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Abstract

Different neurophysiological methods such as evoked potentials (EP), testing of the autonomic nervous system (ANS) or polysomnography have the potential to detect clinically silent lesions or to confirm the existence of an association between a clinical symptom and multiple sclerosis (MS); previously undetected by MRI. Therefore, in the most recent MRI criteria for the diagnosis of MS (MAGNIMS consensus guidelines), neurophysiological confirmation of optic nerve dysfunction (slowed conduction on visual EP), support dissemination in space and, in patients without concurrent visual symptoms, dissemination in time. In this chapter we will review the existing evidence regarding the role of different neurophysiological tests (specifically the role of EPs, autonomic nervous system testing and sleep testing in MS) in the diagnosis and management of MS.

Key words: multiple sclerosis, evoked potentials, autonomic nervous system, sleep disorders

Introduction

Multiple sclerosis (MS) is a chronic idiopathic demyelinating illness of the central nervous system and it is the leading cause of disability in young adults. In the diagnosis of MS, three main principles are applied: demonstration of dissemination in space (DIS), demonstration of dissemination in time (DIT), and reasonable exclusion of alternative explanations for the clinical presentation. The demonstration of DIS and DIT is heavily influenced with MRI, and since its introduction, this method has become the cornerstone in the diagnosis of MS with various MRI criteria applied over time (1,2). The last version of the McDonald criteria allows to make a diagnosis of MS in patients with typical clinically isolated syndrome (CIS). Despite these advancements, there is still a poor correlation between clinical symptoms and MRI findings in a substantial proportion of MS patients (3). Different neurophysiological methods such as evoked potentials (EP), testing of the autonomic nervous system (ANS) or polysomnography have the potential to detect clinically silent lesions or to confirm the existence of an association between a clinical symptom and MS; previously undetected by MRI. A nice example of the latter are EP, which have been widely used in MS, although their clinical use has been reduced after the introduction of MRI. This is not always justifiable since the information provided by evoked potentials is more related to function, unlike the information provided by MRI which is more related to anatomy. (4) Therefore in the most recent MRI criteria for the diagnosis of MS (MAGNIMS consensus guidelines), neurophysiological confirmation of optic nerve dysfunction (slowed conduction on visual EP), support dissemination in space and, in patients without concurrent visual symptoms, dissemination in time. (5)

In this chapter we will review the existing evidence regarding the role of different neurophysiological tests (specifically the role of EPs, autonomic nervous system testing and sleep testing in MS) in the diagnosis and management of MS.

Evoked potentials in multiple sclerosis

The role of EPs in the evaluation of MS has changed over time primarily due to advances in neuroimaging technology, dominantly the MRI. In contrast with MRI, EPs provide information about functionality and pathophysiological involvement of a certain neuroanatomic pathway (6) and their clinical utility is based on their ability to reveal

subclinical involvement of a sensory system in the presence of signs/symptoms suggestive for demyelinating disease (7).

In routine clinical practice, most frequently used EPs are: pattern reversal visual EPs (VEPs), brainstem auditory EP (BAEP), short latency somatosensory EP (SSEP), and motor evoked potentials (MEPs) (6).

VEPs are widely used in assessment of patients with clinical signs of optic neuritis (ON) as well as in evaluation of asymptomatic involvement of visual pathways in patients with MS. The most common finding in acute ON is delayed latency of wave P100 together with amplitude reduction (8). With recovery from ON, the amplitude improves but latency usually persistently increases. The sensitivity of VEPs in patients with MS and a history of optic neuritis is about 77% to 100% while the frequency of abnormal VEPs in overall patients with MS varies between studies; from 42% - 100% (9,10). According to new MAGNIMS criteria, VEP is reintroduced as part of diagnostic MS criteria (5).

BAEPs are used to detect and approximately localize symptomatic, as well as asymptomatic, dysfunctions of the auditory pathways within the auditory nerve and brainstem. The most common BAEP pathological findings in patients with MS reflect dysfunction of the upper or lower brainstem, including increased wave I-III (lower brainstem) or III-V (upper brainstem) interlatencies (11). According to published literature, overall sensitivity in evaluation of brainstem involvement is low (7,12,13) and it is inferior to MRI and vestibular evoked myogenic potentials (VEMP) (12).

