

## TRENDS IN NEUROPHYSIOLOGY OF MULTIPLE SCLEROSIS

### VISUAL EVOKED POTENTIALS IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

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Demyelination of optic nerve fibres causing deficit of visual acuity is often the first clinical manifestation of multiple sclerosis. Patients are indicated for visual evoked potential (VEP) examination to confirm slowing of conduction velocity in the optic nerve. A typical finding during VEP examination and full-field visual stimulation is prolongation of P100 wave latency with relatively preserved shape of the N-P-N complex and normal amplitude. The most sensitive parameter is the side-to-side difference in P100 latency. In some cases, response amplitude is reduced as well and the N-P-N complex is more poorly reproduced but the P100 latency prolongation is present in all cases.

Sensitivity to detect demyelination damage in optic nerve fibres is very high, between 90-100% in the literature. The VEP examination assists in detecting pathology even when the neuro-ophthalmology examination is normal. Past retrobulbar neuritis may be detected by VEP even after recovery.

VEP examination, thanks to its high sensitivity, has a fundamental position in the differential diagnosis of disorders of visual acuity and in diagnosis of demyelination damage to the optic nerve as clinically isolated deficit in the form of retrobulbar neuritis. Correct and early indication of the VEP examination plays an important role in the initiation of proper treatment and lowering the risk of irreversible consequences.

### FUNCTIONAL MRI IN THE DIAGNOSIS AND PROGNOSIS OF MULTIPLE SCLEROSIS

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Whereas morphological MR imaging provides clear evidence of white and gray matter lesions reflecting multiple sclerosis (MS) pathology, functional MRI (fMRI) studies of the motor, visual and cognitive networks in MS patients have provided evidence of more diffuse cortical changes. Compared with healthy subjects, fMRI changes are characterized by expansi-

on within physiological task-related networks, such as more prominent participation of higher-level areas or recruitment of additional areas, as well as differences in resting state networks and disrupted within-network connectivity. Longitudinal fMRI studies have demonstrated that the observed abnormalities vary over the course of the disease, even in patients in disease remission (i.e., outside of relapses). Treatment interventions, such as treatment of leg spasticity with intramuscular botulinum toxin, may cause notable, even if transient, normalization of task-related networks. Functional MRI changes in MS reflect morphological MRI abnormalities, especially when more sensitive techniques are applied to detect normal-appearing white and gray matter of the brain and spinal cord. This phenomenon fits in the more widely described mechanism of increased recruitment within functional networks to at least partially compensate for structural damage in brain diseases as diverse as stroke and amyotrophic lateral sclerosis (Weiller et al., 2006).

While notable progress has been made to improve prognosis of the clinical course of MS using sophisticated morphological markers, e.g., (Kalincik et al., 2012; Zivadinov et al., 2013), functional MRI might also contribute to improve disease monitoring prognosis. Finally, functional MRI may be used to study the effects of different therapies on central nervous system engagement (Filippi and Rocca, 2013).

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## NEUROPHYSIOLOGICAL METHODS IN EVALUATION OF PAIN IN MULTIPLE SCLEROSIS

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Pain of various origin is a common symptom in patients with multiple sclerosis (MS) with the estimated prevalence between 50 to 85%. Central neuropathic pain (which is defined as a pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system) affects about 30% of this group of patients. According to current EFNS (European Federation of Neuropathic Societies) guidelines on neuropathic pain assessment, neurophysiological and psychophysiological methods play an important role in the diagnostic process of neuropathic pain, together with clinical examination and validated screening tools and questionnaires, and functional neuroimaging.

Psychophysiological measures are mainly based on quantitative sensory testing (QST) and its dynamic applications. Common QST methods may be defined as a measurement of perception in response to external stimuli of controlled inten-

sity, which allows the evaluation of detection and pain thresholds for various modalities. A detailed QST protocol has recently been developed and validated by German Research Network on Neuropathic Pain. This protocol consists of the assessment of 13 parameters reflecting the sensitivity and pain perception for thermal, touch, pressure, vibration and pinprick stimuli, and allows the detailed clinical description of particular patient with the evaluation of complex sensory profile. In neuropathic pain patients, it may help to characterize particular painful neuropathic syndromes, and predict or monitor treatment effects including effect of treatments upon different pain components.

