APPLICATION OF AUDITORY EVOKED
POTENTIALS IN SPECIAL CASES

Ferenc Tóth

Ph.D. Thesis

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Supervisor:
Dr. habil. József Géza Kiss

University of Szeged, Faculty of Medicine,
Department of Otolaryngology, Head and Neck Surgery

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Publications related to the thesis


1. INTRODUCTION

The main application area of brainstem evoked response audiometry (BERA) was the objective identification of the subjective hearing threshold. Although the frequency specific threshold could not be identified, the BERA examinations suitable to estimate the hearing threshold accuracy to 20-30 dB in the 2-4 kHz frequency range. In this way BERA became essential method in the early diagnosis of hearing disturbances. In similar examination procedure the parameters of BERA waves (mainly latencies and IPLs) are very reproducible, their changes follow the alterations of the inner ear and the brainstem region of hearing nerve well, and therefore this method is very important in determination of type and origin of hearing impairments. The other important application is the differential diagnosis of retrocochlear lesions. Generally the alteration of brainstem part of hearing pathway (disturb of pulse conduction, vascular lesion, compression, etc.) cause significant changes in the parameters of BERA waves. Because the generators of individual BERA waves can be localised correctly, therefore this parameter changes can show the localisation and type of retrocochlear lesions.

The examinations of cognitive event related potentials (ERP) were usual especially in neurology and psychiatry. In the first place it was applied in examinations of neurodegenerative diseases and old-age cognitive alterations. The latency and the amplitude values of P300 component change continually in parallel with time of life. In case of neurodegenerative diseases (Parkinson-, Alzheimer-, Huntington-syndrome) the parameters of P300 change significantly. Similar alterations can be experienced in case of schizophrenia and alcoholism. Usually the parameters of N2b component follow the parameter changes of P300, but the parameters of MMN change rarely. Generally these parameter changes mark the slowness of basic neuronal processes in information treatment.

1.1. BERA examinations in patients with diabetes mellitus (DM)

Diabetic complications are well-known factors in the pathogenesis of several functional and morphological disorders. Neuropathy is one of the most frequent late complications of diabetes mellitus (DM). Diabetes may alter both the peripheral and the central nerve function, but the peripheral manifestations of diabetic neuropathy are more frequently discussed in the literature than the impairment of the central nervous system. The diabetic neuropathy can be detected usually as autonomic and peripheral nerve impairment in the early period of DM, however data demonstrate the involvement of the central nervous system in diabetic neuropathy.

The method of BERA is a very simple, non-invasive procedure to detect the impairment of the auditory pathway and to analyze the influence of diabetic neuropathy. Delay of the evoked potentials in the central pathways has been reported in diabetic patients, but the exact pathophysiology of these alterations is still unclear.

1.2. BERA and ERP examinations in patients with scleroris multiplex (SM)

Application of auditory evoked potentials has great importance in the examination of hearing pathway, because the parameters of these potentials give relevant information about the origin of hearing loss, and about the form and localization of central alterations. The stimulus rate influences the features of brainstem auditory evoked potentials (BAEP). Usually about a 10 Hz stimulus frequency is employed in BERA examinations. In case of substantially smaller or gigher frequencies than 10 Hz the characteristics of responses change, become deformed.

In many types of diseases (eg pathological change of pulse conduction) the parameters of BERA waves show the alteration in only late phase of illness. However the conduction of the
nerve is slower in this situation. So using higher stimulus rate the differences may be bigger between normal and pathological values of BERA parameters.

The pathological alteration of the hearing nerve can expand not only to brainstem region but to the association part of cortex. This may cause the alteration in cognitive function. Therefore it is suitable to examine the cognitive evoked responses in this patient group.

1.3. Audiological examinations in patients with hypertrophic cardiomyopathy (HCM)

The syndrome of hypertrophic cardiomyopathy (HCM) associated with deaf-mutism was earlier established. This observation gave us the idea of performing a thorough examination as to whether HCM patients suffer from a latent hearing defect or not. For this reason, in one of our previous studies a comparison was made via quantitative audiometric and otoneurologic data on 32 consecutive HCM cases, 38 patients with dilated cardiomyopathy (DCM). The sensorineural hearing disturbances, examined by means of brainstem auditory evoked potentials (BERA) were more frequent (37%) in the HCM group (10/32; combined lesions in an additional 2 cases) than in the other groups. The reason why we examined patients who were using β-blockers for hypertension and/or ischemic heart disease was that patients we regularly use β-blockers in the treatment of HCM. The occurrence of this hearing disturbance indicates that neither the general condition nor the pressure gradient of aortic stenosis is responsible for the higher incidence of latent hearing disturbances. The use of β-blockers could be ruled out as a primary cause of any hearing disturbances, too. Thus, we found latent “sensorineural” hearing disorders much more often in the HCM patients than in any other control group.

These hearing disorders can be either cochlear (myogenic) or retrocochlear (neurogenic) disorders of the internal ear and/or central nervous system. Previously, the BERA method was used to differentiate between cochlear and retrocochlear lesions, but this method allowed only a rough differentiation between cochlear and retrocochlear lesions. Subsequent developments of audiological testing methods have furnished the distortion product otoacoustic emission (DPOAE) procedure, which permits a more exact analysis of the myogenic function and it has become possible to differentiate precisely between abnormalities of cochlear and retrocochlear origin. The inner ear responds to high-intensity noise exposure with a temporary hearing stage shift, which originates in physical and physiological alteration of the outer hair cells. This effect should therefore be detectable as changes in otoacoustic emission (DPOAE).

