ORIGINAL ARTICLE

ADVANCED ELECTROPHYSIOLOGICAL DIAGNOSTICS OF HEPATIC AND PORTOSYSTEMIC ENCEPHALOPATHY

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Summary: In 28 patients with liver cirrhosis, pre- and post-TIPS (transjugular intrahepatic porta-caval shunt), pattern-reversal visual evoked potentials (PREPs) and motion-onset visual evoked potentials (M-VEPs) examinations, EEG spectral analysis and Number Connection Test were performed. The M-VEPs (representing an activity of the magnocellular system of the visual pathway and reactions of the mediotemporal associate visual area) displayed the highest sensitivity (latencies delay) for detection of subclinical hepatic encephalopathy. The PREPs (originating in the primary visual cortex - area striata) were not significantly changed in comparison with a group of age matched controls. The EEG frequency spectrum exhibited significant slowing of the dominant frequency which was more pronounced in the post-TIPS examination. Combined analysis of the M-VEPs latency and EEG dominant frequency seem to be a recommendable method for early detection and objective classification of subclinical hepatic or portosystemic encephalopathy.

Key words: *EEG spectral analysis; Visual evoked potential; Motion-onset VEP; Hepatic encephalopathy; Porta-caval shunt*

Introduction

Decompensated liver disease or portosystemic shunting leads to encephalopathy the pathophysiology of which is not clear yet (6,9). High blood ammonia levels, an imbalance between plasma concentrations of branched-chain and aromatic amino acids, false neurotransmitters and neurotransmitters receptor changes in the central nervous system (CNS) are the commonly recognized pathogenetic mechanisms of this syndrome (19). Because of a great interindividual variability in the sensitivity of the CNS, there is no systematic relationship between these mechanisms and the presence or severity of encephalopathy (2). That is why there is a persisting problem to diagnose encephalopathy. It is of great importance to recognise the early stages of encephalopathy for a successful prevention of its consequences. Recently, also the significant changes of CNS function should be monitored after an artificial portacaval anastomosis (e.g. Transjugular Intrahepatic Porto-systemic Shunt - TIPS) applied in portal hypertension (15). The portosystemic encephalopathy remains the most serious complication of this medical help (16). Because no morphological changes are usually detected in encephalopathy, functional disorders of CNS must be tested. Different noninvasive electrophysiological methods can be used for these purposes. For the time being, EEG spectral analysis as well as different kinds (modalities) of evoked potentials (EP) are reported to be most appropriate (4,14,17). EEG dominant frequency slowing and increase of EEG activity in theta and delta bands are the most common changes described in any kind of encephalopathy (4,5,17). The EPs display prolonged latencies. Among the EPs, responses of higher associate brain cortical areas were found to be more sensitive than those of the primary sensory areas (7,14). Hence, the cognitive EPs seem to be preferable. However, this method depends on a good subject cooperation and results can have a larger interindividual variability which can limit the validity of the collected data.

Therefore, we tried to test possibilities of a newly developed variant of visual evoked potentials (VEPs) - responses of the brain cortex to the onset of motion in the visual field. These motion-onset VEPs (M-VEPs) reflect probably an activity of the magnocellular system of the visual pathway and they seem to originate in secondary visual areas in the associate temporal cortex (12,13). In this study the sensitivity of the M-VEPs for encephalopathy detection is compared with standard pattern-reversal VEPs (PREPs) representing mainly the parvocellular system and primary visual cortex (striate area) activities. Additionally the EEG spectral analysis was performed for evaluation of

the suspected encephalopathy. The standard Number Connection Test (measurement of the time needed for a connection of randomly placed numbers in ascending order) was simultaneously used to compare results of the objective electrophysiological testing with a simple psychometric screening (3).

Subjects and methods

Altogether 130 examinations of the EEG and VEPs in 69 patients with hepatic cirrhosis suspected of hepatic encephalopathy were performed. However, only 28 patients who underwent the TIPS were examined both before and at least once after the TIPS. In all of them the pre- and post-TIPs examinations were done within 3 days before and after the TIPS. Only data of these examinations are presented in this paper. The subjects (age range 13 - 65 years) had no psychopharmacological therapy at the time of the investigation. Their visual function was normal (visual acuity of 6/6 or better - with correction if needed). All VEP and EEG recordings were performed at approximately the same time of the day (9 - 11 a.m.). The subjects were seated in a comfortable chair in an electrically shielded, sound-attenuated room with the background luminance of 0.5 cd/m.

