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DYNAMIC CHANGES OF VISUAL EVOKED POTENTIALS AND BRAINSTEM AUDITORY EVOKED POTENTIALS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Abstract

Evoked potentials are widely used in diagnosis of multiple sclerosis (MS), but not sufficient data are available for their prospective role in the course of disease. The presentation is a longitudinal study in the Clinic of Neurology at MHAT – NHH – Sofia from Aug 2009 to Mar 2012. It includes 52 patients with clinically definite multiple sclerosis according to revised MacDonald criteria (2005/2010). Paternal visual evoked potentials (PVEP) and brainstem auditory evoked potentials (BAEP) were examined consecutively during the study and these results were compared with the grade of disability according to Expanded Disability Statement Scale (EDSS). The follow-up was done at registered relapses and also at patients without new complaints – one or two years since the initial examination. For quantitative assessment of pathological EP changes, a total evoked potential (EP) score was formulated. This score is a sum of the individual PVEP and BAEP scores. The time interval to the first change of total EP score and the time interval to the first change in EDSS were assessed. The results were compared to Kaplan–Meier survival curves. We found more prominent sensitivity of the total EP score compared to EDSS in the course of disease. Our study concludes that the neurophysiologic method is more sensitive test than EDSS for earlier detection of deterioration and disease progression.

Key words: multiple sclerosis, monitoring, total EP score, EDSS

Introduction. Despite major advances in the knowledge of multiple sclerosis, there are still difficulties when setting this diagnosis. The main diagnostic tools remain clinical assessment by EDSS and brain MRI [1–3]. But some studies have found poor correlation between conventional MRI and the grade of disability in MS patients, the so-called clinico-radiological paradox in MS [4]. The most

widely-used MRI-parameter for damage in MS is T2-lesions load, but there is poor correlation with EDSS score-the Pearson correlation coefficient r is between 0.2–0.5.

In recent studies it was found that T2 lesion load is associated with EDSS scores ranging from 2.0 to 4.0 [5, 6]. Indicators and predictors of the disease symptoms are still in process of searching. In the recent years, particularly useful is the monitoring of both clinical assessment and paraclinical examinations in MS, inclusive evoked potentials [7–12].

Evoked potentials are widely used in diagnosis of multiple sclerosis (MS), but not sufficient data are available for their prospective role in the course of disease [13–18]. Attempt to quantify the severity of EP changes was made in 1998 by Fukutake who introduced 4-graded conventional EP score. In the same year, O'Connor et al. used EPAS (Evoked Potentials Abnormality Score) based on the results from 8 tests examining the following 4 modalities on the left and right: PVEP, BAEP, SSEP (Somatosensory evoked potentials) of n. medianus and posterior tibial nerve). For a period of 3 years the authors found a correlation between EDDS and EPAS scores. This means that the correlation is available between the clinically defined grade of disability and the EPAS value, i.e higher EDDS is associated with higher EPAS score. However, they did not detect correlation between the severity of MRI findings and EPAS [12]. In 2006 Kallman et al. [19] found correlation between abnormalities of multimodal evoked potentials and EDSS in the fifth and the tenth year of their study in patients at early stage of the disease [5]. Around the same time, Leocani et al. applied total EP score modified by Fukutake as a sum of scores from left and right stimulation in: PVEP, BAEP, SSEP (n. medianus and posterior tibial nerve), MEP (motor evoked potentials). This summary EP score ranges from 0 to 36 points, as its greater score corresponds to more severe abnormalities of the evoked potentials. Their results support the predictive role of the EP for clinical deterioration in MS. In 2011 Invernizzi et al. modified the EP score which was proposed by Leocani et al. They summarized the individual scores of bilaterally-performed PVEP, BAEP, SSEP from median nerve and posterior tibial nerve, MEP from upper and lower extremities. The maximum score for each modality was 10 (5 for each side). In conclusion, they confirm the correlation between EDSS and EP results in MS patients in the period out of relapses, suggesting predictive role of evoked potentials [5].

Prognostic role of EP is searched from different authors in the recent years. Several longitudinal studies have found correlation between the severity of EP abnormalities and the degree of disability according to EDSS despite differences in the methodological approaches [12, 20]. Safety, lack of invasiveness, relatively low cost and the possibility for continuous monitoring make the evoked potential relevant test for assessment of the severity of the disease, including the assessment of the degree of impairment of the different sensory modalities. The study is

informative when monitoring the effect of immunomodulating therapy, as well as for assessment of recovery after attack.