SSEP, elicited from the upper and lower limbs, evaluate dorsal columns and the thalamo-cortical sensory system. The diagnostic value of SSEP is most pronounced in diagnostic evaluation of patients with no evidence of demyelinating lesions on the spinal MRI. Tibial SSEP is considered to be among the most valuable EPs (14), giving pathological findings in up to 80% of patients with MS who do not have sensory symptoms and signs (15). Pathological findings commonly found in tibial SSEP are increased latencies of upper thoracic and cortical response. SSEPs of the median nerve add additional value because through the P14 wave they provide information about the degree to which the lower brainstem is affected. Abnormalities of P14 were found to be a significant contributor to the functional brainstem assessment battery.

MEPs are evaluating the corticospinal tract and together with SSEPs represent a valuable neurophysiological method for evaluation of the spinal cord. Beside its diagnostic value, MEP studies in MS serve as an indication of corticospinal pathway dysfunction (16). The pathological finding in MS is an increased central motor conduction time (CMCT), which is found to be related with EDSS values (17) and can predict long term disability (18).

Vestibular evoked myogenic potentials (VEMPs) have been proven to be useful in the assessment of brainstem involvement in MS (3). VEMP presents a myogenic response to a loud acoustic stimulus and is divided into two parts, depending where the myogenic response is measured: cervical VEMP (ipsilateral sternocleidomastoid muscle, waves P13 and N23), which provides information about vestibulospinal pathways; and ocular VEMP (contralateral ocular muscle, waves N10 and P13), which provides information about the functionality of vestibuloocular reflex. The sensitivity for MS patients varies from 30% to 100% and results are characterized with an absent response, prolonged latencies and reduced amplitudes of major waves (19, 20). According to some studies, VEMP is superior to clinical examination, MRI and BAEP in detection of brainstem lesions (21).

The EP score

Different modalities of evoked potentials show correlation with disability and disease progression in MS patients, so it could be assumed that a combination of different evoked potential could provide even more useful information. VEP, BAEP, SSEP and MEP could be combined into a multimodal EP score, a specific scale calculated according to normative values for each of the EPs. A different degree of the significance is assigned to each of the types of abnormalities (prolonged latencies, reduced amplitude, absent response), and the level of significance is specific for every study. If the EP score consists of VEP, SSEP of upper and lower extremities where a normal response is scored with 0, prolonged latency with 1, reduced amplitude with 2 and an absent response with 3; then a patient with prolonged VEP latencies on the left side, a reduced amplitude of P40-N50 complex on the left side for tibial nerve SSEP and an absent response on the right side for the medial nerve SSEP has an EP score of 6 (1+2+3), as presented on Figure 1. The EP score could be defined with ordinal values calculated according to normative values or with different transformations of raw EP data (z transformation).

Multimodal evoked potentials (mEPs measure and moderately predict clinically relevant disease activity in patients with early relapsing remitting MS (22). The mEPS at baseline has shown correlation with EDSS after 24 months and changes in mEPS correlated with changes in EDSS, where patients with EDSS progression showed stronger mEPD deterioration than clinically stable patients (22). A combination of VEP, BAEP, SSEP and MEP results gathered in an EP score has demonstrated a significant correlation between the EP score and EDSS score at the time of neurophysiological study and at 1, 3 and 5 years of follow-up, particularly for MEP and SEP; thus, giving rise to the evidence that EPs, particularly MEP and SEP, have significant value in predicting neurological disability (23). Patients with an EP score at a baseline higher than the median value had an 72.5% increased risk of disability progression at follow-up; meanwhile, patients with a lower EP score had a risk of only 36.3% (24), suggesting a predictive role of the multimodal EP score. This was confirmed by the fact that patients with worsening at follow-up had a significantly worse global EP score at baseline in comparison with patients without worsening (24).

Different EPs (VEP, BAEP, SSEP and MEP) associated with the EP score have shown moderate and useful correlation with clinical status in patients with primary progressive MS – PPMS (25). The numerical score based on VEP, SSEP and MEP results correlates well with disability in PPMS and allows some prediction of the disease course over three years (26). Combination of VEP, BAEP and SSEP could be used as an outcome variable for determining the efficiency of a particular treatment (27). Treatment effects did not show any significance for EDSS, but there was improvement in EP score (mainly because of the significant decrease in VEP score) between different treatment groups (27).

Finally, brainstem involvement in MS patients is very important in the prediction of disease progression. In an EP score that includes BAEP (24), it has not been shown to have any statistically significant correlation between BAEP and EDSS, neither on baseline or follow-up suggesting that BAEP is insufficient in the neurophysiological evaluation of the brainstem in MS and it is necessary to include another measure of brainstem dysfunction.