Visual stimuli with the mean luminance of 17 cd/m were generated on a computer monitor (ViewSonic 21"; 100 frames/s; total display size 30 x 40 deg) under the computer (PC 486) control. For PREPs a square-wave black and white checkerboard with an element size of 40' and contrast 96% reversed at a rate of 2 rev/s. In the motion stimulation 40' isolated checks with 5% contrast moved at a velocity of 5 deg/s in the direction varying from trial to trial (left, right, up or down). The movement lasted 200 ms and the interstimulus interval (during which the pattern was presented stationary) was 1 s. During binocular visual stimulation the patients were instructed to fixate on a red point of 15' diameter in the center of the stimulus field. Four channel recordings - the unipolar leads O_z, O_r, O_l (lateral leads 5 cm to the right and left from the midline) and the bipolar lead O_z - C_z (according to the international 10 - 20 system) were used for the VEP and EEG examination. The choosen electrode placement was optimal for both the striate PREPs and the extrastriate M-VEP recordings. 40 - 100 single VEPs were averaged (number of sweeps depended on the on-line monitored signal/noise ratio) using the Pentium PC. Both pattern-reversal and motion-onset were evaluated in 400 ms recording periods with 2 ms resolution. For the EEG spectral analysis, 64 s of the resting EEG with eyes closed was recorded via Tektronix AM-502 amplifiers (0.1 - 100 Hz) and Data Translation DT-2811PGH A/D convertor on the Pentium PC with a sampling frequency of 128 Hz. Recordings were visually inspected to eliminate periods with artifacts. 16 periodograms were computed using Fast Fourier Transformation in 4 s segments of EEG and the average spectrum of the total 64 s EEG recording was estimated. The absolute and relative EEG power in the frequency bands delta (1.75 - 4 Hz), theta (4.25 - 8 Hz), alpha (8.25 - 13 Hz), beta1 (13.25 - 20 Hz), beta2 (20.25 - 30 Hz) and the dominant frequency (frequency of the maximum EEG „power") were evaluated.

The Number Connection Test was done immediately after the electrophysiological examinations. Different variants of the test were used in case of a repeated patient's assessment.

Results

Group mean values of the EEG dominant freguency and the latencies of both VEP variants for pre- and post-TIPS examination are given in Table 1., where also the laboratory norms for each parameter are included (based on the examination of age matched control subjects).

Tab. 1: Group mean values of EEG dominant freguency and VEP latencies with statistical evaluation

	EEG dom. freq. [Hz]	PREP lat. [ms]	M-VEP lat. [ms]
Control values	10.1±0.9	110.2±5.6	160.3±8.8
t-test	p<0.001	n.s.	p<0.001
Pre-TIPS values	8.9±1.1	112.5±7.1	180.7±23.0
paired t-test	p<0.01	n.s.	n.s.
Post-TIPs values	8.4±1.1	113.5±8.0	181.6±22.1

While no significant differences in PREP average latencies in patients were found, the M-VEPs were delayed both in pre-TIPS and post-TIPS examinations showing no distinct change due to the TIPS. No systematic changes in the VEP amplitude were found. Average EEG dominant frequency was decreased in the patients (showing more slowing in post-TIPS period) in comparison with the control subjects. The other EEG parameters (absolute and relative EEG „power" in the frequency bands) exhibited not so distinct changes in patients with suspected portosystemic encephalopathy because of their rather high interindividual variability in humans (11).

Evaluation of the individual changes in the M-VEP latencies and EEG dominant frequency related to the TIPs is provided in Fig. 1. There are large interindividual differences not only in reaction of the brain to the artificial porta-caval shunt but also in the pre-TIPS electrophysiological parameters. There is no systematic unique tendency to the deterioration of the parameters after the TIPS - mainly in the M-VEP latency. Nevertheless, the highly significant negative correlation ($r = -0.55$, $p<0.01$) between the post-TIPS EEG frequency and post-TIPS M-VEP latency (with non-significant correlation between their pre-TIPs values) shows that the portosystemic encephalopathy has about the same effect on both electrophysiological examinations.

