STIMULUS RELATED POTENTIALS IN ADHD-EPILEPSY COMORBIDITY IN CHILDREN. PRELIMINARY REPORT

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Abstract

Stimulus related potentials (SRPs) are important findings regarding sensorial systems. Disturbances of these systems are revealed in attention deficit-hyperactivity disorder (ADHD) and epilepsies also. Our goal was to determine if the presence of these pathologies could influence the recorded SRPs. 26 children, divided into four groups – controls, ADHD group, epilepsy group and a group with the comorbidity of epilepsy and ADHD – were evaluated using brainstem auditory evoked potentials (BAEPs) and pattern reversal visual evoked potentials (VEPs). The presence of epilepsy increases the latency of some VEP components; the comorbidity reduces this effect. ADHD prolongs the latencies of the BAEP components elicited in the brainstem. Epilepsy has no significant effect on the BAEP.

Keywords: evoked potentials, VEP, BAEP, ADHD, epilepsy.

POTENŢIALE DEPENDENTE DE STIMULI IN COMORBIDITATEA ADHD-EPILEPSIE LA COPII. RAPORT PRELIMINAR

Rezumat

Potenţialele evocate dependente de stimuli (SRPs) sunt explorări importante în ceea ce priveşte sistemele senzoriale. Tulburări în cadrul acestor sisteme sunt menţionate atât în tulburarea hiperkinetică cu deficit atenţional (ADHD) cât şi în epilepsii. Scopul nostru a fost să determinăm dacă prezenţa acestor patologii poate influenţa potenţialele evocate dependente de stimuli. Au fost evaluaţi 26 de copii, divizaţi în patru loturi – control, grup cu ADHD, grup cu epilepsie şi un grup prezentând comorbiditatea epilepsie şi ADHD – utilizând potenţiale evocate auditive de trunchi cerebral (BAEP) şi potenţiale evocate vizuale prin tehnica pattern-reversal (VEP). Prezenţa epilepsiei a crescut latenţa unor componente ale VEP; prezenţa comorbidităţii atenuează acest efect. ADHD prelungeşte latenţele componentelor BAEP evocate la nivelul trunchiului cerebral. Epilepsia nu prezintă efecte semnificative asupra BAEP.

Cuvinte cheie: potenţiale evocate, VEP, BAEP, ADHD, epilepsie.

Introduction

Evoked potentials are generated by diverse cortical areas, as a response to different external stimuli presented to the subject. Recording these potentials requires a stimulus presenting and a stimulus receiving system, and specific stimuli for each sense.

Evoked potentials are divided into two major categories: stimulus related potentials (SRPs) and event related potentials (ERPs). In SRPs the parameters of the potential are depending only on the stimulus, permitting the evaluation of these potentials even during sleep or coma. During ERPs the subject is required to perform simple cognitive tasks in order to elicit the potential.

In epilepsy and in attention deficit-hyperactivity disorder (ADHD) there are several studies showing different alterations of either the SRPs or the ERPs, but there's a need to confirm in an organized study the combined

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influence of these two diseases. In epilepsy, along with the EEG modifications, it is presumable to have alterations of the evoked potentials parameters, since these are extracted from the EEG trace. On the other hand, ADHD is known to produce modified patterns of the cognitive evoked potentials.

ADHD and SRPs

Initial research using visual evoked potentials for the characterization of cerebral activities linked with visual stimuli among children with ADHD concluded that VEP components are not changed, in conclusion the method's utility is reduced in ADHD [1,2]**.** In opposition, newer studies showed contradictory end-results. A study conducted on children with behavioral disorders showed a significant increase of the P100 amplitude [3]. Similar results were found in another study also, highlighting increased P100 latencies in ADHD groups, using VEPs and ERPs with visual stimuli [4]. A hypothesis was built, that involves the dopamine deficit of ADHD also in the cells of the retina, affecting the connections of the cone cells, and through this the colored vision. This deficit could produce difficulties in processing visual information, affecting the parameters of the VEPs also [5,6].