So called “dynamic QST“ (dQST) is a group of methods, where the pain-perceiving system is stimulated in a way that exposes a certain mechanism of pain processing, particularly its central modulation. These methods include the tests of central integration, such as temporal summation (TS, also called wind-up) and spatial summation, and tests of descending control, e.g., the conditioned pain modulation (CPM). These methods can't be used for diagnosis or confirmation of the presence of pain. However, their setting is probably one of the factors, predetermining the development of chronic pain. They thus may reflect the „pro-nociceptive“ disposition of the particular patient.

Among neurophysiological methods, pain-related evoked potentials and some of the pain-related reflexes are the most

relevant tests for the assessment of pain in MS patients.

Pain-related evoked potentials are the easiest and most reliable neurophysiological methods for assessing the function of nociceptive sensory pathways. Various types of stimuli can be used to evoke the response of pain-related neuronal structures: laser-evoked potentials (LEPs), contact-heat evoked potentials (CHEPs) and potentials elicited by a surface concentric electrode that provides a preferential activation of superficial terminals (i.e. small-diameter afferents) (PREPs). These methods show a clear correlation with pain and are highly specific in its confirmation, while their sensitivity depends on the definition of abnormality (being quite low if only the absence of the response is considered to be abnormal, with a rapid increase if also a reduction of amplitude is taken into consideration).

Pain-related reflexes appear to be diagnostically useful particularly for facial pain (e.g. trigeminal neuralgia, which represents one of the most frequent types of pain in MS patients). Two brainstem reflexes (early (R1) blink reflex and early (SP1) masseter inhibitory reflex) are efficient tools to reveal symptomatic forms of trigeminal neuralgia with a very satisfactory sensitivity and specificity.

The cutaneous silent period (CSP) is a spinal inhibitory reflex with cortical modulation. The response is recorded from the small hand muscles after noxious stimulation of the fin-

gers, which reflects the suppression of activity in spinal motor nuclei. The method has been tested in various pain conditions and is clearly related to clinical symptoms of thermal and pain perception disturbance. CSP was not systematically studied multiple sclerosis, but has repeatedly been shown to display clear abnormalities in spinal cord lesions (e.g. cervical myelopathy). However, its correlation with presence of pain seems to be limited.

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## NEUROPHYSIOLOGICAL ASSESSMENT OF SPASTICITY IN MULTIPLE SCLEROSIS

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**Objective:** Spasticity is a frequent and often disabling feature of multiple sclerosis (MS). Up to 80%–85% of MS cases suffer from different levels of spasticity. Appropriate management of spasticity is therefore an important part of the patient's care. Muscle hypertonia is generally easy to recognize clinically, quantifying it is quite a complex matter. Correlation between the clinical and neurophysiological measures makes it especially difficult. The aim of the study is to review the main methods of evaluating spasticity published in the scientific literature with stress on our own experience.

**Methods:** In this session we will present neurophysiologic tests used in assessment of spasticity with a special stress on the comparison of commonly used Modified Ashworth Scales scores (MAS), H-reflex testing, cutaneous and cortical silent periods, and brainstem reflexes. The main treatment options of pharmacological and non-pharmacological approaches will be discussed.

**Results:** Oral antispastic medication, therapeutic exercise and physical modalities are commonly used. From a phar-

macological perspective of spasticity treatment, it is strongly recommended to use local chemodenervation with botulinum toxin for intramuscular administration under the EMG guidance. A modern approach to treat generalised spasticity is a continuous intrathecal baclofen (ITB) administration directly into the cerebrospinal fluid under neurophysiological monitoring.