1.4. ERP examinations and speech understanding

Interpretation of daily sound and noise exposure is difficult to many people. Severally the problem of speech recognition calls attention to hearing defect. Speech understanding means discrimination and classification of sounds, and it is a cognitive process. Therefore the problems of speech understanding can be related to cognitive alterations. Usually cognitive alterations can be related to the change of the parameters of cognitive ERP components. There may be correlations between speech understanding and the cognitive components of ERPs.

1.5. ERP examinations in cochlear implant users

Using cochlear implant the microphone detects the external sounds. The speech processor prepares the sounds and converts them into digital signs. Through a transmitter coil these signs get through the skin to the internal unit when the electrodes stimulate the spirale ganglion cells and generate an action potential. After this the process of hearing is similar to the normal hearing. The generators of cognitive event-related potentials can be stimulated, thus ERPs elicited through the cochlear implant can be registered on the scalp.

1.6. Neural response telemetry (NRT) in cochlear implant users

The threshold levels in cochlear implant patients are well correlated to electrically evoked brainstem responses (E-BERA). The electrically evoked compound action potentials (ECAP)
which are closely related to the E-BERA, would also show a similar correlation with behavioral threshold. In the modern cochlear implant systems bidirectional information flow is available. This creates the right conditions for not only stimulating in the cochlea, but detecting different signals there. Using this telemetry system we can perform neural response telemetry (NRT) measurement. The NRT system makes the measurement of compound action potential possible inside of the cochlea. The electrically evoked compound action potential (ECAP) from the auditory nerve is characterised by a large negative peak (N1) with a very short latency (within a fraction of a millisecond), followed by a positive peak (P1).

The SP sets the appropriate electrode pair into action and stimulates the close spiral ganglion cells and generates action potentials in them. Then the summation action potential can be measured with an other electrode pair. The signal returns to the SP and it can be averaged and analysed. With the adequate selection of electrodes the condition of neurons near by each electrode can be mapped. The parameters of registrated potentials can help in specifying the right programming modes in device fitting.

2. OBJECTS

The aim of this study was:

1. to evaluate the hearing function in homogenous group of diabetic patients with cardiovascular autonomic neuropathy, to compare the BAEP of normal hearing diabetic patients with controls and to look for the possible correlation between the alteration of the auditory brainstem function and cardiovascular autonomic neuropathy;

2. to specify how the values of latency times and amplitudes change at stimulus rates above the generally used 10 Hz in healthy persons, to see what differences occur in case of patients with demyelination problem; and to determine how the demyelination progress influence the parameters cognitive ERP components;

3. to differentiate between the two types of hearing disorders (i.e. cochlear or retrocochlear) in patients with HCM, as compared with DCM patients and normal controls, by means of DPOAE.

4. to look for the correlations between the dysfunction of speech understanding and the cognitive components of ERPs;

5. to study the correlations between the parameter changes of cognitive ERP components measured in CI users and the hearing performance measured by subjective cognitive tests;

6. to look for correlation between behavioral subjective thresholds and compound action potentials: how the NRT measurement can help in programming the SP.

3. SUBJECTS AND METHODS

3.1. BERA examinations in patients with diabetes mellitus (DM)

Our audiological investigations were performed in 15 patients with long-standing type-1 DM. These insulin-treated patients were middle-aged (42.8±4.3 years) and non-obese (body mass index: 26.7±1.3). The duration of DM was 23.0±2.6 years. None of these patients had subjective hearing complaint. The control group included 15 age-matched normal hearing subjects.

The presence of the cardiovascular autonomic neuropathy was investigated by five standard cardiovascular reflex tests: heart rate response to deep breathing, Valsalva ratio, 30/15 ratio, systolic blood pressure response to standing and diastolic blood pressure response to handgrip were included. A score (AN) was applied (0–10) to express the severity of the autonomic disorder.
All subjects underwent a thorough audiological evaluation including pure-tone audiometry, tympanometry, stapedius reflex, distortion product otoacoustic emission (DPOAE) and brainstem auditory evoked potential (BAEP) investigations. BAEP examinations were performed with Dantec Counterpoint MK2 using unfiltered click stimuli with a repetition rate of 16/s. The stimulus level was 80 dB HL. Vertex-earlobe electrode array was applied. The latency and the amplitude values of wave I, II, III, V and the inter-peak latencies (IPL III-I, IPL V-I) were calculated. For statistical analysis the Student’s t-test and the Pearson correlation arithmetic were used.

3.2. BERA and ERP examinations in patients with scleroris multiplex (SM)

We recorded auditory brainstem and cognitive responses to study the central auditory processes in 14 healthy persons with normal hearing and 10 patients suffering from central nervous system disease (sclerosis multiplex).

We performed BAEP examinations at 14 different frequency levels of stimuli (10, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 Hz) in case of healthy persons and at 7 different frequency levels of stimuli (16, 20, 28, 32, 40, 52, 64 Hz) in case of patients. Our investigations were performed with Dantec Counterpoint MK 2. In each case vertex-ear-lobe electrode and unfiltered click stimuli were applied. The intensity of the tones was 80 dB above the threshold.

Our ERP investigations were performed with Dantec Concerto EEG-EP equipment. We used acoustic oddball paradigm under active condition. The stimuli consisted of 1000 Hz frequent and 2000 Hz deviant (20 % sequential probability) stimuli presented in pseudorandom order with a fixed interstimulus interval of 1 ms. All tones were 50 ms long with 5 ms rise/fall time presented binaurally. The intensity was 80 dB HL. ERPs were recorded from 22 electrodes. Electrical activity from all contacts was amplified relative to a chin reference. For statistical analysis the linear regression arithmetic and the Student’s t-test were used.

