Current role of evoked potentials in the neurological diagnostic process

PhD Thesis

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INTRODUCTION

Evoked potentials (EP) constitute a relatively new method of clinical neurophysiology allowing functional evaluation of the nervous system. These non-invasive methods give information about the functional state of different tracts within the central nervous system, particularly when the clinical signs and the results of neuroimaging methods are either non-informative or non-conclusive. Evoked potentials are especially useful in the detection of subclinical dysfunction.

The first recognition of visual evoked potentials (VEP) coincides with the discovery of electroencephalography. It was observed already towards the end of the 19th century, that electrical activity of the brain is altered when an intensive light stimulus is applied. However - since these potentials are of very low amplitude - widespread use of the method was made possible only by the introduction of computerized averaging techniques.

Visual evoked potentials are suitable for the functional evaluation of the optic system from the retina to the occipital cortex. In clinical practice, it is mainly used for the detection of lesions anterior to the optic chiasm, such as optic neuritis (ON). VEP is a very sensitive method, and in case of optic neuritis it is even more sensitive than magnetic resonance imaging (MRI). VEP is also able to detect subclinical lesions, as it may be positive in patients without any complaints or clinical signs.
Somatosensory evoked potentials (SEP) can detect lesions within the proprioceptive sensory system from the peripheral nerve to the cortex. It is however not suitable to examine the spinothalamic system.

In theory, responses over the somatosensory cortex may be evoked by the stimulation of any peripheral nerve, however in clinical practice the median and the tibial nerves are examined most often. According to the literature, evoked potentials of lower limb nerves are more frequently positive than of the upper limbs, as a longer segment of the tract is assessed. Therefore, we chose to examine the tibial nerve for our studies.

In patients with multiple sclerosis (MS), somatosensory evoked potentials were first carried out in 1968; by the 1980’s, it became a routine and important method in the diagnostic process of MS.

Motor evoked potentials (MEP) are mainly used to assess the function of the corticospinal tract. MEP differs from the sensory evoked potentials described above in that here not a peripheral nervous structure but the motor cortex is stimulated. Non-invasive electric stimulation of the motor cortex hasn’t gained widespread popularity, because it is painful and poorly tolerated by subjects. Transcranial magnetic stimulation (TMS) - introduced in 1985 - however allows painless, non-invasive excitation of neural structures located deep in the body such as the cortex, spinal nerve roots, and the intracranial portion of the facial nerve. The main diagnostic value of TMS is to detect subclinical dysfunction of the corticospinal tract. It is most often used in multiple sclerosis, amyotrophic lateralsclerosis and myelopathies. It should be emphasized though that normal MEPs do not rule out the possibility of corticospinal dysfunction, only make it less likely.

Vestibular evoked myogenic potential (VEMP) is regarded as the electrophysiological correlate of the vestibulocollic reflex, which plays a role in stabilizing head position in space. A loud click applied over the ear induces peripheral vestibular activation and results in a short latency inhibitory potential in the tonically contracted ipsilateral sternocleidomastoid muscle (SCM). The reflex pathway starts in the saccular macula, passes through the lateral vestibular nucleus, the medial vestibular tract and ends on the motoneurons of the ipsilateral SCM.

The benefit of VEMP in the clinical setting was first demonstrated in peripheral vestibular pathologies, such as Menière’s disease and vestibular neuronitis. In contrast, little attention has been focused, thus far, on the potential use of VEMP in different central vestibular or brainstem pathologies. In contrast to other evoked potentials, there were only a few studies carried out with VEMP in MS patients.

Evoked potentials are sensitive neurophysiological techniques that have a crucial role in the detection of clinically silent lesions of the nervous system. Prior to the era of modern neuroimaging methods, they played an essential role in the diagnosis of several neurological conditions. Since the introduction of MRI, however, their role in diagnosis has become less important.

**Cervical myelopathy**

Cervical spondylosis and discopathy are common clinical and radiological diagnoses. Among elderly patients, cervical spondylotic myelopathy is the most common myelopathy. With the introduction of MRI an increasing number of patients are identified where spondylotic changes and discal
herniations reach and compress the cervical spinal cord. The significance of these radiological findings with respect to the development of myelopathy is however unclear. MRI scans of the cervical spinal cord might show signal intensity changes in the cord as a sign of compressive myelopathy, but this is not an obligatory finding. In some cases the radiological results are negative, however the patient has clinical signs of myelopathy. In these patients it is obligatory to reveal that the mostly atypical clinical signs of the patients are caused by subclinical myelopathy or not. The treatment of patients with subclinical cervical myelopathy is mainly surgical, the best results are achieved in the initial phase of myelopathy.