**Conclusion:** Adequate evaluation and management of spasticity requires multidisciplinary approach and the setting of realistic goals that need to be achieved on an individual level, with regard to every single patient's needs. Different options for spasticity management are available, however, choice of treatment hinges on a combination of the extent of symptoms, patient preference, and availability of services.

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## NEUROPHYSIOLOGICAL METHODS OF AUTONOMIC NERVOUS SYSTEM TESTING IN MULTIPLE SCLEROSIS

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Autonomic dysfunction (AD) is commonly seen in patients with multiple sclerosis (MS). The most common manifestations of AD in MS patients include bladder or bowel dysfunction, impairment of sexual performance, pupillomotor or sweating alterations and orthostatic hypotension. Furthermore, AD is supposed to be related to fatigue. The incidence and severity of the symptoms related to AD correlated with the degree of disability. The lifetime prevalence of autonomic impairment reaches up to 80 % in MS population.

Besides medical history and validated questionnaires, neurophysiological testing of cardiovascular and sudomotor functions are most commonly used for evaluation of autonomic nervous system impairment in MS patients.

Of the cardiovascular tests, analysis of heart-rate variability in the time- and frequency-domain has repeatedly been pub-

lished as a suitable method for evaluation of cardiovascular autonomic nervous system status in MS patients (the latter being mainly represented by spectral analysis of heart-rate variability). Autonomic challenge manoeuvres (suited for activation of sympathetic or parasympathetic nervous system) are also frequently used for this purpose and comprise Valsalva manoeuvre, deep metronomic breathing, response to active standing, sustained handgrip test, cold pressor test or cold face test. Furthermore, orthostatic challenge testing represented by head-up tilting (besides above mentioned active standing) can be useful in MS patients.

Sudomotor functions in MS are most frequently tested using the sympathetic skin response (mainly because of wide availability of testing equipment), which seems to be less sensitive comparing cardiovascular tests. The availability of other testing methods, which may be used for the sweating evaluation (thermoregulatory sweat test, quantitative sudomotor axon reflex or similar tests) is lower, but they seem to have higher sensitivity in evaluation of sudomotor dysfunction in multiple sclerosis.

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## NEUROPHYSIOLOGY IN DIAGNOSIS AND PROGNOSIS OF MULTIPLE SCLEROSIS IN AGE OF MAGNETIC RESONANCE IMAGING

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**Objective:** The advent of magnetic resonance imaging techniques has greatly reduced the diagnostic value of neurophysiological tests in MS, particularly evoked potentials. In disease progression, most of MS patients accumulate inflammatory lesions, axonal damage, and progressive brain atrophy, along with an increasing degree of disability. More promising is the utilization of neurophysiological tests to quantify the severity of white matter involvement.

**Methods:** Evoked potentials (EP) have been still used in multiple sclerosis (MS) especially in its early diagnosis. Recently, multimodal EPs appears to be a prognostic factor for

disease progression. Deeper insights about causal and functional relationships in plasticity of the motor system in patients with MS were gained by neurophysiological techniques, predominantly by transcranial magnetic stimulation.

**Results:** Visual evoked potential (VEP) are preferentially used in early diagnosis of MS for detection of subclinical optic neuritis. Somatosensory (SEP) and motor (MEP) evoked potentials reveal subclinical lesions in the CNS and could be a supplementary diagnostic tests for sensory and motor system disturbances. MEP abnormalities correlate with the degree of motor impairment and disability. A number of functional imaging studies have assessed patterns of brain activation during simple motor tasks in MS patients and their relationship with CNS damage and motor function.

**Conclusion:** Evoked potentials are functional neurophysiological methods highly sensitive in revealing „silent lesions“ especially at the beginning of MS. Multimodal evoked potentials have indisputable benefit of prognostic value to determine non-responders, „benign“ course of the disease and identification of patients with significant disease progression. A battery of neurophysiological tests could be useful in monitoring the disease progression in individual patient and as surrogate endpoints in clinical trials.

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