3.3. Audiological examinations in patients with hypertrophic cardiomyopathy (HCM)

47 patients [mean age 40 (10-75) years] with HCM were enrolled in the study. Age-matched groups of patients with DCM (n=29) [mean age 40 (17-75) years] and volunteers with a negative cardiac history [mean age 41 years (n=30)] served as controls. The diagnoses of HCM and DCM were made by echocardiography on the basis of a standard technique.

Primary standard audiological examinations were carried out in all cases to exclude noise-induced and conductive hearing loss. Patients who had been subjected to extreme noise exposure for several years and whose ears gave typical audiological findings for noise-induced or conductive hearing loss were excluded. This fact explains the unpaired numbers of ears.

The myogenic function of the internal ear was evaluated by DPOAE while the neurogenic function was established by BERA. DPOAEs were recorded by scanning the frequency interval 0.5-5 kHz (3 measuring points/octave). The stimulus intensity (sounds I F1=IF2) was 70 dB. The influence of acoustic stimulation on the amplitude of the DPOAEs was studied at a frequency of 2F1-F2. DPOAE measurements were performed with GSI 60 DPOAE equipment.

The neurogenic function was evaluated by BERA. Our investigations were performed with a Dantec Counterpoint MK2 instrument. Vertex-ear-lobe electrode and unfiltered click stimuli were applied. The stimulus intensity was 80 dB above the threshold. The frequencies of the different lesions were determined by direct counting. The correlation between the clinical groups and hearing disturbances was calculated by means of the chi-square test. Between-group DPOAE amplitude comparison were performed using one-way across-group analysis of variance (ANOVA) and Student t-test.

3.4. ERP examinations and speech understanding

Cognitive event-related potential components including MMN, N2b and P300 were recorded from patients suffering from different troubles of speech understanding. Group 2
includes 12 patients (6 men and 6 women, mean age: 37 (27-58) years) suffering from cochlear origin hearing loss. All of them had discrimination deficit 5-25 % and characteristic recurved speech audiogram at least one side. Group 3 includes 10 patients (7 men and 5 women, mean age: 38 (26-61) years) suffering from central nervous system origin hearing loss. All of them had discrimination deficit (15-50 %) and characteristic saturated speech audiogram at least one side. 12 healthy persons (7 men and 5 women, mean age: 30 (23-57) years) with sound hearing and normal speech understanding formed the control group (Group 1).

Our investigations were performed with DANTEC CONCERTO EEG-EP equipment. We used acoustic oddball paradigm under active condition. The subjects were instructed to press a button following the presentation of deviant, target stimuli. Binaural stimulation were used with tone-burst stimuli (intensity:70 dB HL, duration: 10-50-10 ms) The stimuli consisted of 1000 Hz frequent and 2000 Hz deviant (20 % sequential probability) stimuli presented in pseudorandom order with a fixed interstimulus interval of 1 s. The ERPs were recorded on 22 channels with Ag-AgCl scalp-elektrodes. Electrical activity from all contacts was amplified relative to a chin reference. Between-group amplitude and latency comparison were performed using one-way across-group analysis of variance (ANOVA) and Student t-test.

3.5. ERP examinations in cochlear implant users

Our investigations were performed in 14 (mean age: 32 (16-54) years) cochlear implant users (with Nucleus CI24 and MEM-EL 40+ cochlear implants). All of them used the CI for long time (4-10 years), had good speech understanding and were able to follow the instructions. The control group includes 12 normal hearing subjects (mean age: 28 (22-46) years) who had normal pure-tone audiogram (0-10 dB) and DP-gram.

We performed pure tone audiometry in free fields at 250-500-1000-2000-4000 Hz measuring frequencies. In parallel speech recognition tests were performed in quiet and in 30-40-50-60-70-80 dB background noise. The tests covered number, word, and sentence recognition tests. The mean intensity of speeches was 75 dB A in ear position in all cases.

Our ERP investigations were performed with Pegazus EEG/MP equipment in a camera silenta. We used acoustic oddball paradigm under active and passive conditions. The stimuli (intensity: 80 dB A, duration: 10-50-10 ms) were generated by Helios II. sound generated system and consisted of 1000 Hz frequent and 1500 Hz deviant (20 % sequential probability) stimuli presented in pseudorandom order with a fixed interstimulus interval of 1 s. Free field stimulation was applied using loudspeaker (not earphone). The subjects were instructed to count the number of target stimuli. The ERPs were recorded on 19 channels with Ag-AgCl scalp-elektrodes.

Between-group amplitude and latency comparison were performed using one-way Student t-test. The correlation between subjective and objective test was calculated by Pearson correlation arithmetic.

3.6. NRT examinations in cochlear implant users

Neural Response Telemetry examinations were performed in 27 cochlear implant users (23 children and 4 adults) with Nucleus 24 channels cochlear implants and Sprint speech processors. The patients had to have good cooperation capacity to perform subjective fitting procedure.

