Luka Crnošija[1], Magdalena Krbot Skorić[2], Tereza Gabelić[2], Mario Habek[1,2]

THE ROLE OF EVOKED POTENTIALS IN MULTIPLE SCLEROSIS

[1] University of Zagreb, School of Medicine
[2] University Hospital Centre Zagreb, Department of Neurology

INTRODUCTION

Multiple sclerosis (MS) is chronic inflammatory demyelinating disease of the central nervous system (CNS), and the leading cause of disability in young adults. Considering that inflammation can affect any part of the CNS, this disease can present itself with myriad of symptoms, thus it is sometimes called "the disease with thousand faces". Symptoms that patients develop are caused by inflammation leading to demyelination (i.e. the disruption of the myelin sheath) which results in slowing of impulse conduction through neuronal pathways, and functional deficits in systems innervated by demyelinated nerve fibres (e.g. locomotor and sensory system). For example, one of the more important and frequently affected functions, particularly in patients with longer disease duration, is walking. According to North American Research Committee on Multiple Sclerosis registry 45% of MS patients aged between 18-64 years use some form of mobility devices (1). Moreover, MS is the leading cause of wheelchair use in this age group (2). It is only recently that a wider range of drugs for treating MS became available, and they can be divided in two groups, i.e. the first and second line. The second line of treatment includes more efficient drugs, but with more severe possible side-effects. This line of treatment is used in patients with more aggressive disease course or in patients who were unresponsive to the first line treatment.

Considering this wider range of therapies available today, one of the challenges is to estimate which therapy is the best choice for specific patient taking into account his or her current health state and factors which may indicate future course of disease in this patient. In addition to neurological examination, brain and cervical spinal cord magnetic resonance imaging (MRI) is typically used in order to gain insight into patients' current state and disease activity. Studies have shown that demyelinating lesions detected with the MRI in some parts of the CNS, such as the brainstem, carry higher risk for worse disease course (3-5). On the other hand, it is also known that MRI findings do not always correlate with clinical finding, meaning that patient may have some symptoms, but no corresponding lesions are evident on MRI. The latter is referred to as the clinico-radiological paradox (6), which is particularly emphasized in the brainstem region (7). Thus there is a need for additional methods and tools for assessing different neurological system, and evoked potentials are one of these methods.

EVOKED POTENTIALS

Evoked potentials (EP) are a group of different slightly different diagnostic procedures, but all share the same principle; the response of specific neural pathway to appropriate stimulation is recorded and analysed. Using this principle, numerous neural pathways and systems can be inspected, for example somatosensory system (somatosensory evoked

potentials – SSEP), vestibular (vestibular evoked myogenic potentials – VEMP), visual (visual evoked potentials – VEP), auditory (brainstem auditory evoked potentials – BAEP), and motor system. For instance, one of the most commonly used types of stimuli is the electric impulse. The electric impulse is sensed by sensory nerve fibres which then emit the information from the place of stimulation (e.g. ankle) to cerebral sensory cortex. The sensory information is transduced as a transient "travelling" change of the electric potential on the membrane of nerve cells, and these changes in the electric potential (so called evoked potentials) can be recorded via electrodes placed along the examined neural pathway. Several parameters of the recorded response are analysed (i.e. the amplitude, latency and morphology of the response) and compared to the referent values of healthy population. The name of the recorded response (the so called "wave") usually contains information on the polarity of electric potential change (i.e. positive (P) or negative (N)), and the approximate time (measured in milliseconds) needed for the evoked potential to travel the distance from the site of stimulation to the measuring electrode in healthy population. For example, P100 wave describes positive change of the electric potential measured at 100 ms after the stimulation.

THE ROLE OF EVOKED POTENTIALS IN MULTIPLE SCLEROSIS

The role of EPs in the assessment of MS patients changed over time, and with the emergence of new technologies, especially the magnetic resonance imaging (MRI), EPs were unjustifiably considered less useful. In recent years EPs are becoming increasingly important in MS diagnostics, which is clearly reflected in the fact that visual evoked potentials became enlisted in the new criteria for diagnosing MS (8). In contrast to imaging methods, such as the MRI, EPs can give us insight in the actual function of the specific neural pathway. Since demyelinating inflammation of the central nervous system is the hallmark of MS, typical finding on EPs in MS are prolonged latencies of responses. Other common findings are decreased amplitudes or even absence of response depending on the degree of damage of myelin sheaths or neurons themselves.

VISUAL EVOKED POTENTIALS (VEP)

Considering that the first manifestation of MS in about 20% of patients is the inflammation of the optic nerve (i.e. optic neuritis – ON), VEPs are one of the most commonly used methods among Eps (9). Typical finding on VEP in the acute phase of ON are prolonged latencies (Figure 1) and reduced amplitudes of the responses. Although the amplitudes of VEP responses return to normal some time after the ON, the latency of the response usually remains prolonged. The sensitivity for identifying a patient who experienced ON some time in the past is 77-100% (10, 11). It is for this reason that VEPs can be used for estimating whether the patient fulfils one of the criteria for diagnosing MS, i.e. the dissemination in time.