It is known that VEMP is superior to BAEP in detection of brainstem involvement and because of that, the VEMP score was designed. The VEMP score presents interpretation of VEMP results quantified according to cut-off values (0 = normal response, 1 = prolonged latency, 2 = reduced amplitude, 3 = absent response) calculated separately for every recording position and combined in a unique score, with a minimal value of 0 and maximal of 12. The VEMP score is higher for MS patients with clinical signs of brainstem involvement, correlates with EDSS and disease duration and, according to multiple regression analyses, the VEMP

score is a statistically significant predictor for EDSS (28). These results indicate that the VEMP score is sensitive to brainstem involvement and it could replace BAEP in the EP score and improve its sensitivity to brainstem involvement.

Autonomic dysfunction in multiple sclerosis

The importance of the autonomic nervous system (ANS) is well appreciated, as it is paramount for regulating function of each and every organ in the body. However, our capacity to test its activity somewhat lags behind its significance. The reason is that the ANS is unavailable for direct assessment. As we are unable to test it directly, we must rely on testing its reflexes. This kind of testing is mainly related to cardiovascular and sudomotor autonomic reflexes. The cardiovascular autonomic system is tested by the following methods: blood pressure and heart rate response to Valsalva maneuver, heart rate variability during deep breathing and blood pressure and heart rate changes during tilt table testing (29). Sudomotor function is most precisely assessed by the Quantitative Sudomotor Axon Reflex testing (30). Combining all of these tests we can quantify the severity of ANS dysfunction using the Composite Autonomic Scoring Scale and render the impairment more precisely using the adrenergic, cardiovagal and sudomotor indexes (31). Another method of ANS assessment, nowadays gaining popularity, is the analysis of heart rate variability (HRV). In this method differences in sympathetic and parasympathetic effects on cardiac activity, reflected in the variability of beat-to-beat R-R intervals on ECG, are exploited to estimate the level of activity of each ANS branch (32).

Cardiovascular ANS dysfunction is commonly present in multiple sclerosis (MS) (33). Furthermore, it is recognized in the early stages of the disease as the clinically isolated syndrome (34). Altogether, it affects up to two thirds of patients during the course of the disease (35). It is mainly caused by demyelinating lesions located in the periventricular region of the fourth ventricle that affect the autonomic nuclei, as well as due to the descending and ascending autonomic pathways in the medulla also being affected (36,37). Half of MS patients experience orthostatic intolerance with presenting symptoms that can be insidious and nonspecific such as dizziness, lightheadedness and general malaise (38). The failure of blood pressure to remain stable in an upright position in MS patients is due to impaired sympathetic vasocostrictory reflex that is responsible for maintaining adequate blood pressure during postural change (39). This, in turn, results in orthostatic hypotension (OH), a

significant and sustained decrease of blood pressure upon standing (40) (Figure 2). The symptoms are caused by cerebral hypoperfusion and are typically induced by standing and quickly resolve when lying flat. If the fall of blood pressure is sufficiently pronounced it can lead to falls and even loss of consciousness with the hazard of traumatic injuries. Patients with OH are commonly fatigued and, using the HRV analysis, it has been found that reduced sympathetic activity during standing correlates with the Modified Fatigue Impact Scale in MS patients (41). Another variety of orthostatic intolerance is the postural orthostatic tachycardia syndrome (PoTS). It is characterized by sustained heart rate increase on orthostatic challenge without concomitant OH (40). PoTS is recognized to be present in MS more frequently than in healthy controls and its presence is explained by demyelinating brainstem and hemispheral lesions disrupting the physiological heart rate variability modulation (42,43). Although the true significance of PoTS in MS is not completely elucidated, it is known that PoTS patients have a restricted ability to exercise and an increased sensation of fatigue, which may aggravate preexisting symptoms in MS. Another factor adding to the problem of fatigue in MS is reduced vagal activity that is seen to occur at a younger age in MS (44).

