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Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype

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HIGHLIGHTS

- MS disease type is an independent predictor of dysautonomia.
- There is a difference in pattern of dysautonomia in pwRRMS and pwPMS.
- Sweating dysfunction is common in MS, particularly in advanced disease.

ABSTRACT

Objective: To determine autonomic dysfunction (AD) differences in patients with relapsing remitting multiple sclerosis (pwRRMS) and progressive MS (pwPMS).
Methods: Composite autonomic scoring scale (CASS) and heart rate variability (HRV) were performed in 40 pwRRMS and 30 pwPMS.
Results: pwPMS had a significantly higher sudomotor index and total CASS score compared to pwRRMS ($p < 0.001$ and $p < 0.001$, respectively). Disease duration positively correlated with sudomotor index and total CASS ($r_s = 0.409$, $p < 0.001$ and $r_s = 0.472$, $p < 0.001$, respectively), while the Expanded Disability Status Scale (EDSS) positively correlated with sudomotor index and total CASS ($r_s = 0.411$, $p < 0.001$ and $r_s = 0.402$, $p = 0.001$, respectively) in all patients. Type of multiple sclerosis (pwRRMS or pwPMS) corrected for age, sex and disease duration, was a statistically significant predictor of CASS value ($B = 1.215$, $p = 0.019$). Compared to pwRRMS, pwPMS had a significantly lower standard deviation of NN intervals (SDNN), low frequency (LF), and high frequency (HF), during both the supine and tilt-up phases (all p-values <0.006). pwPMS had a significantly lower LF/HF ($p = 0.008$) during tilt-up.
Conclusion: There is a significant difference in autonomic function in pwRRMS and pwPMS; with pwPMS having a higher burden of AD, which is particularly evident for sweating dysfunction.
Significance: Further research is needed to establish whether parasympathetic and sudomotor dysfunction may serve as markers of progressive MS.

1. Introduction

Multiple sclerosis (MS) is an idiopathic demyelinating disorder of the central nervous system. It most commonly affects young individuals, between 20 and 40 years-of-age and represents the leading cause of non-traumatic neurologic disability in young adults (Edmonds et al., 2010). Although the exact etiology is unknown, there is a complex interaction between several environmental factors and a distinct genetic susceptibility which results in demyelinating lesions, the pathological hallmark of MS (Compston and Coles, 2008). The pathogenesis of the disease is marked by the production of autoreactive lymphocytes that cross the blood-brain barrier and enter into the central nervous system causing demyelination, axonal loss and, ultimately, neurodegeneration (Wu and Alvarez, 2011).

The natural history of MS seems to be divided into two distinct phases. First is the relapsing-remitting phase, characterized by bouts of acute exacerbation of disease activity. Pathologically, this is correlated with central nervous system (CNS) inflammation. The second phase is determined by a slow but steady progression in neurologic deficit, associated with CNS degeneration (Compston and Coles, 2008). The differentiation between these two phases

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of the disease (on an individual level) can sometimes be difficult. It is based on a temporal relationship between relapses from which patients typically experience partial or complete recovery, while simultaneously undergoing a progression of irreversible central nervous system dysfunction. Deciding whether increased disability is a consequence of a partially recovered relapse or a sign of the progressive form of the disease is still a troublesome task for the clinician. Onset of a progressive disease course in MS is defined by the onset of insidiously worsening and irreversible decline in neurologic function, regardless of the absence or presence of relapses; and, which cannot be explained purely with a step-wise worsening, associated with ongoing relapses (Tutuncu et al., 2012). Although somewhat simplistically dichotomized, this distinction between relapsing-remitting MS (RRMS) and progressive MS (PMS) does reflect disease evolution in a real life setting. In most patients, MS will begin with a relapsing-remitting course, with a smaller number of patients having progressive disease from the start, primary progressive MS (PPMS). Approximately 50% of RRMS patients will go on to develop secondary progressive MS (SPMS), in about nineteen years' time (Confavreux and Vukusic, 2006). Altogether, 80% of RRMS patients will ultimately develop SPMS after an average of 25 years. About 20% of patients will remain in the relapsing-remitting form of the disease, ultimately experiencing a reduced number of relapses as time passes (Kremenchutzky et al., 2006). It is not clear which patients will eventually progress to SPMS, but frequent relapses and the number of demyelinating lesions seem to carry a certain risk for future progression (Bsteh et al., 2016).