Our examinations were performed with WinDPS R116.00 and NRT 2.04 software. We identified subjective electric thresholds levels (MAP-T) and comfort levels (MAP-C) in each electrode using SPEAK (Spectral Peak) speech encoding strategy, monopolar (MP1+2, two extracochlear reference electrodes were used) stimulation mode and 250 Hz stimulation frequency. In parallel we performed NRT measurement series in five electrodes (3, 5, 10, 15, 20). We used MP1 stimulation and MP2 recoding mode. The second electrodes from the stimulation electrodes (5, 7, 12, 17, 22) were used as recording electrodes. The starting current level was 10 µA below the subjective threshold level and the stimulus intensity was increased.
up to the comfort level by 5 µA steps. The NRT-T was identified as the minimum intensity value when the action potential could be evoked and the NRT-C was identified as the intensity value when the linearity of the amplitude growth function was changed. We compared the subjective T and C levels (MAP-T and MAP-C) with the objective NRT-T and NRT-C levels. For statistical analysis the Pearson correlation arithmetic were used.

4. RESULTS

4.1. BERA examinations in patients with diabetes mellitus (DM)

The results of our audiological evaluation show that 3 of 15 diabetic patients had sensorineural hearing loss, and 12 patients had normal hearing (pure-tone thresholds are between 0-10 dB in the 125-8000 Hz frequency range). Analysing the BERA results recording from a diabetic patient, the wave latencies increased, amplitudes decreased in each cases. The latency growth and the amplitude deficit were more definite in patients with hearing loss.

The group consisting 12 diabetic patients with normal hearing was compared with age matched controls. Our results of BERA investigations are summarised in Table I. There were significant latency differences in the case of all BERA waves. The latency values were significantly higher in diabetic patients than in the control group (wave I: 58±0.13 vs 48±0.10 ms p<0.01, wave II: 2.51±0.09 vs 2.60±0.12 ms p<0.05, wave III: 4.02±0.16 vs 3.74±0.07 ms p<10^7 and wave V: 5.61±0.18 vs 5.29±0.1 ms p<10^7; diabetics vs controls; mean ± SD). The amplitudes of all BAEP waves were definitely lower in comparison with healthy controls (wave I: 0.19±0.07 vs 0.24±0.05 µV p<0.05, wave II: 0.09±0.03 vs 0.12±0.04 µV p<0.05, wave III: 0.24±0.09 vs 0.35±0.09 µV p<0.005 and wave V: 0.14±0.06 vs 0.24±0.08 µV p<10^4). Analysis of the IPLs of BERA revealed a significant difference between diabetics and healthy controls (IPL I-III: 2.42±0.25 vs 2.26±0.10 ms p<0.05, IPL I-V: 4.02±0.25 vs 3.81±0.11 ms p<0.005).

Looking for relation between the alteration of the auditory brainstem function and the degree of cardiovascular autonomic neuropathy, a positive correlation was observed between the overall autonomic score and the latencies of wave III (r=0.62, p<0.05) and wave V (r=0.61, p<0.05). The latency intervals I-III (r=0.54, p<0.05) and I-V (r=0.49, p<0.05) were in positive correlation with the autonomic score.

Table I The mean values of the parameters of BAEP waves and standard deviations are presented in the table.

<table>
<thead>
<tr>
<th></th>
<th>L.I.</th>
<th>L.II</th>
<th>L.III</th>
<th>L.IV/V</th>
<th>IPL I-III</th>
<th>IPL I-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.48±0.10</td>
<td>2.51±0.09</td>
<td>3.74±0.07</td>
<td>5.29±0.10</td>
<td>2.26±0.10</td>
<td>3.81±0.11</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.58±0.13</td>
<td>2.60±0.12</td>
<td>4.02±0.16</td>
<td>5.61±0.18</td>
<td>2.42±0.25</td>
<td>4.02±0.25</td>
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<tr>
<td>Significance</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>p &lt; 10^-7</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A.I.</th>
<th>A.II</th>
<th>A.III</th>
<th>A.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0.24±0.05</td>
<td>0.12±0.04</td>
<td>0.35±0.09</td>
<td>0.24±0.08</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.19±0.07</td>
<td>0.09±0.03</td>
<td>0.24±0.09</td>
<td>0.14±0.06</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.005</td>
<td>p &lt; 10^-7</td>
</tr>
</tbody>
</table>

4.2. BERA and ERP examinations in patients with scleroris multiplex (SM)

The results of BERA investigations on healthy persons show that the latencies of single waves become longer when the stimulus rate increases. The extension of wave I. and wave II. is moderate, that of wave III. is bigger, and that of the wave IV/V. is the most definite. We
estimated that the increase of latency depends linearly on stimulus rate, so we performed linear regression arithmetic. In pathological case the regression straight line of wave III. is moved to the direction of higher latency values. The regression straight line of the IV/V. wave moved away and the rise of the line decreased. Using higher stimulus rate, the latency difference between the two groups increased and became significant (p<0.05).

MMN latency and amplitude was determined at the frontal midline electrode (Fz), N2b and P300 at the central midline electrode (Cz). There was a significant across-group latency difference between the two groups in all cases of cognitive components of ERPs. There was a significant decrease of amplitude in the patients’ group compared with the control group in the cases of N2b and P300 components. In the case of MMN component there was no significant amplitude difference. Analysing our results of ERP measurements as a latency-amplitude function, we can see that the values belonging to the patients’ group are separated from those that belong to the control group, especially in the case of the P300 component.

4.3. Audiological examinations in patients with hypertrophic cardiomyopathy (HCM)

After applying our exclusion criteria, we examined 69 ears of 47 HCM patients, 39 ears of 29 DCM patients and 48 ears of 30 control persons. Myogenic (cochlear) abnormalities were found in 39/69 (57%) and neurogenic (retrocochlear) abnormalities in 19/69 (28%) of the HCM cases, and in 14/39 (36%) and 8/39 (21%) cases of DCM, respectively. The cochlear lesion was significantly more common in the HCM group than among the DCM patients and the control persons (χ², p<0.05) Detailed results are given in Table 2.