MS patients can also present with more severe cardiovascular symptoms, which can actually be secondary to disease activity. Acute central nervous system lesions, including demyelinating lesions, can induce an increased release of catecholamines causing necrotic changes in cardiac myocytes and disrupt the endocardial conduction system leading to arrhythmias such as sinus bradycardia or paroxysmal atrial fibrillation (45,46,47). There have even been reports of cardiogenic shock and pulmonary edema as a presenting symptom of MS due to active lesions in the brainstem affecting the solitary tract nucleus (48). Furthermore, studies have shown that HRV is reduced in MS patients compared to healthy subjects (49,50) and this reduction seems to be related to disease duration (51). This is important since it has been found that reduced HRV is associated with an increased risk of cardiac events (52). Therefore, the occurrence of cardiac symptoms in an MS patient with no known cardiac disease should prompt consideration of MS relapse as a possible etiology. An interesting finding is that HRV analysis may also be useful in predicting the known cardiac side effects of fingolimod, an immunomodulatory treatment, in an individual MS patient. (53)

Reduced sweating ability has also been documented in MS patients. Quantitative assessment has shown a lower sweating response compared to healthy controls without a disease specific pattern (54). The MRI lesion load as well as neurologic disability is associated with development of thermoregulatory hypohydrosis. However, sweating impairment can already be seen in the early stage of multiple sclerosis, the clinically isolated syndrome (34). These

abnormalities of sweating to heat exposure seem to result from the disruption of central sudomotor pathways connecting the anterior hypothalamus with the intermediolateral columns of the spine (55). It is important to stress that heat intolerance in MS patients can lead to pseudorelapses, the so called Uhthoff phenomenon, which underlines the importance of adequate thermoregulation in MS.

Although autonomic dysfunction is usually considered as a consequence of MS activity, the interaction is more complex and not completely one-sided. Namely, the ANS participates in the regulation of the immunological system via adrenergic and cholinergic receptors on the immune cells (56). Its anti-inflammatory effect is mainly based on sympathetic activity that inhibits production of Th1-derived proinflammatory cytokines while stimulating production of Th2-dervied antiinflammatory cytokines (57). Thus, sympathetic dysfunction, which is more pronounced in the relapsing remitting phase, increases inflammation and further potentiates MS activity. Therefore, research of ANS dysfunction in MS is not only important for the assessment of disease manifestation but also contributes to unfolding the complex mechanisms of interaction between MS and the immune system.

Sleep disorders in multiple sclerosis

Sleep disorders in multiple sclerosis (MS) are more common than in the general population and, depending on the study, they account from 25% to 54% of cases (58). The immunological background of disease development in both multiple sclerosis and sleep disorders has been proposed as a possible common pathophysiological mechanism and recent findings of disrupted melatonin pathways in MS patients suggest a multi-level causative mechanism of the development of sleep disorders in MS. Importantly, sleep disorders are considered to be one of the crucial etiological factors in development of fatigue, a common and debilitating symptom of MS. More precisely, decreased sleep efficiency detected by overnight polysomnography significantly correlated with fatigue and lack of energy in MS patients compared to controls (59). Furthermore, a recent study showed that obstructive sleep apnea and sleep disturbance in MS patients were significantly associated with multiple-domain cognitive impairment such as visual memory, verbal memory, executive function, attention, processing speed, and working memory (60). However, sleep disorders are commonly undiagnosed and untreated in the MS population (61).

Although almost all of the major subgroups of sleep disorders such as insomnia, sleep disordered breathing, REM sleep behavior disorder, narcolepsy and restless legs syndrome have been described in MS patients, a higher prevalence in the MS population than in healthy controls was well established for insomnia, obstructive sleep apnea, and restless legs syndrome (RLS) (62,63,64). Insomnia is more frequent in patients with multiple sclerosis (40%) than in the general population (10-15%) and it has been proposed that insomnia in MS occurs due to a multifactorial etiology associated with MS *per se* like nocturia, spasticity, pain and depression (65).

Sleep-disordered breathing are disorders characterized by respiratory abnormalities during sleep. The most common among them is obstructive sleep apnea (OSA) which is characterized by repeated collapse of the upper airway during sleep with consecutive sleep fragmentation and intermittent hypoxia resulting in increased daytime sleepiness and higher risk for development of atherosclerosis. Multiple sclerosis brainstem lesions could be additional risk factors for development of OSA (66). One study included 62 MS patients and 32 healthy controls who where evaluated by overnight polisomnography, showed the prevalence of obstructive sleep apnea was 58% and 47%, respectively (67).

A high prevalence of restless leg syndrome (RLS) in MS patients has been confirmed in several studies (68,69,70,71) and they have been correlated with disease duration, older age and cervical cord lesions. Distinguishing RLS from other motor and sensory symptoms in MS can be difficult. Unlike leg discomfort encountered in RLS which is worse in evening, leg spasms, often seen in MS patients, are worse on awakening and can occur at any time of the day.