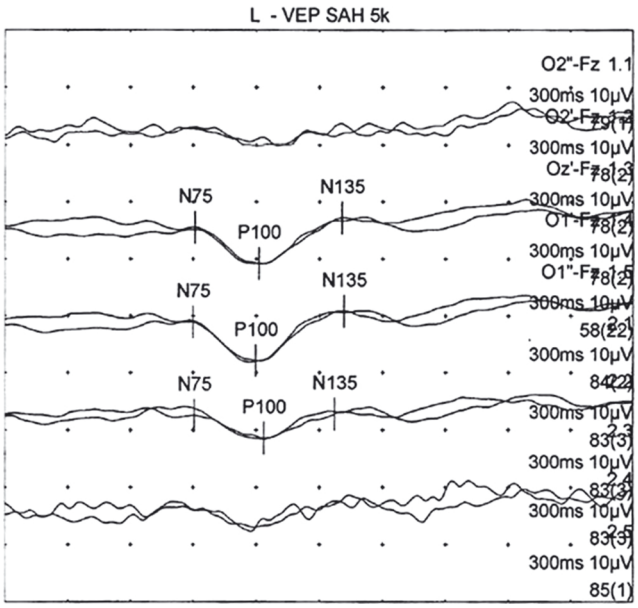

Fig. 1: An example of prolonged latency of visual evoked potential response. P100 wave was recorded more than 120 ms after the stimulation.

SMATOSENSORY EVOKED POTENTIALS (SSEP)

SSEPs of upper and lower extremities can give us insight in the function of somatosensory pathway in dorsal columns of the spinal cord and thalamo-cortical sensory system in the brain. The value of evoked potentials as a method lies primarily in their ability to detect subclinical damage of the nervous system, and SSEPs of lower extremities (Figure 2) are considered to be one of the most valuable methods among Eps (12). Studies have shown that SSEPs of lower extremities can detect the damage of spinal cord somatosensory system in as much as 80% of MS patients without corresponding clinical symptoms (13).

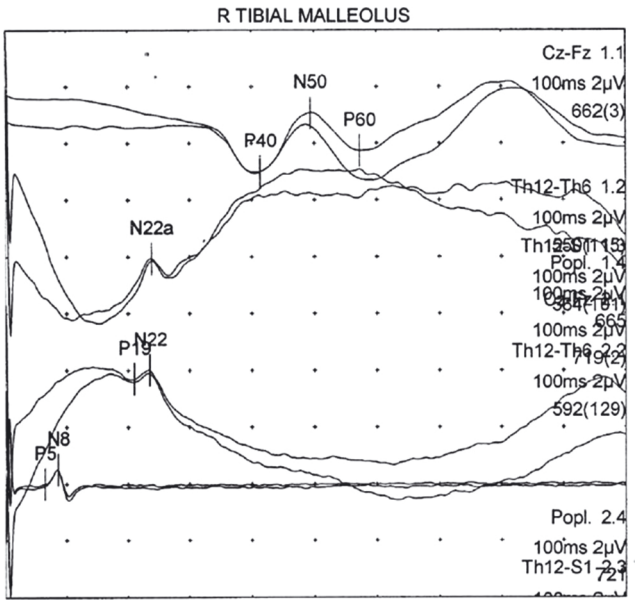

Fig. 2: An example of normal response recorded during SSEP of lower extremities. In this diagnostic procedure tibial nerve is stimulated via electric impulse at the level of ankle, and the responses are recorded at several spinal cord levels, as well as over sensory cortex of the brain.

BRAINSTEM EVOKED POTENTIALS

Brainstem auditory evoked potentials (BAEP) and vestibular evoked myogenic potentials (VEMP) evaluate the function of auditory and vestibular system (i.e. system responsible for sense of balance) at the level of the brainstem. While BAEP is one of the least sensitive methods among EPs (14), VEMP has been shown to be superior compared to BAEP, as well as compared to neurological exam and brain MRI (15). SSEP of the trigeminal nerve has also proven to be valuable in detecting lesions of upper portion of the brainstem (i.e. the mesencephalon) in MS patients (16).

THE EVOKED POTENTIAL SCORE

Considering that by using different EP methods various parts of the nervous system can be evaluated, an idea to create an indicator of the global state of function of MS patients' nervous system was born. By marking every VEP and BAEP response, and motor and SSEP responses of upper and lower extremities according to hypothetical degree of damage, and summing-up all of the result, Leocani et al. developed the so-called evoked potential score (EP score). In this model normal responses were marked as 0, prolonged latencies as 1, abnormal morphologies of waves was marked as 2, and an absence of response was marked as 3 (17). In this longitudinal study patients were followed-up for about three years, and EP score correlated well with neurologist's clinical findings, but it also showed predictive value. Subjects who had EP score higher than the median of this sample had 72.5% higher risk for clinical worsening in the control period. Also, another retrospective study with longer follow-up period confirmed the predictive value of EP score (18).

One of the shortfalls of both studies is that only BAEP was used to evaluate the function of the brainstem. This is especially important considering the before-mentioned correlation between brainstem lesions and higher risk for worse course of the disease. It is for that reason that the VEMP score was developed. VEMP score correlated well with both clinical and MRI findings of brainstem integrity, and it also had independent predictive value of clinical state of MS patients (19, 20). The value of VEMP score as a predictor of disease course is still a matter of study.

CONCLUSION

Evoked potentials are very valuable neurophysiological method in diagnostics and follow-up of MS patients. The biggest advantage of EPs is the ability to detect subclinical damage of the nervous system. Also, considering that this method gives us information about the functional state of the inspected neural pathway, it is complementary to MRI when evaluating MS patients. Some studies have shown that by using a battery of EPs can be used to gain better understanding of the current state of individual MS patient, and can even be used to identify patients at higher risk of disease progression. This predictive value is especially important when deciding which therapy is the most suitable one for specific MS patient.

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