The DPOAE method, which can differentiate between the two types of hearing disorders in patients with HCM, revealed that the cochlear (myogenic?) lesions were around twice as frequent (57%) as the retrocochlear (neurogenic) lesions (28%); the corresponding data for the DCM patients were 36% and 21% respectively. The neurogenic lesions were only slightly more frequent in those with HCM than in patients with DCM. The cardiologically negative persons exhibited the lowest occurrence of hearing abnormalities. The amplitudes of DPOAE were significantly lower in HCM patients comparing with control groups in all of measured frequencies.

Table 2. The frequency of cochlear and retrocochlear hearing disturbances in HCM, DCM and healthy control group

<table>
<thead>
<tr>
<th>Hearing disturbances</th>
<th>Patients</th>
<th>Ears*</th>
<th>Age</th>
<th>Cochlear</th>
<th>Retrocochlear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cochlear</td>
<td>Retrocochlear</td>
</tr>
<tr>
<td>HCM</td>
<td>47</td>
<td>69</td>
<td>40.4</td>
<td>39 (56.5%)</td>
<td>19 (27.5%)</td>
</tr>
<tr>
<td>DCM</td>
<td>29</td>
<td>39</td>
<td>40.2</td>
<td>14 (35.8%)</td>
<td>8 (20.5%)</td>
</tr>
<tr>
<td>Normal</td>
<td>30</td>
<td>48</td>
<td>39.9</td>
<td>14 (29.1%)</td>
<td>6 (12.5%)</td>
</tr>
</tbody>
</table>

* Noise induced hearing loss was excluded.
+ Cochlear hearing disturbance is more frequent in HCM than in controls (χ² test: p<0.005)
++ Retrocochlear hearing disturbance is more frequent in HCM than in normal controls (χ² test: p<0.01)
+++ Cochlear hearing disturbance is more frequent than retrocochlear hearing disturbance in HCM (χ² test: p<0.001)

4.4. ERP examinations and speech understanding

Averaged amplitude and latency values in case of different groups are presented in Table 3. The latencies of all cognitive ERP components increased and the amplitudes decreased in
the case of group 2 (patients with cochlear origin trouble of speech understanding) compare to controls (group 2). These differences are more definite in the case of group 3 (patients with retrocochlear origin trouble of speech understanding). Between-group amplitude and latency comparison were performed using one-way across-group analysis of variance (ANOVA). MMN latency and amplitude was determined at the frontal midline electrode (Fz). There were no significant across-group latency and amplitude differences analysing this component. Finding the between-group pair significances Student t-test was used. There was a significant latency difference between group 3 and group 1.

Latency and amplitude of N2b component was measured at central midline electrode (Cz). There was significant across-group latency and amplitude differences (p<0.05) analysing this component. There was significant increase of latency (p<0.05) and decrease of amplitude (p<0.01) in case of group 2 and group 3 compared with controls, but not between group 2 and group 3.

**Table 3** The mean latency and amplitude values of MMN, N2b and P300 components in patients with different troubles of speech understanding (Group2: cochlear origin N=12; Group3: retrocochlear origin, N=10) comparison with healthy subjects with normal hearing (Group1, N=12).

<table>
<thead>
<tr>
<th>Component</th>
<th>Group 1 (control)</th>
<th>Group 2 (cochlearis laesio)</th>
<th>Group 3 (retrocochlearis laesio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMN</td>
<td>123.79 ± 13.47</td>
<td>135.30 ± 11.37</td>
<td>147.34 ± 11.02</td>
</tr>
<tr>
<td>Latency [ms]</td>
<td>-4.42 ± 1.99</td>
<td>-5.08 ± 2.95</td>
<td>-5.55 ± 4.21</td>
</tr>
<tr>
<td>Amplitude [µV]</td>
<td></td>
<td></td>
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<tr>
<td>N2b*</td>
<td>193.84 ± 7.13</td>
<td>215.36 ± 17.89</td>
<td>216.46 ± 16.74</td>
</tr>
<tr>
<td>Amplitude [µV]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P300*</td>
<td>295.74 ± 13.76</td>
<td>340.16 ± 14.86</td>
<td>386.39 ± 11.41</td>
</tr>
<tr>
<td>Latency [ms]</td>
<td>22.05 ± 3.62</td>
<td>16.67 ± 2.88</td>
<td>13.45 ± 2.86</td>
</tr>
<tr>
<td>Amplitude [µV]</td>
<td></td>
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</tbody>
</table>

* significant across-group latency (p<0.01) and amplitude differences (p<0.05) p

Amplitude and latency of P300 component was determined by analysis of the deviant minus frequent difference waveform at central midline electrode (Cz). There was significant across-group latency and amplitude differences (p<0.01) in the case of this ERP component. P300 latency was increased (p<0.01) and the amplitude was decreased (p<0.01) significantly in group 2 and group 3. Compared with group 2, P300 latency was increased and amplitude was decreased significantly (p<0.01) in case of group 3 too.

4.5. ERP examinations in cochlear implant users

1. Subjective audiometry

Comparing free field pure-tone audiograms 20 dB threshold shift can be revealed in all measured frequencies in CI users. This difference issue from programing technique of CI, because of this hearing level is optimal to good speech understanding.