**Multiple sclerosis**

Multiple sclerosis is one of the most common neuroimmunological disorders. As it starts in young adulthood, MS presents a considerable burden for both the individual and the society.

According to the McDonald criteria, MRI is the first step in the diagnostic process of MS. In case of a typical clinical picture, the diagnosis of MS may be confirmed with MRI, even without the help of other examinations (i.e. evoked potentials and cerebrospinal fluid examination).

In the era of chronic immunomodulatory treatments, early diagnosis of MS and prediction of disease course have gained increasing interest and importance. The early knowledge of possible disease course may help in identifying the subgroup of patients who will benefit the most from early immunomodulatory treatments.

**AIMS**

The aim of our prospective study was to assess the new and changing role of evoked potentials after the introduction of the modern neuroimaging methods in neurological conditions where evoked potentials were traditionally important in the diagnostic process.

Two patient populations were chosen. In the first group, patients had neuroradiological evidence of cervical spinal cord compression due to cervical spondylosis. Motor and somatosensory evoked potentials were performed to confirm or exclude subclinical myelopathy. We were interested in sensitivity of these methods in detecting spinal cord dysfunction.

The second group consisted of MS patients. The aim was to assess the sensitivity of somatosensory and motor EPs in patients with a first episode of clinically isolated ON in predicting the risk of conversion to MS based on the McDonald criteria, and to compare the sensitivity of EP and MRI results in predicting clinically definitive MS. This issue has lately gained special importance with respect to the timing of the introduction of immunomodulatory treatments. We aimed to characterize the new role of evoked potentials in MS in the MRI era.

In our third examination, we performed vestibular evoked potentials in MS patients, and analyzed its sensitivity and specificity in comparison to MRI.
METHODS

Cervical spondylosis

Fifty-one patients were included in this study (mean age: 54.1 years, range: 35–74 years; 14 women and 37 men). Patients were referred to our Laboratory of Clinical Neurophysiology with the diagnosis of cervical spondylosis and the question of cervical spondylotic myelopathy. All patients had undergone MRI of the cervical spine and had findings of pronounced spondylosis, including ventral ridging, discal herniations, narrowing of the spinal canal; at least some degree of spinal cord compression was an obligatory finding for the inclusion of the patient in the study. We have first classified patients according to the clinical symptoms suggestive of cervical myelopathy and set up three groups accordingly.

Group I (n = 29) contains those patients who showed spinal cord compression on the MRI, but had no complaints or symptoms suggestive of cervical myelopathy. The referral diagnosis for the MRI of these patients had been cervical radiculopathy.

In group II (n = 15), in addition to the MRI findings patients also had minor complaints or symptoms that raised the suspicion of myelopathy, such as gait problem, paresthesias in the legs, subjective complaints of weakness in the legs; definite signs of corticospinal lesion were however not present.

Patients in group III (n = 7) had complaints and neurological signs that confirmed clinically the presence of myelopathy, including signs of corticospinal lesion. Patients in group II and III could also have complaints or symptoms of cervical radiculopathy.

Motor and somatosensory evoked potential examinations were performed in all patients, using the Cadwell Sierra EMG/EP machine (Cadwell Laboratories, Inc., Kennewick, WA, USA).

Muscle responses were recorded by superficial electrodes on both lower limbs from the tibialis anterior muscle. Magnetic stimulation was performed by Magstim 200 stimulator (The Magstim Company Ltd., Spring Gardens, Whitland, UK), with a large 90 mm round coil (peak magnetic field of 2.0 Tesla and monophasic magnetic pulse lasting 1 ms). First the supramaximal electrical stimulation of the common peroneal nerve at the head of the fibula was performed. Next, magnetic spinal nerve root stimulation was carried out, the coil being centered tangentially on the fifth lumbar vertebra. For cortical stimulation, the coil was placed tangentially on the vertex and slid slightly forward and contralaterally to the target muscle. To facilitate the response, patients were asked to perform a slight contraction of the target muscle during cortical stimulation. At least four responses were recorded, but stimulation was continued until the potential was reproducible and its onset was easy to identify. The central motor conduction time (CMCT) was calculated by subtracting the latency of the response to spinal magnetic stimulation from the shortest corticomuscular latency. Abnormality was established either if no cortical response was present or the CMCT was prolonged or showed a side difference in comparison with our laboratory norm values. Amplitude values were not used because of their pronounced variability.

Somatosensory evoked potentials were elicited by the electrical stimulation of the tibial nerve at the ankle. Responses were recorded with superficial cup electrodes on the 12th thoracic vertebra (the spinal N22 response) with the reference electrode 6 cm above on the spine, and on the cortex 3 cm posterior to the vertex (the cortical P40 response) with an Fz reference
electrode. At least 500 stimuli were averaged and each side was examined twice. Stimulation rate was 3 Hz. As the spinal responses were often unreliable, the presence and latencies of the P40 responses were used to determine abnormality with comparison with our laboratory norm values. The amplitude of the P40 waves was not used, only the absence of the responses was considered abnormal in this respect. If the P40 response was abnormal and the suspicion of concomitant polyneuropathy was raised, sural nerve neurographies were performed as well.

