65. Zellini F, Niepel G, Tench CR, Constantinescu CS. Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2009;15:1442-49.
66. Oka Y, Kanbayashi T, Mezaki T, et al. Low CSF hypocretin-1/orexin-A associated with hypersomnia secondary to hypothalamic lesion in a case of multiple sclerosis. J Neurol. 2004;251:885-6.
67. Constantinescu CS, Niepel G, Patterson M, et al. Orexin A (hypocretin-1) levels are not reduced while cocaine/amphetamine regulated transcript levels are increased in the cerebrospinal fluid of patients with multiple sclerosis: no correlation with fatigue and sleepiness. J Neurol Sci. 2011;307:127-31.
68. Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. Sleep Med Rev 2010;14:121–9.
69. Bamer AM, Johnson KL, Amtmann DA, Kraft GH. Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis. Clin Epidemiol. 2010;2:99-106.
70. Caminero A, Bartolomé M. Sleep disturbances in multiple sclerosis. J Neurol Sci. 2011;309:86-91.
71. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest. 2000;118:372–9.
72. Gallup AC, Gallup GG Jr, Feo C. Yawning, sleep, and symptom relief in patients with multiple sclerosis. Sleep Med. 2010;11:329-30.
73. Saari A, Tolonen U, Pääkkö E, et al. Sweating impairment in patients with multiple sclerosis. Acta Neurol Scand. 2009;120:358-63.
74. Noronha MJ, Vas CJ, Aziz H. Autonomic dysfunction (sweating responses) in multiple sclerosis. J Neurol Neurosurg Psychiatry 1968;31:19–22.
75. D.G. Baker. Multiple sclerosis and thermoregulatory dysfunction. J Appl Physiol. 2002:92:1779–80.
76. Guthrie TC, Nelson DA. Influence of temperature changes on multiple sclerosis: critical review of mechanisms and research potential. J Neurol Sci 1995;129:1–8.
77. Berger JR, Sheremata WA. Persistent neurological deficit precipitated by hot bath test in multiple sclerosis. JAMA 1983;249:1751–3.

78. Ku YT, Montgomery LD, Wenzel KC, Webbon BW, Burks JS. Physiologic and thermal responses of male and female patients with multiple sclerosis to head and neck cooling. Am J Phys Med Rehabil. 1999;78:447-56.

Figures

Figure 1. An example of head-up tilt test in MS patient with OH: Upper line shows continuous heart rate monitoring, lower line shows continuous blood pressure monitoring. Note the decrease of blood pressure after the tilt (vertical red line) > 20 mmHg/10 mmHg, with a compensatory rise in blood pressure.

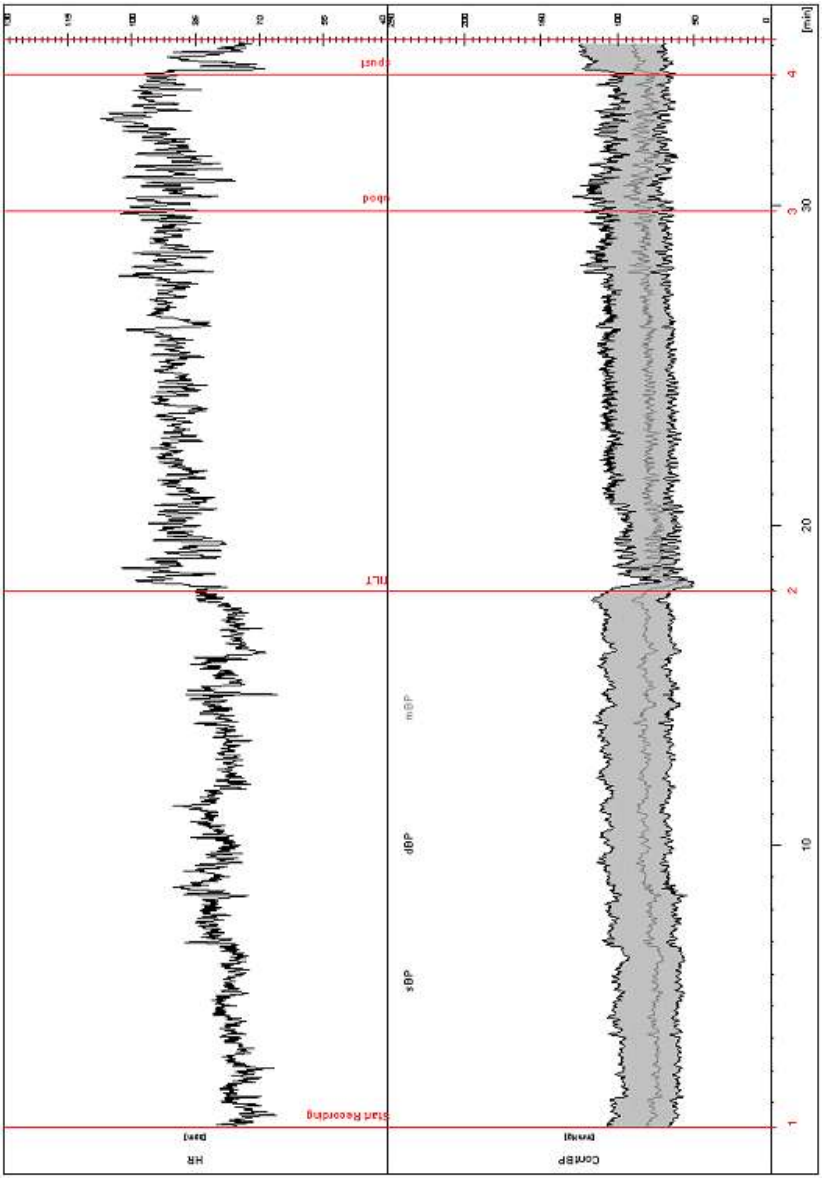

Figure 2. An example of head-up tilt test in MS patient with POTS: Upper line shows continuous heart rate monitoring, lower line shows continuous blood pressure monitoring. Note the increase of heart rate after the tilt (vertical red line) >30 beats/minute, without fall in blood pressure.