When the progressive phase occurs, there are many clinical similarities in patients with SPMS and PPMS, leading to a unifying theory that SPMS and PPMS can be considered as a distinct disease entity when compared to RRMS. This observation is mainly related to patients' age and the time it takes them to reach certain disability milestones, such as impaired walking or walking with a cane, referenced to the time that passed from one particular milestone to the other. The expanded disability status scale (EDSS), a standardized tool for neurologic disability assessment in MS, reflects this. Specifically, it takes patients with SPMS and PPMS about the same amount of time to reach EDSS 6 from EDSS 4, around 12 years. Bearing this in mind, RRMS can be regarded as a 'younger' disease that has not yet had time do develop into the progressive type; while SPMS and PPMS represent disease which 'got older' or was, in fact, 'old' to begin with, respectively (Confavreux and Vukusic, 2006). The diagnosis of RRMS in clinical practice begins with the clinically isolated syndrome (CIS), which represents the first clinical episode suggestive of MS. The course of the disease is marked by an acute exacerbation and periods of clinical stability, characterized as relapsing-remitting. On the other hand, when the disease progresses after an initial relapsing-remitting period, the disease is characterized as secondary progressive. Lastly, when there is progression of neurologic disability from the start, the disease is considered primary progressive in its nature. Therefore, the diagnosis of PMS is actually made retrospectively and the difference between RRMS and PMS is based on clinical evidence.

Little is known about how different disease courses affect different non-motor symptoms of MS, impeding prognosis and disease management. In a recent meta-analysis, for example, it has been shown that cognitive impairment significantly differs between RRMS and PMS (Johnen et al., 2017). These results imply that patients with PMS (pwPMS) display severe degrees of cognitive impairment and need more specialized disease management than patients with RRMS (pwRRMS).

Knowing that autonomic dysfunction (AD) in MS can affect virtually every end organ that the autonomic nervous system (ANS) innervates, the lack of studies on AD in MS – in particular studies investigating differences between RRMS and PMS – is surprising (Adamec and Habek 2013). The most extensively investigated part of the ANS is the cardiovascular autonomic system, due to its convenience for testing. In general, ANS research can be divided into research regarding patient reported symptoms (usually using a variety of questionnaires) and assessment of ANS function/dysfunction in a controlled setting. In structural disorders of the ANS (dysautonomia caused by different pathological processes in the central or peripheral nervous system), a great discrepancy between patient reported symptoms and laboratory findings can be observed. One study has shown that even patients with severe sympathetic dysfunction (orthostatic hypotension with a decrease in systolic blood pressure more than 60 mm Hg from baseline during a head-up tilt table test) can be completely asymptomatic during the head-up tilt table test in up to one third of cases (Arbogast et al. 2009). Therefore, in patients with structural ANS disorders, like MS, autonomic dysfunction should actively be searched for with laboratory tests.

In recent years there has been an upsurge in cardiovascular ANS laboratory investigations, involving patients with MS. It has been demonstrated that AD is frequent in MS and is present even in the earliest stages of the disease (CIS) with parasympathetic dysfunction present in 5%, sympathetic in 42.6% and sudomotor in 32.7% of patients (Habek et al., 2016). Furthermore, there is emerging evidence suggesting that certain ANS disorders, like postural orthostatic tachycardia syndrome, may serve as significant predictors of early conversion from CIS to MS (Habek et al., 2017). Several studies, using standardized tests of cardiovascular autonomic function (heart rate and blood pressure responses to Valsalva maneuver and heart rate response to deep breathing), have suggested a distinct pattern of AD in different phases of the disease. In the CIS stage there is predominant sympathetic dysfunction (both adrenergic and cholinergic), with sparing of the parasympathetic system (Crnošija et al., 2016). A similar finding was observed in pwRRMS, where adrenergic sympathetic dysfunction was higher in patients with active MS compared to healthy controls or stable patients (Flachenecker et al., 2001). In contrast, parasympathetic, but not sympathetic dysfunction, increases with disease duration significantly correlating with an increase in clinical disability (Flachenecker et al., 2001). In order to confirm this distinct pattern of autonomic involvement in MS, and due to lack of studies specifically assessing the difference in autonomic function in relapsing-remitting and progressive stages of the disease, we aimed to determine differences in AD in pwRRMS and pwPMS.

2. Materials and methods

2.1. Patients

This was a prospective study performed from September 2015 to September 2016 that included consecutive patients diagnosed with RRMS and PMS; with the PMS group including patients with both PPMS and SPMS. The patients were recruited during their regular follow-up visits at the Outpatient Clinic of the Department of Neurology, University Hospital Center Zagreb – a tertiary medical center and a referral center for autonomic nervous system disorders. Patients were diagnosed with RRMS and PPMS based on the 2010 revision of the McDonald criteria (Polman et al., 2011). SPMS was defined based on the criteria by Lublin et al. (2014). The patients were examined by two of the authors (MH and IA), neurologists with more than five years of experience dealing with individuals with MS, and they performed the EDSS examinations. The EDSS is a standard tool used to evaluate neurologic disability in patients with MS (Kurtzke, 1983).

Exclusion criteria included significant cardiac or pulmonary disease and medication with known influence on the autonomic