The M-VEPs were prolonged (latency longer than M + 2.5 SD in controls) in 38% of all pre-TIPS and post-TIPS

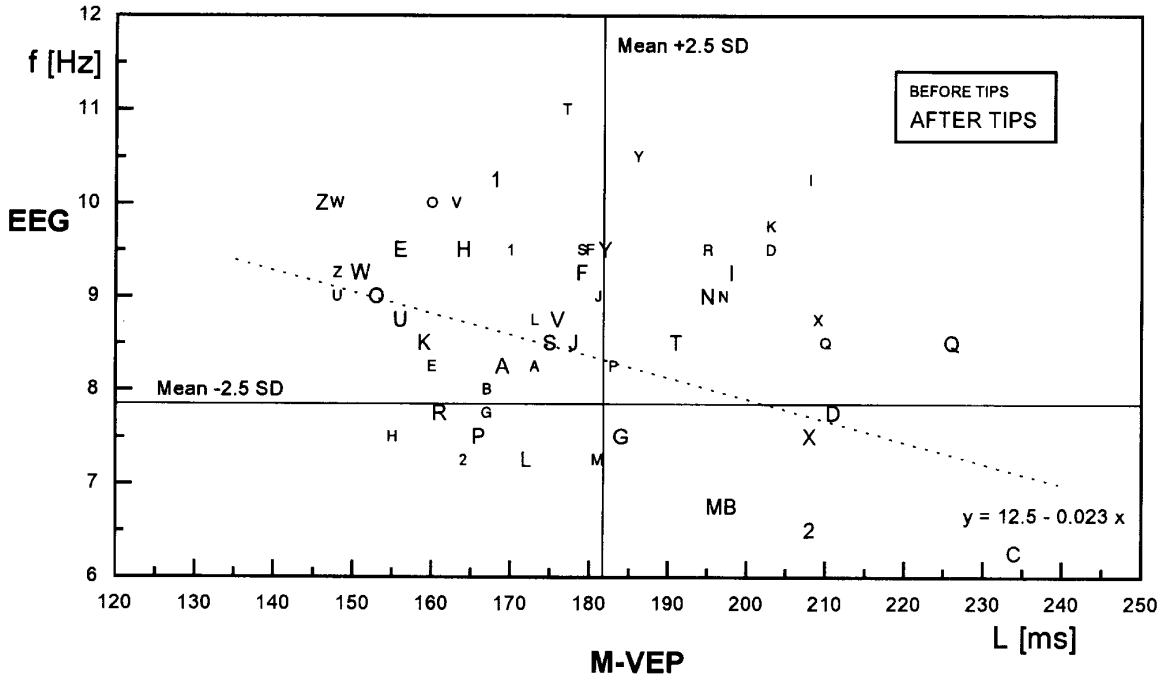

Fig. 1: Individual changes in M-VEP latencies and EEG ••••dominant frequency In this scatter diagram small letters and digits represent pre-TIPs and capitals post-TIPS values. Normal limits for M-VEP latency and EEG frequency are indicated by the vertical and horizontal line. Dashed line represents a regression between post-TIPS EEG dominant frequency and M-VEP latency. In the patient „C" the pre-TIPs data are missing because of an undetectable M-VEPs (the EEG dominant frequency was the same as in the post-TIPs examination).

examinations (PREPs only in about 7%). Pathologic EEG dominant frequency (M - 2.5 SD) was seen in 25% cases. Thus, the M-VEPs examination seems to be more sensitive for the encephalopathy detection than the EEG spectral analysis. The Pre-TIPS findings displayed 33% of pathologic M-VEPs latencies and 15% of pathologic EEG spectra. The post-TIPS M-VEPs were delayed in 43% of the cases and the post-TIPS EEG slowing was found in 36% of the patients. It is an interesting finding that in all pre-TIPS examinations only one of the parameters was pathologic (if any) and a combination of the prolonged M-VEP latency and the EEG slowing was observed in the post-TIPS examinations only (in seven patients = 25%). The Number Connection Test gave about the same results before and after the TIPS without any significant correlation with the electrophysiological examinations. Its results were in agreement only in three patients with most advanced encephalopathy with visible clinical symptoms.

In four patients, we had a possibility to repeat the examination in a longer period after the TIPS. The most common development included an improvement of the electrophysiological parameters in several weeks after the TIPS (in comparison with immediate post-TIPS examination). However, later (after several months) the parameters deteriorated again.

In one patient the TIPS function was limited because of some obstruction. In this patient the EEG and the M-VEPs promptly improved to the pre-TIPS values. In Fig. 2 a typical example of the electrophysiological findings is presented. Deterioration of the brain functions after TIPS is recognizable in the M-VEP delay and EEG dominant frequency slowing but not in the PREP.

Discussion

The examination of the VEPs has shown that in uremic or dialysis encephalopathy they differ from a norm and so they might be used for an objective early assessment of the degree of the disorder, even before the manifestation of clinical symptoms (8,10). However, in experimental hepatic encephalopathy, the normal findings of either flash or pattern-reversal VEPs despite significant changes in the EEG dominant frequency were reported (2,5).