Short latency brainstem auditory evoked potentials were investigated repeatedly in the studies performed to record ERPs with auditory stimulus. Some investigators believe that ADHD can affect information transmission and processing, and also auditory attention, but there are other opinions also. A study designed to investigate BAEPs in ADHD [7] shows an extensive involvement of the main components, with increased latencies of the I and V waves and of the intervals III-V and I-V. In the same set, these ADHD children had a high rate of assimetries between sides. These changes are limited to the brainstem, component I not being affected. Another study supports the same information, documenting a longer conduction in the brainstem of ADHD subjects, as in controls [8]. There are case reports showing significant differences between classical and BAEP audiometry, the latter revealing the presence of ADHD [9]. In opposition with these results, there are researchers **s**upporting the lack of any changes of the brainstem responses [10].

Epilepsy and SRPs

The first studies performed to determine if VEP technique is applyable in epilepsies showed results difficult to compare, mainly due to different recording methods [11,12,13]. A study on subjects with idiopathic epilepsy, prior to treatment, concluded that both photosensitive epilepsies and patients without photosensitivity show differences [14]. N75 had a reduced latency and P100 increased amplitude in the photosensitive epilepsy group. Epileptics without photosensitivity presented increased latency of P100. Other researchers sustain the utility of VEPs in photosensitive epilepsy [15]. Another approach investigated the effect of skizophrenia, bipolar disease and epilepsy on VEPs, affirming the existence of individual types of evoked potentials for these pathologies [16]. Other investigations approached the subject from the point of view of new therapies: gabapentin and vagal nerve stimulation [17]. The mechanism of the previous therapies has a facilitatory effect on GABA-ergic mediation, the parameters of the VEPs seemingly depending on this type of mediation and the relative deficit of it, met in epilepsies, having a possible influence. Recent reports were published on VEPs in febrile seizures [18], using gamma band steady-state VEPs. The magnitude and the tendency towards sincronization was a marker. It was formulated the possibility of using these potentials as a diagnostic tool. Another study showed no differences when febrile seizures were compared with the controls using the obtained values, but there were revealed significant changes after spectral analysis in the delta band [19].

A study involving epileptic children showed no pre-treatment differences between base BAEP values [20]. Similarly, there were no alterations recorded in a case report of a non-convulsivant status epilepticus [21]. However, after treatment, the main components, along with the I-III and III-V intervals were prolonged in children with carbamazepine and valproate, sustaining the hypothesis of electrophysiological modifications due to CNS-toxicity, mainly on the auditory pathways. Others confirm only the toxicity of carbamazepine, attributing relatively few effects to valproate [22]. As newer antiepileptics appeared, the need to investigate their effect on BAEPs occurred. The use of zonisamide as an add-on therapy [23], or the use of vigabatrin had no significant influence over the BAEP components of the investigated children [24].

Materials and methods

For the present research subjects were selected from the Pediatric Neurology and Pediatric Psychiatry clinics of Cluj-Napoca. There were formed four groups, group I of healthy controls (n=7), group II of patients with ADHD (n=8), group III (n=7) of epileptics and group IV (n=4) of subjects showing the signs of both ADHD and a type of epilepsy. Inclusion criteria were at first the age between 6-12 years – imposed by the used psychological test's validations –, and by the relative ease of objective behavioral evaluation at this age group. Another condition was a positive diagnostic of ADHD among the members of the ADHD and ADHD+Epilepsy groups, established in the above-presented clinics, using the DSM IV recommendations. No subject being under ADHD pharmacotherapy, using either atomoxetine or methylphenidate, was included. For the Epilepsy and ADHD+Epilepsy groups children were required to present a positive epilepsy diagnosis, and to have a proper, ongoing treatment. The type of epilepsy was not taken into account. Exclusion criteria were represented by retardation, diabetes mellitus, dyselectrolytemias,

psychiatric comorbidities and pathological asymmetry of the electrophysiological evaluations.

The selected patients underwent electrophysiologic evaluations: VEPs and BAEPs.