For statistical comparison of the number of abnormal MEP and SEP examinations within one group and between groups the chi-square or the Yates corrected chi-square analysis was used. Statistical significance was set at P < 0.05.

**Sclerosis multiplex – optic neuritis**

We studied 27 patients with unilateral ON referred to the Department of Neurology of Semmelweis University, Budapest by ophthalmologists or general practitioners between 2003 and 2006. The mean age of patients was 31.8 years (range: 19–50 years, female–male ratio was 15:12). The patients had no previous neurological disorders. Optic neuritis was defined as a decreased monocular visual acuity developing within a few days, with normal funduscopi, decreased central fusion frequency (CFF) and abnormal visual EPs (VEPs) confirming a prechiasmal lesion. Computerized perimetry was also carried out.

At the presentation of the ON (baseline) a complete neurological examination, tibial nerve somatosensory EP, motor EP examinations and brain MRI scans were performed in all patients. None of the patients had other neurological signs beside the ON and all patients improved after treatment with high-dose methylprednisolone. Follow-up examination was carried out after 4–48 months (mean: 20 months), which included a neurological examination with determination of the extended disability severity scale (EDSS) score and a brain MRI.

**Sclerosis multiplex – VEMP**

Thirty healthy subjects (11 women and 19 men; age range: 21-75 years; mean age: 45 years) and 30 patients with definite MS (20 women and 10 men; age range: 27-60 years; mean age: 43.4 years) were studied. Subjects or patients with either a history or the presence of conductional hearing loss, loss of peripheral vestibular function and with any pathology affecting the SCM were excluded. All MS patients had MRI examinations previously carried out. The time elapsed between the first MRI and the VEMP examination was on average 5.8 years (range: 3 months to 16 years). Control subjects and patients first underwent a neurological and ear, nose and throat (ENT) examination, caloric stimulation of the ears and positional tests. Each ear was stimulated twice (two trials on the left ear and two trials on the right ear). The clicks (0.1 ms rarefaction square waves of 133 dB SPL) were presented through headphones. Patients were lying supine on a bed and were asked to raise and turn their head contralaterally to the ear tested to achieve maximal activation of the SCM ipsilateral to the stimulation. Surface electromyographic (EMG) activity was recorded with superficial electrodes on symmetrical sites over the upper half of each SCM, with the reference electrode located on the upper sternum and the ground electrode on the middle of the forehead. For each trial, EMG responses were averaged over a series of 250 click stimuli delivered at a frequency of 5 Hz.
RESULTS

Cervical myelopathy

In group I, where there were no clinical signs of myelopathy; three patients (10%) had abnormal MEP examinations; in two patients, CMCT was slightly prolonged; one patient had unilateral markedly prolonged CMCT and absent response on the other side. SEP examinations were abnormal in two patients (7%); in one patient P40 latency was slightly prolonged, the other patient had markedly prolonged P40 latency on one side and absent cortical response on the other side as in the MEP examination.

In group II, where suspicious but nonconfirmative clinical signs of myelopathy were present, 12 patients had MEP abnormalities (80%); two patients had absent responses, 10 had prolonged CMCT. Abnormalities were usually bilateral. SEPs were abnormal in four cases (27%), mostly in the form of P40 latency prolongation (only one patient had a unilateral absent response). The difference between the number of abnormal MEP and SEP examinations was statistically significant in this group (P ≈ 0.0034). The difference between the numbers of abnormal MEP examinations in group II and I was statistically highly significant (P < 0.0001), whereas this difference for SEP examinations was not significant (P ≈ 0.0701).

In group III almost all patients had both abnormal MEP and SEP examinations (85% for both), which were in most cases bilateral. In this group the different sensitivity of the two types of examinations was no longer apparent.

Sclerosis multiplex

After analyzing the results, patients were classified into three subgroups based on baseline EP and follow-up MRI results. In Group 1 (n = 6), all patients had abnormal baseline EP results. In Group 2 (n = 2), all patients had normal baseline EP results and normal baseline and follow-up MRI results. In Group 3 (n = 19), all patients had normal baseline EP results and abnormal follow-up MRI results.