Therefore, we tried to verify our presumption that the magnocellular system of the visual pathway, which terminates in the mediotemporal visual associate area (MT area, V5 (18)), is more sensitive to blood chemistry changes in the brain related to a hepatic cirrhosis or TIPS. Our results confirmed the expected higher sensitivity of M-VEPs in case of brain function alteration due to hepatic encephalopathy when compared with standard pattern-reversal VEPs. The M-VEPS displayed even better discrimination than the EEG spectral analysis. Since the pathological findings in EEG and M-VEPS are not overlapping completely, our combination of both methods in a search for early brain dysfunction increases probability of its successful detection. The Number Connection Test results did not confirm its usefulness in the early subclinical encephalopathy screening. The time needed to perform this task was pathologically prolonged only in patients with marked encephalopathy, where no tests are needed for a detection of brain function disorder.

In comparison with our previous study concerning the electrophysiological findings in the uremic and dialysis encephalopathy (10,11), there are less distinct changes of the PREPs but much more significant „slowing" of EEG in the patients with suspected hepatic encephalopathy (M-VEPs examination was not available in the previous study). These differences in results of single electrophysiological tests might point to a diverse basis of brain function deviations in case of particular encephalopathies.

From the clinical point of view it seems to be very important that the combination of EEG dominant frequency and M-VEP latency examination represents recently one of the most sensitive and simultaneously relatively simple method (independent on good subject cooperation) for an early detection of subclinical encephalopathy. Moreover, it provides good information if there is some distinct change in the brain function after TIPS, which can be considered as a criterion for an adequate stent (TIPS) size choice. Longitudinal electrophysiological examination of four patients after TIPS has shown about the same time dependent development of electrophysiological indicators of encephalopathy as described by Brůha (1) and Sanyal et al. (16). The improvement about one month after TIPS might be explained as a partial adaptation of the brain to the biochemistry of the shunted blood.

Conclusions

The pattern-reversal VEPs and the Number Connection Test are not sensitive enough for an early detection of subclinical hepatic encephalopathy. On the basis of our repeated observations in cirrhotic patients before and after TIPS, we recommend to use the combination of M-VEPs

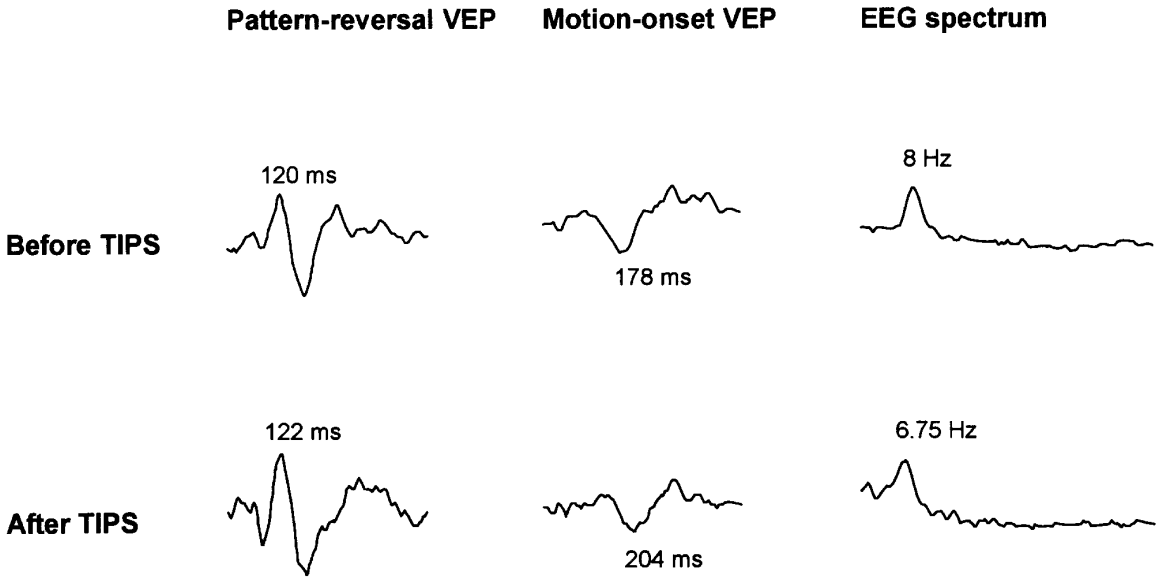

Fig. 2: An example of typical VEP recordings and EEG frequency spectra in one patient

latency and EEG dominant frequency examination for an objective diagnosis and classification of hepatic/ portosystemic encephalopathy.

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