The results of subjective speech recognition tests (incuding number, monosylabic word and simple sentence tests) show that the two digit numbers are well audible for CI users in quiet. The mean recognition level was over 90%. By increasing the intensity of noise the hearing level decrease continously. While control subjects repeat the numbers perfectly in 60 dB noise, the CI users’ hearing level decreased to about 50%. In higher background noise the CI will be unusable in almost every case. The performance with CI is very similar in the understanding of simple sentences. In quiet or small background noise it’s almost 100%, but it...
decreases drastically in higher noise. The most difficult is the understanding of short words. In many times normal hearing subjects cannot perform it to 100%. This difficulty is more obvious in hearing with CI. The mean performance is about 60% in quiet and it decreases in noise.

2. Cognitive ERP examinations

Measuring cognitive components we can registered stable, reproducible responses in only 6 of 19 channels. These electrodes represent the central (C3, Cz, C4) and parietal (P3, Pz, P4) area. Moreover the communication frequency of transmitter-emitter system interfere the EEG waves measuring in parietal elektrodes (P3 or P4), so only the opposite parietal electrode was usable in CI users. Because of we couldn’t evoked required potentials in frontal electrodes MMN component couldn’t be analysed.

Amplitude and latency values of N200 and P300 can be determined by analysis of the deviant minus frequent difference waveform. However the potential are interfered with another disturbing sign in several registration of CI user. This periodic wave could be seen in the grand average curve (summation the potentials in all electrodes and subjects) very well. Studying the Fouries-spectrums we found a wave component with about 20 Hz which could be localised in one type of cochlear implants using brain mapping technique.

Analysing the parameters of ERP component we got interesting results. The latencies of N200 components were shorter in CI users than controls in all electrodes. These differences were significant apart from C4 electrode. In parallel the amplitude values were bigger significantly in CI group apart from C4 electrodes.

In case P300 component the difference of parameter values was less definite. There was a slight (but not significant) latency increase in controls comparing with CI group except in C4 electrode. Analysing amplitude values there was no significant deviation. The relative peak to peak amplitude (P300-N200) values were significantly higher in case CI patient apart from C4 electrode.

4.6. NRT examinations in coxlear implant users

The compound action potentials could be elicited in 23 patients in all measured electrodes and in 3 patients in some measured electrodes. The NRT could not be evoked in case of only one subject.

The comparison of the subjective and objective T and C levels showed that the mean values of NRT-T and NRT-C are between MAP-T and MAP-C. Usually NRT-T values are 10-20 μA above the MAP-T (mean 18,35 μA) and the NRT-C values are 10-20 μA below the MAP-C (mean 12,13 μA). The objective NRT thresholds were inside the dynamic range in every case.

V. DISCUSSION

5.1. BERA examinations in patients with diabetes mellitus (DM)

BAEP represents the electrical events generated along the auditory pathway. So it is able to detect the early impairment of the brainstem function. Delay of BAEP waves in diabetic patients has been reported earlier. Some authors found deviations in latency interval I-V, but not in latency of wave I. Other authors demonstrated that diabetic patients are characterized by impairment in latency values of all BAEP major components. The amplitude values were generally, but not significantly, reduced. The results of our study show that all parameters of BAEP components measured in normally hearing diabetic patients were impaired in comparison with healthy controls. We experienced significant latency increases and amplitude decreases particularly in the case of wave III and wave V.

Very few data exist about the relation between the alteration of the auditory brainstem function and the cardiovascular autonomic neuropathy. Martini et al. found a high incidence of BAEP impairment (53 %) in diabetics with cardiovascular autonomic failure. Kondo et al. could not show significant correlations between IPL-s and autonomic nervous system dysfunction as determined by orthostatic hypotension. Our results demonstrate that the overall
autonomic score (including 5 standard cardiovascular reflex tests) significantly correlate with latencies (wave III, V) and inter-peak latencies (I-III, I-V).

In conclusion, cardiovascular autonomic neuropathy is a frequent complication of diabetes mellitus (DM), however the BAEP abnormalities point towards the presence of neuropathy in the acoustic nerve too. The parameters of autonomic neuropathy consequently worsen together with several abnormalities of brainstem function. Our data support the hypothesis that diabetic neuropathy might be revealed as a cause of certain dysfunctions of the peripheral the central auditory pathways.

5.2. BERA and ERP examinations in patients with sclerosis multiplex (SM)

The application of BERA was not really successful in differential diagnosis in the event of diseases with demyelination. The ordinary BERA examination showed pathologic results in only third part of cases. Only one author mentioned that the diagnostic level of BERA become higher in examination of patients with sclerosis multiplex if higher stimulation rate was applied.

Our results supported that by increasing the stimulus rate the latencies of all BAEP–peaks and interpeak latencies became longer and the amplitudes decreased. In case of examined patients suffered from sclerosis multiplex these disturbances were more definite. The most definite changes were seen in the case of latencies of wave IV/V. Therefore the normal BAEP examinations could be expanded with these forced increases of the stimulus rate in this patient group (and in case of other problem of impulse conduction).

The different problems of central nervous system (e.g. demyelination) may influence the waveform of cognitive event-related potential components including MMN, N2b and P300. Several papers related it in case of N2b and P300 components, but not in case of MMN component measuring patients with sclerosis multiplex. Our results showed that the amplitudes were decreased and the latencies were increased in the patients’ group compared with the control group. The difference was most definite in the case of the P300 component.

Finally we suggest that the BAEP examinations using different frequencies of stimuli and cognitive ERP could be a useful method in differential diagnosis of the central nervous system diseases (in particular sclerosis multiplex).