Purpose. Assessment and follow-up of changes in paternal visual evoked potentials (PVEP) and brainstem auditory evoked potentials (BAEP) in patients with MS and their comparison to the grade of disability according to EDSS.

Material and methods. The presentation is a longitudinal study in the Clinic of Neurology at MHAT – NHH – Sofia from Aug 2009 to Mar 2012. It includes 52 patients with clinically-definite multiple sclerosis according to revised MacDonald criteria (2005/2010). The patients had a mean age of 40.6 years (from 19 to 59), from which 37 were women and 15 – men. We registered the time interval to the first change in total EP score, and the time interval to the first change in EDSS. The results were compared to Kaplan–Meier survival curves. To fulfill the aim, we used a new, modified total EP score which is a sum of the individual scores of PVEP and BAEP. The follow-up was done at registered relapses and also at patients without new complaints – one or two years since the initial examination. The scores are based on the grounds of quantitative neurophysiological criteria. We introduce new quantitative neurophysiological criteria for more exact assessment of the EP results, in particular:

In PVEP:

- 0 – normal;
- 1 – configuration abnormalities only;
- 2 – prolonged latencies up to 20 ms;
- 3 – latencies prolonged with 20 ms to 40 ms;
- 4 – prolonged latencies more than 40 ms;
- 5 – severe abnormalities with difficult identification of the components.

In BAEP:

- 0 – normal;
- 1 – disturbed amplitude ratios (AR) only;
- 2 – prolonged interpeak intervals (IPI) and/or bilaterally disturbed ARs;
- 3 – both bilaterally disturbed AR and prolonged IPI;
- 4 – severe abnormalities with difficult wave identification.

So formed EP score, unlike the proposed to this moment, includes isolated configuration disturbances of PVEP without latency prolongation. Thus it detects minor violations in the visual afferentation. Proposed PVEP score does not include decrease of wave amplitudes because they are extremely variable even in healthy controls, i.e. they have low informative value.

The goal is to set parameters with proven relevance. Latency time (LT) is the most definitive indicator for impaired visual aferentation, especially in demielinating diseases such as MS, since it could be informative for the degree of demyelination. LT values by themselves do not provide sufficient information about the brain circuitry, but their change during longitudinal assessment supposes worsening of the neurological impairment. For this reason, we introduce

quantitative evaluation of the impaired conduction time, which has not been done up to now.

Newly introduced BAEP scores include disturbed amplitude ratios (AR) besides extended interpeak intervals (IPI) and configuration abnormalities. It is consistent with modern concepts, by which MS is caused not only by demyelination but also by degeneration of the brain gray matter. Disturbed AC usually results from mild brainstem lesions and most often precedes the conduction time delay. In the currently used BAEP scores, only the individual amplitude decrease of more than 50% is included compared to the contralateral side. The large variability of the absolute values of individual BAEP amplitudes is a reason to prefer assessment of their ratios. The last parameter is more informative about brainstem damage with different level of localization. This was the reason to include the AC values in our quantitative neurophysiological evaluation.

The assessment under this 10-grade total EP score was compared with EDSS examination. PVEP and BAEP were investigated by two-channel apparatus Neuro-MEP 4. For PVEP a chess-board pattern with frequency of reversion of 1 Hz was used, the filter bandwidth was 1–100 Hz. Monocular foveolar (15') and peripheral retinal stimulation (60') were consistently applied. Epoch of analysis was 300 msec. The active electrodes were positioned at 3 cm apart from occipital external protuberancia, and the indifferent electrode was placed over the vertex. In each study, 100 averagings were conducted with at least two replications. In BAEP consistent monoaural click stimulation with intensity of 90 dB nHL and 40 dB masking noise of the contralateral ear was held. The duration of the stimulus was 100 µsec, polarity-contraction, filter bands 100 to 2000 Hz, stimulation frequency 10 Hz. Epoch analysis was 10 msec. At least two stimulations with 2000 averagings for each ear were applied. Recording electrodes were placed over the mastoid process and the active electrode – on the vertex. IPI and amplitude ratios (AR), also mono- and binaural disturbances, were analyzed.