Visual evoked potentials were recorded with a Medtronic Keypoint 4 device, using the pattern reversal technique, with the following parameters: a resolution of 30 ms, respectively 20 μV per division, low pass filter at 1 Hz, high pass filter at 0.2 kHz, maximum tolerated impedance of the recording electrodes at 5 kOhms, stimulation frequence of 1 Hz, applied stimuli under the form of 12x16 sized checkers.

The recordings were made using cup type silver electrodes, the active placed in Oz, reference in Fz and ground in Cz of the 10-20 systems. There were performed 2 examinations for each eye, with a mean of 50 mediations per recording. Children with differences between the two sides were excluded in this stage of the study. The recorded parameters for the statistical evaluation were the latency, in milliseconds (ms), and the amplitude, measured in microVolts (μV), of the main components of the VEP: N75, P100 and N135.

Brainstem auditory evoked potentials were recorded using a Micromed MyoQuick/EvoQuick 2 channel device, the stimulus being presented through earphones, using the following parameters: resolution of 1 ms, respectively 500 nV per division, low pass filter at 3000 Hz, high pass filter at 100 kHz, maximum impedance fixed at 5 kOhms, the length of the stimulus of 100μs, „compression" technique, the volume of the stimulus at 80 dB, of the noise at 60 dB, stimulus frequency at 9.5 Hz.

The recordings were made using cup type Ag electrodes in A1 and A2, reference in Cz and ground in Fz of the 10-20 systems. There were performed 2 examinations for each ear, with a mean of 2000 mediations per recording. Children with differences between the two sides were excluded in this stage of the study. The recorded parameters for the statistical evaluation were the latency of the main components of the BAEP: I, II, III, IV, and V, and the intervals I-III, III-V and I-V. N75, P100 and N135.

Statistical analysis was performed using the "t"-Student test, after the calculation of means and standard errors ($\bar{x} \pm s.e$) for the parameters of each group, with a treshold for significance of $p<0.05$.

Results and discussions

The results are presented as follows, in table format for each parameter type and evaluation, the included data being the mean and standard error ($\bar{x} \pm$ s.e.) and the obtained p values of the statistical evaluation. The statistically significant p values are bolded.

At first we should remind that this is an ongoing research, extended already on ERPs also, which is going to be continued in order to refine the end-results.

The applied evaluations – VEPs and BAEPs – present differences compared to the control group, some of these being statistically significant and some showing only tendencies. These probably will be validated along with the increase of the number of patients taken into the study and using other statistical tests also.

For the beginning we present the data regarding VEPs parameter alterations (table I). The main components of the VEPs – N75, P100 and N135 – show a tendency for increased latencies in the epilepsy group compared to the control and ADHD groups, statistically significant increase for the latency of P100 and N135. The presence of ADHD seems to reduce this tendency, without statistical significance, excepting the N135 component, significantly reduced in the ADHD+Epilepsy group compared to the Epilepsy group. There are no significant differencies regarding amplitudes compared to the control group (table I). These data are not comparable with the above-presented studies, but since various previous researches were unable to conclude in a common pathway, we think that our results can constitute a further step taken for better understanding.

The effect on the main components of the BAEPs is observed particularly regarding the waves I, III and V (table II). A significant increase of the latencies of the waves I, III and V is observed in the values of the group ADHD+Epilepsy versus control, and the latency of the V component is significantly increased in the ADHD group versus control and in the ADHD+Epilepsy group versus Epilepsy group also. The I-III interval shows no significant difference between the groups. The III-V interval is significantly increased in the groups with ADHD and ADHD+Epilepsy, and the I-V interval shows a strong

Table I. The effect of ADHD and epilepsy on the latencies (ms) and amplitudes (μV) of VEP components.