5.3. BERA examinations in patients with hypertrophic cardiomyopathy (HCM)

Both our previous and the present studies clearly demonstrate that sensorineural hearing disturbances are more frequent in HCM than in controls or in any other group of patients examined by us. The question arises as to the cause of this finding. It was earlier accepted as a general rule that such hearing disturbances are sensorineural, in other words HCM is probably associated with a neurological congenital anomaly. However, our present study shows that the neurological cause is responsible for only a small proportion of the HCM cases with this hearing defect: in a majority of the patients it is of cochlear origin. Myosin may play an important role in the contractility of the cilium in the cochlear function of the inner ear.

A syndrome named hypertrophic cardiomyopathy and deaf-mutism was described first by Csanady. According to the London dysmorphology database it is called Csanady’s (1987) cardiomyopathy deaf-mutism. Subsequently Mohiddin et al. described a similar family and they found an abnormal mutation in unconventional myosin6 (MYO6). Mutation in MYO6 (a gene encoding a non-muscle or unconventional myosin) have been identified in all affected members of the pedigree. MYO6 is found in the hair cells. Progressive sensorineural hearing loss and cardiac hypertrophy may result from the expression of mutant non-muscle myosin VI.

There are convincing data too, that in a relatively large proportion of the patients, HCM is associated with a functional disturbance of the skeletal muscle; it has also been postulated that sudden cardiac death occurs mainly in HCM cases when the genetic defect is not expressed in the skeletal muscle cells.
Our findings suggest that abnormal myosin may also be present in the muscular structures of the internal ear in some HCM patients, and this may be responsible for the hearing disorders in these patients.

Further studies are needed to assess the correlation between the type of auditory disturbance (myogenic or sensorineural), and the molecular genetic cause of HCM whether only the abnormal unconventional myosin VI or other gene defects can lead to the abnormal hearing in HCM patients.

Cochlear (myogenic) lesions are more frequent than retrocochlear (neurogenic) lesions in patients with HCM. Both myogenic and neurogenic lesions are more frequent in HCM patients than in patients with DCM. Cardiologically negative persons display the lowest occurrence of hearing abnormalities. It may be hypothesized that abnormal sarcomeric proteins possibly present in the muscular structures of the internal ear in HCM, are responsible for the hearing disorders in those patients, and this cannot be considered exclusively merely a neurological defect.

5.4. ERP examinations and speech understanding

The examinations of cognitive ERP were usual especially in neurology and psychiatry. In the first place it was applied in examinations of neurodegenerative diseases and old-age cognitive alterations. The audiological application of cognitive ERP examinations came to the front because of spreading of cochlear implants. Since it was important to follow up the hearing performance through cochlear implant. The cognitive ERP components give information from auditory and cognitive system, so they are useful to study the degree of sound and speech discrimination in patients with different pathological changes of speech understanding.

Our results show that the problems of speech understanding are related to cognitive alterations. Different pathological changes of speech understanding can bring into connection with changing parameters (latency, amplitude) of cognitive ERP components (P300, N2b and MMN). The amplitudes were decreased and the latencies were increased significantly in group 2 (patients with cochlear origin hearing loss) compared with control group in case of N2b and P300 components. The difference was most definite in the case of P300 component. Comparing group 3 (patients with retrocochlear origin hearing loss) to healthy controls the parameter changes was significant all of the three components. Studying P300 the two patient groups can be separated from one another too. This method can be applied in examination of speech understanding as a nearly objective method.

5.5. ERP examinations in cochlear implant users

By the aid of cochlear implant deaf patients obtained hearing sensation. They are able to discriminate sounds and speeches, and in many cases they can use telephone and enjoy music. By the optimal programming of the speech processor, a normal hearing level and good sound discrimination is available to almost all of cochlear implant users. It means that they hear and recognise all of external sounds. Our results showed that mean pure tone threshold is about 30 dB at the measured frequencies in free field. Even if better hearing level can be achieved, speech understanding can be worse because of bad signal to noise ratio.

Understanding the continuous speech is more difficult with cochlear implant. Third of the patients cannot learn it perfectly. The attainable level of speech understanding depends on many factors (origin, seriousness and onset of deafness, the age, the time of implantation after onset of deafness, etc). Our CI group includes patients with good speech understanding. The results of subjective speech recognition tests (including number, monosyllabic word and simple sentence tests) showed that the speech understanding level of CI group is very close to healthy controls' results in quiet and under low level background noise. But in higher background noise conditions the recognition level decreases drastically.
The audiological application of cognitive ERP examinations came to the front because of spreading of cochlear implants. Since it was important to follow up the hearing performance through cochlear implant. Our previous study and several papers showed that cognitive evoked potentials registered in cochlear implant recipients are similar to the waveforms measured in normal hearing individuals to the same stimuli. The central auditory system can process consistently certain aspects of tone, independent of whether the stimuli are processed through a healthy cochlea, or mediated by a cochlear prosthesis. All of the three cognitive components can be registered already in early period of rehabilitation. In these cases the latency values increased and the amplitude values decreased significantly compared with healthy controls.

The results of our present study showed that CI patients (with good speech understanding) had better parameter values of cognitive ERP components. Analysing the N2b and P300 components the latencies decreased and the amplitudes increased compared with controls. These parameter changes were significant in case of N2b component except from C4 electrode. Studying relative peak-to peak amplitude (P300-N2b) values, significant amplitude decrease was found in all electrodes except from C4 in case CI group. Whereas CI users had good sound and speech recognition level, this result is very interesting.

Recording cognitive evoked potentials in CI users we found an about 20 Hz periodic sign in the registration in some cases. Using brain mapping technique we localised it in one type of cochlear implants.