The prevalence of REM sleep behavior disorder (RBD) in the general population ranges from 0.38% to 0.5% (72). RBD is a parasomnia characterized by loss of muscle atonia during REM sleep and consecutive abnormal motor or verbal behaviors associated with unpleasant dreams (73). A study that investigated prevalence of RBD in 135 MS patients and 118 healthy individuals using RBD questionnaires found four (2.9%) MS patients and none of the healthy controls having RBD (74). There are also case reports of RBD in MS patients which suggest that a MS lesion in the proximity of the penduculopontine nucleus causes this disorder of REM sleep (75,76).

In addition to the case series describing narcolepsy features in MS patients (77), a study on the secondary causes of narcolepsy has revealed that MS is the fourth most common cause after inherited disorders, CNS tumors and brain injury; in this study, 12% of the cases of

secondary narcolepsy were due to MS (78). The fact that both of these diseases are related to human leukocyte antigen DQB1*0602 might suggest that similar autoimmune process may be important in development of narcolepsy and MS. Finally, hypothalamic MS lesions resulting in low CSF hypocretin levels have been described to cause hypersomnia in affected patients (79).

Several humoral immunologic factors, such as IL-1 and TNF alpha, have been implicated in development of sleep disorders and sleepiness. Since MS is proven to be characterized by immune abnormalities, the notion that MS and sleep disorders share a similar background seems plausible. However, sleep disorder should be viewed separately due its differing etiopatological grounds. Considering the fact that sleep disorders largely contribute to development of fatigue, the most common and debilitating symptom of MS, assessment of sleep disorders in multiple sclerosis is important.

Conclusions

In conclusion, EPs are reliable procedures to predict disability in MS patients. The index of global EP alteration (EP score), which combines alterations in VEP, BAEP, motor and somatosensory EP, shows significant correlation with the EDSS score at the time of neurophysiological study and at 1, 3 and 5 years of follow-up. Furthermore, autonomic nervous system dysfunction can lead to an array of clinical symptoms often observed in MS patients. There is a connection between dysfunction of autonomic cardiovascular reflexes and development of cardiac side effects of several drugs that are used in MS treatment; and cardiovascular and thermoregulatory autonomic dysfunctions in MS have considerable potential to adversely affect exercise. Finally, sleep disorders largely contribute to fatigue in MS, making formal assessment of sleep important.

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Figures

Figure 1.

Example of EP score (VEP, SSEP of upper and lower extremities) where normal response is scored with 0, prolonged latency with 1, reduced amplitude with 2, and absent response with 3: presented EP score has value of 6 (1+2+3)

a) VEP: Prolonged latency of P100 wave = 1;
b) Tibial nerve SSEP: Reduced amplitude of P40-N50 complex on the left side = 2;
c) Medial nerve SSEP: Absent response on the right side = 3

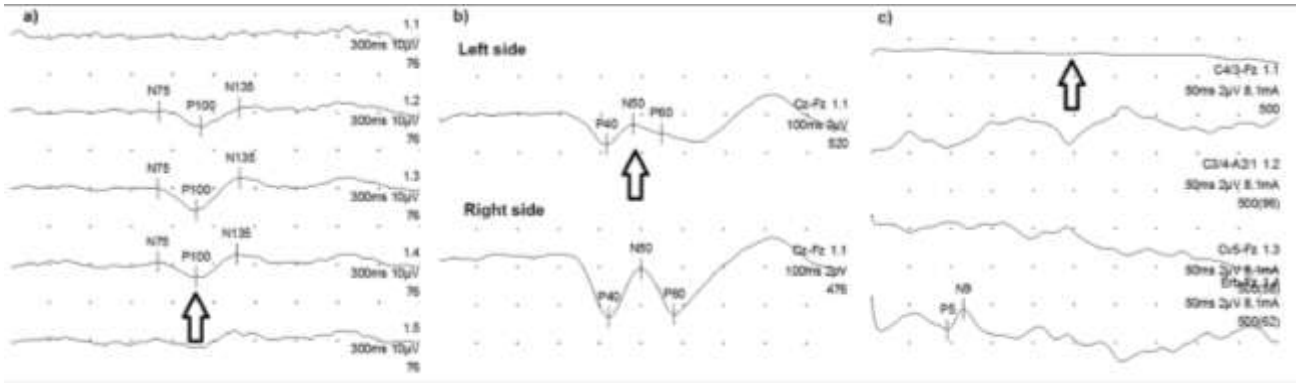

Figure 2.

Autonomic nervous system testing in an MS patient showing abnormal blood pressure response to Valslava maneuver and significant drop in blood pressure upon tilt-up.