	Groups	Latency ($\bar{x} \pm s.e.$)			Amplitude ($\bar{x} \pm s.e.$)		
		N75	P100	N135	N75	P100	N135
I	Control	68.04 ± 0.77	98.06 ± 1.18	133.27 ± 1.78	3.22 ± 0.32	11.81 ± 0.75	3.61 ± 0.49
II	ADHD	67.68 ± 1.90	97.59 ± 2.36	135.69 ± 2.33	3.13 ± 0.67	13.62 ± 2.36	6.10 ± 1.36
III	Epilepsy	69.70 ± 1.42	102.90 ± 1.83	140.95 ± 2.47	4.41 ± 0.92	13.38 ± 2.27	6.12 ± 1.85
IV	ADHD+Epilepsy	69.05 ± 1.53	100.28 ± 2.29	129.31 ± 2.42	2.36 ± 0.43	10.65 ± 1.81	3.38 ± 0.85
p	I vs II	0.86	0.85	0.41	0.90	0.45	0.08
	I vs III	0.29	**0.03**	**0.01**	0.19	0.48	0.15
	I vs IV	0.52	0.35	0.22	0.14	0.48	0.81
	II vs III	0.41	0.09	0.13	0.26	0.94	0.99
	II vs IV	0.64	0.48	0.10	0.45	0.42	0.20
	III vs IV	0.77	0.39	**0.01**	0.12	0.42	0.30

Table II. The effect of ADHD and epilepsy on the latencies (ms) of BAEP components and intervals.

Groups		Latency of BAEP components ($\bar{x} \pm s.e.$)					Latency of BAEP intervals ($\bar{x} \pm s.e.$)		
		I	II	III	IV	V	I-III	III-V	I-V
I	Control	1.44 ± 0.02	2.51 ± 0.03	3.53 ± 0.03	4.69 ± 0.08	5.37 ± 0.05	2.10 ± 0.03	1.82 ± 0.04	3.93 ± 0.04
II	ADHD	1.48 ± 0.06	2.45 ± 0.08	3.55 ± 0.08	4.71 ± 0.08	5.60 ± 0.08	2.07 ± 0.07	2.06 ± 0.09	4.13 ± 0.09
III	Epilepsy	1.42 ± 0.08	2.46 ± 0.08	3.60 ± 0.05	4.67 ± 0.07	5.45 ± 0.04	2.18 ± 0.11	1.87 ± 0.04	4.06 ± 0.11
IV	ADHD+Epilepsy	1.54 ± 0.04	2.60 ± 0.05	3.62 ± 0.02	4.70 ± 0.06	5.61 ± 0.04	2.09 ± 0.04	1.98 ± 0.04	4.07 ± 0.06
p	I vs II	0.61	0.52	0.85	0.84	**0.02**	0.74	**0.03**	0.06
	I vs III	0.75	0.55	0.22	0.84	0.19	0.46	0.35	0.28
	I vs IV	**0.02**	0.12	0.06	0.90	**0.0037**	0.81	**0.01**	0.06
	II vs III	0.55	0.93	0.57	0.68	0.13	0.39	0.09	0.62
	II vs IV	0.48	0.22	0.49	0.95	0.96	0.89	0.58	0.68
	III vs IV	0.30	0.21	0.71	0.71	**0.02**	0.53	0.11	0.93

tendency in the same direction (p=0.06), presumably given by the summative effect of the unchanged I-III interval on the prolonged III-V interval, both being part of the I-V interval (table II). The obtained data are in concordance with some of the cited studies, increasing the probability of their conclusions, but the value of these results resides also in the fact that these problems were insufficiently investigated, and no undoubtable conclusions were suggested to this point.

Conclusions

The presence of epilepsy increases the latencies of the P100 and N135 components of the VEP. The concomitant presence of ADHD reduces the above-mentioned effect. ADHD prolongs the latencies of the main BAEP components (I-III-V) and of the III-V interval, having an effect mainly on the components elicited in the brainstem. Epilepsy has no significant effect on the BAEP.

The obtained results are contouring promising outcomes regarding our work hypothesis, but we consider necessary to increase the number of cases in each group to obtain sufficiently solid arguments to formulate conclusions in a pathogenetic context.

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