At baseline, the tibial nerve SEP and/or the MEP examination of the lower extremities were abnormal (i.e. at least on one side) in six out of the 27 patients (Group 1). In five patients, SEP and MEP examinations were both abnormal, in one patient only MEP was positive. Of these six patients, baseline MRI examination was abnormal in four patients, according to the modified Barkhof/Tintore criteria (confirming dissemination in space). The MRI of the remaining two patients had lesions suspicious for MS, but they did not meet the Barkhof/Tintore criteria. However, this may be due to the circumstance that the scans were performed with 1.5 T field strength. The follow-up MRI examination of all the six patients was abnormal according to the revised McDonald criteria, but only four of them were diagnosed as clinically definitive MS, with one or two relapses during the time elapsed. Two patients remained symptom-free. The EDSS score of all the six patients was 0.0 at the time of neurological examination.

The rest of the patients had normal EP examinations (21/27, 77%, P = 0.0293). Of them only two patients (Group 2) had negative SEP and MEP examinations together with negative baseline and follow-up MRI
examinations. Not surprisingly, they remained symptom-free and were considered to have had an isolated, non-MS associated episode of ON. The majority of the patients, 19 out of 27 (Group 3), had normal baseline SEP and MEP examinations, but abnormal follow-up MRI based on the revised McDonald criteria. The baseline MRI in these patients was abnormal in 14 and normal in five cases. Of the 19 patients, only three showed the conversion to clinically definitive MS but had an EDSS score of 0.0 at the time of neurological examination. The other 16 patients, in spite of MRI results supporting the diagnosis of MS (McDonald criteria), remained clinically symptom-free. Altogether of the 27 ON patients, 25 (Group 1-3) (P = 0.0002) fulfill the diagnosis of MS in a relatively short period of follow-up (two years on the average) based on the revised McDonald criteria.

Sclerosis multiplex - VEMP

A total of 22/30 MS patients (73%) had a reproducible biphasic response upon stimulation of both ears. In four patients, there was no recordable response upon stimulation of either side, while four patients had only a unilateral response. Four patients showed prolongation of P13 latencies, three patients on both sides and one patient on the left side only. In one patient, prolonged N23 latency was observed. In total, 12/30 MS patients (40%) showed some type of abnormality (absent response or prolonged latency). No significant differences were found between male and female subjects. The interside difference for P13 latency in controls was 1.00 ms (SD: 1.12 ms). In those MS patients with responses on both sides, it was 0.57 ms (SD 0.82 ms). Only one patient had an interside difference of >/mean+2.5 SD. Statistical comparison of control subjects and MS patients showed a significant difference on both sides with respect to the mean P13/N23 amplitude (P<0.05 on both sides), the amplitude in MS patients being significantly lower. There was also a significant difference between mean P13 latencies on both sides (P<0.01 on both sides), the latency being longer in MS patients, but not for mean N23 latencies.

CONCLUSIONS

Based on our examinations, the following conclusions can be drawn concerning the changing role of evoked potentials in the diagnosis of central nervous system disorders.

The results of our study first show that pronounced cervical spondylosis with spinal cord compression is not necessarily accompanied by the development of myelopathy; in fact the large majority of these patients - undergoing MRI examination because of cervical radiculopathy - have neither clinical, nor electrophysiological evidence of myelopathy. Electrophysiological evaluation of the spinal cord in cases of MRI proven cervical spondylocytic spinal cord compression has its greatest value when patients present with mild, non-specific, non-confirmative complaints and symptoms with respect to myelopathy. In this select group of patients, MEP is significantly more sensitive than SEP; it proved very useful in detecting myelopathy in its early stages.

If evoked potentials are negative, clinical and electrophysiological follow-up of patients is necessary. Patients with positive evoked potentials are referred for neurosurgical evaluation. Therefore, EP results play an important role in the appropriate management of patients.
In MS patients, abnormal EP results at the time of first clinical episode (optic neuritis) anticipate early clinical conversion; therefore, this subgroup of patients may benefit more from early immunomodulatory treatments. Abnormal EP results at baseline can be considered as a predictive factor only for the quicker development of the clinical signs of MS, but do not have a predictive value for the development of MS itself as diagnosed by the McDonald criteria. Therefore, it appears that the significance of EP examinations in the diagnosis of MS – at least in one of the most common clinical settings of MS, presenting initially, as ON – has diminished in the MRI era and EPs play more a role in prognosis by indicating the severity of the disease and forecasting earlier clinical conversion. In this respect, however, they proved to be more sensitive than MRI performed at the time of first clinical episode.

The results of vestibular evoked myogenic potentials (VEMP) in patients with multiple sclerosis have shown that VEMP is a simple and quick method to detect silent lesions in central vestibular pathways, commonly affected in MS. In some cases, it proved to be even more sensitive than MRI.

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PUBLICATIONS

Publications related to the thesis


Other publications


Simó M. Sclerosis multiplex és kezelése. Orvosképzés, 2008; LXXXIII.évf, 5:355-357.


Abstracts