The parameters of cognitive ERP components reflect to the tone perception and the patient’s performance with the cochlear implant. Accordingly, this is a useful method for assessing the discriminability of stimulation patterns produced by cochlear implant, which may yield important information for developing rehabilitation programs for individual cochlear implant users.

5.6. NRT examinations in cochlear implant users

The electrically evoked compound action potential (ECAP) from the auditory nerve is characterised by a large negative peak (N1) with a very short latency (within a fraction of a millisecond), followed by a positive peak (P1). Neural Response Telemetry is a feature of the Nucleus 24 cochlear implant (CI) system combined with the Windows® based NRT software. It enables measurements of the ECAP via bi-directional telemetry using the electrodes of the implant without the need of external electrodes. Abbas et al. and Dillier et al. validated a simplified and reliable clinical procedure for ECAP measurements in adults. Several authors have reported on possible clinical uses of NRT, such as confirmation of response to electrical stimulation from the cochlear implant, and prediction of speech processor programming parameters (T-/C-Levels) in adults and children.

Usually ECAP thresholds could be determined in 85-100% of the subjects in the literature. At least one response was measured in 96% of our subjects. The reason of unsuccessful measures may be narrow dynamic range, non-optimal electrode array and NRT parameters (gain, delay), etc. The score of 96% responses compares favourably with other objective measures of CI performance, such as the scores for electrically evoked brainstem response (EABR) of 71-91% and electrically evoked stapedius reflex threshold (ESRT) of 69-83%.

All of the authors agree with it that NRT-T levels are between subjective levels (MAP-T and MAP-C) and follow the changes of them. But the placement inside the dynamic range and the degree of correlation is questionable. Our results show that using SPEAK encoding strategy NRT threshold values (NRT-T) were on lower third part of dynamic range and highly correlated with electrical T levels obtained through subjective responses.

The concept of NRT-C was not publicated before. Usually subjective comfort levels are estimated using NRT-T and the slope of amplitude growth function. By increasing stimulus level above NRT threshold the amplitude of neural responses increase nearly linearly. Near the comfort level this linearity changed in many cases (because of eg saturation). NRT-C could be
determined in 85% of our subjects. The subjective comfort levels were well estimated from below with the NRT-C values.

Our results suggested that the electrically elicited neural response thresholds do not accurately predict comfort levels in all individual cases, but may provide valuable information for programming the speech processor in patients who are unable to make reliable psychophysical judgments.

IV. SUMMARY AND NEW RESULTS

1) All parameters of BAEP components measured in normally hearing diabetic patients were impaired in comparison with healthy controls. We experienced significant latency increase and amplitude decrease particularly in the case of wave III and wave V. The overall autonomic score (including 5 standard cardiovascular reflex tests) significantly correlate with latencies (wave III, V) and inter-peak latencies (I-III, I-V). The BAEP abnormalities point towards the presence of neuropathy in the acoustic nerve. Our data support the hypothesis that diabetic neuropathy might be revealed as a cause of certain dysfunctions of the central auditory pathways [II][III][VI][X].

2) Increasing the stimulus rate the latencies of all BAEP-peaks and interpeak latencies became longer and the amplitudes decreased. In case of examined patients suffered from sclerosis multiplexes these disturbances were more definite. Examining cognitive ERP components, the amplitudes were decreased and the latencies were increased in the patients' group compared with the control group. The difference was most definite in the case of the P300 component. The BAEP examinations using different frequencies of stimuli and cognitive ERP could be useful methods in early differential diagnosis of sclerosis multiplex [IX].

3) Cochlear (myogenic) lesions are more frequent than retrocochlear (neurogenic) lesions in patients with HCM. Both myogenic and neurogenic lesions are more frequent in HCM patients than in patients with DCM. The amplitudes of DPOAE are significantly lower in this patient group. Cardiologically negative persons display the lowest occurrence of hearing abnormalities. It may be hypothesized that abnormal sarcomeric proteins possibly present in the muscular structures of the internal ear in HCM, are responsible for the hearing disorders in those patients, and this cannot be considered exclusively merely a neurological defect [XI].

4) The problems of speech understanding are related to cognitive alterations. Different pathological changes of speech understanding can bring into connection with changing parameters (latency, amplitude) of cognitive ERP components (P300, N2b and MMN). This method can be applied in examination of speech understanding as a nearly objective method [VII].

5) The results of subjective speech recognition tests (including number, monosyllabic word and simple sentence tests) showed that the speech understanding level of CI group is very close to healthy controls’ results in quiet and under low background noise. But in higher background noise conditions the recognition level decreased drastically. CI patients (with good speech understanding) had better parameter values of cognitive ERP components. Analysing N2b and P300 components the latencies decreased and the amplitudes increased compared with controls. The parameters of cognitive ERP components reflect to the tone perception and the patient’s performance with the cochlear implant. Accordingly, this is a useful method for assessing the discriminability of stimulation patterns produced by cochlear implant. Recording cognitive evoked potentials in CI users, application of 20 Hz notch filter may be necessary in case of certain CI [I].

6) Using neural response telemetry (NRT) measurements in CI users at least one response was measured in 96% of our subjects. Using SPEAK encoding strategy NRT threshold values (NRT-T) were on lower third part of dynamic range and correlated with electrical T levels obtained through subjective responses. NRT-C could be determined in 85% of our subjects. The subjective comfort levels could be well estimated from below with the NRT-C values. The
electrically elicited neural response thresholds do not accurately predict subjective levels in all individual cases, but may provide valuable information for programming the speech processor in patients who are unable to make reliable psychophysical judgments [IV][V].

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