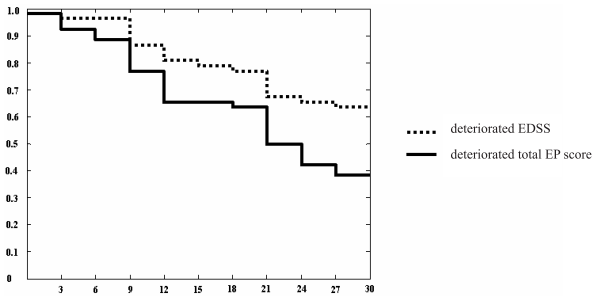

Fig. 1. Kaplan–Mayer curves, presenting the change of EDSS and EP score for 30-month follow-up period

Results and discussion. At the end of the 30-month period, we found increased EP score in 62% of the patients from our sample. This score was calculated based on neurophysiological criteria which we established. Clinical deterioration according to EDSS was registered in significantly lower rate – particularly in 37% of the patients (see Fig. 1). During the first three months from the follow-up period, a very small percentage of the subjects deteriorated both clinically and neurophysiologically. The graph in Fig. 1

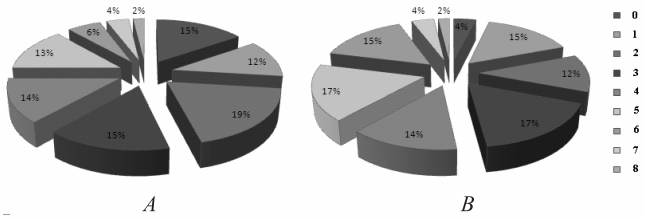

Fig. 2. Summarized EP score during: *A*) – baseline investigation; *B*) – last investigation (digits from the legend on the right correspond to the EP value)

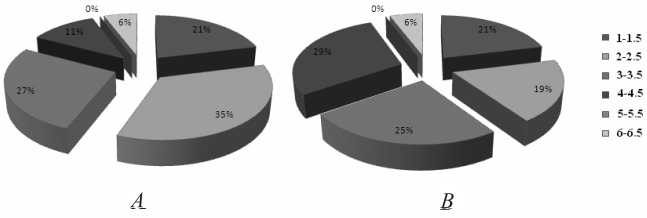

Fig. 3. EDSS during: *A*) – baseline assessment; *B*) – last assessment (digits from the legend on the right correspond to the EDSS in the definite ranges)

shows that the difference between two main indicators (summarized EP score and EDSS) is particularly perceptible after the ninth month of the follow-up. Since that time, we have registered faster deterioration of the summarized EP score than EDSS, i.e. the neurophysiological changes have preceded the clinical manifestation of the symptoms.

Increased EDSS score is usually associated with relapse occurence and less frequently with progradient deterioration. This suggests that the neurophysiological method is more sensitive for early detection of disease progression and has more predictive value for the course of disease. The diagrams in Fig. 2 and Fig. 3 show that the cumulative EP score detects changes prior to clinical manifestation evaluated by EDSS.

EDSS preserved its value in the patients with lowest disability, while EP score increased rather in these patients. At the baseline study, in 15% of the examined, the cumulative EP score was "0", i.e. both modalities of EP were in normal limits (PVEP and BAEP). In a further test, 3/4 of these patients showed increased total EP score, i.e. abnormalities in at least one modality of evoked potentials appeared (see Fig. 2). Only 4% of all examined patients in the two-year and 6-month period did not show pathological findings in EP score. It is apparent that in 16% of the patients, the EDSS increased from 2–2.5 at baseline to 3–3.5 at the follow-up examination and in 18% of the examined the EDSS increased from 3–3.5 at the initial assessment to 4–4.5 at the follow-up. Actually, EDSS was not changed in the rest of the patients (about 38% of the entire sample), i.e. patients with EDSS of 1–1.5 and those with EDSS of more than 4.0.

Conclusion. On the basis of our results, we can conclude that the neurophysiological method is a more sensitive test for progression of MS compared to the clinical evaluation by EDSS and it registers the worsening of disease earlier. The period whithin the study conducted, however, is not long enough for definite conclusions, and it requires further research in this direction.

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