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Age aspect of neurophysiological diagnostics of post-concussion syndrome in patients with mild blast traumatic brain injury

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Introduction. It is generally accepted that age influences neuropsychological and neurophysiological findings due to a decrease in memory and attention in older age groups as a result of diseases and damage to the central nervous system of various origins. This should be taken into account when dealing with patients who underwent mild blast traumatic brain injury (mbTBI), and focus on standard characteristics considering the age factor.

Purpose: to investigate the influence of the age factor on the characteristics of cognitive evoked potentials in patients with post-concussion syndrome (PCS) in the long-term period of mbTBI.

Materials and methods. The study involved 41 patients with PCS aged 18-45 years (study group) and 30 healthy subjects (control group). The patients were in the late period of trauma (from 6 months to 3 years). The age distribution of patients in the study group was the following: 6 patients under 30 years old, 18 patients aged 31-40 years, 17 patients over 40 years old. Neuropsychological testing was performed according to the Montreal Cognitive Assessment Scale. Quantitative electroencephalography was performed according to standard parameters (sensitivity – 70 μV/cm, time constant – 0.1 s, filter – 40 Hz).

The results. Neurophysiological testing using the CEP P300 method allows us to verify the dysfunction of brain activity in the form of attention and memory disorders in patients with PCS as a result of mbTBI in the chronic period of damage. Exceeding the upper limit of the age norm of P2 and P3 latency components of CEP P300 is statistically significantly associated with the presence of cognitive impairment in patients with PCS.

Conclusions. The CEP P300 method can be recommended for the use in the complex diagnostics of cognitive disorders in patients with PCS in the subacute and chronic periods of the injury. In the clinical interpretation of latency characteristics of CEP P300 components, it is reasonable to focus on standard parameters, including age factor.

Key words: *mild blast traumatic brain injury; post-concussion syndrome; cognitive disorders; quantitative electroencephalography*

Introduction

Blast injury remains the hallmark injury of military personnel in modern wars. The Russia-Ukraine war, which has been ongoing since 2014, is characterized by the widespread use of tube, rocket and missile artillery, which led to a large number of victims with fragment and blast injuries [1].

In our study [2], neurophysiological criteria were defined, which allow to objectify the presence and severity of post-traumatic cognitive impairments of attention and memory in patients with post-concussion syndrome (PCS), due to mild blast traumatic brain injury (mbTBI), it is proposed to identify three variants of PCS based on the prevalence of pronounced and significant cognitive impairments and the degree of severity of clinical manifestations. It has been proven that neurophysiological testing using the method of cognitive evoked potentials (CEP P300) in blast trauma victims during the long-period of mild TBI can verify brain dysfunction and the degree of cognitive impairment, clarifying the variant of the clinical course of PCS. The expediency of including the CEP P300 method in the diagnostic complex in patients with PCS to objectify the presence and severity of cognitive impairments has been substantiated.

It is generally accepted that age affects the results of neuropsychological and neurophysiological research due to memory and attention impairment in older age groups due to diseases and damage to the central nervous system of various origin [3-5]. This should be taken into account when working with patients who have suffered a TBI, and be guided by standard indicators considering the age factor.

Purpose: to investigate the influence of the age factor on indicators of cognitive evoked potentials in patients with post-concussion syndrome in the long-term period of mild blast traumatic brain injury.

Materials and methods

Study participants

The study involved 41 patients with PCS (study group) and 30 healthy individuals (control group). The diagnosis of PCS after mbTBI (2014–2017) was established by the special military medical commission of the Ukrainian Military Medical Academy on the basis of life record and clinical data, accompanying medical documentation. All patients were men and they were in the long-term period of injury (from 6 months to 3 years). The age distribution of patients in the study group was the following: 6 patients under 30 years old, 18 patients aged 31-40 years, 17 patients over 40 years old. Neuropsychological and neurophysiological studies were carried out at the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine. All subjects of the study and control groups gave written consent for conducting the study and processing of the information obtained.

The study was conducted in accordance with the requirements of the Declaration of Helsinki of 1975 and editions of 1996–2013. Participants were recruited and data were processed after written informed consent.

The study was approved by the Committee on Ethics and Bioethics of the Institute of Neurosurgery named after Acad. A. P. Romodanov, Ukraine (Minutes No1 dated January 16, 2018).

Inclusion criteria

The criteria for inclusion in the study were: participation in hostilities, presence of mild TBI due to a mine-blast injury, age 18–45 years, no history of previous TBI, cerebrovascular disorders, surgery on the central nervous system. Exclusion criteria from the study were: previous TBI, any cerebrovascular accident, alcohol abuse, using drugs, psychiatric observation.

Study design

All study participants underwent neuropsychological testing according to the Montreal Cognitive Assessment (MoCA) and recording of cortical "evoked potentials (EPs) associated with the event" (CEP P300).

The MoCA scale is a rapid instrument for determining cognitive deficits. It assesses disorders of attention, concentration, executive functions, memory, language, visual and constructive skills, abstract thinking, calculation and orientation [6]. Subjects perform tests on: 1) executive function (drawing a line from a number to a letter in ascending order), 2) visuospatial skills (copying a cube), 3) visual-constructive skills (drawing a clock), 4) naming (correct names of drawn animals is assesed), 5) memory (memorizing a list of five words), 6) attention (repeating words in forward and backward order), 7) vigilance (reaction by tapping the letter A with the hand on the table when reading a list of letters), 8) sequential counting (subtracting 7 from 100, then 7 from the answer until the examiner stops), 9) repeating a phrase, 10) verbal fluency (naming maximum number of words in a minute that begin with a certain letter of the alphabet), 11) abstraction (explaining what each pair of words has in common), 12) memory (repetition of previously mentioned words), 13) orientation (name the year, month, exact date and day of the week, place and city). Each task is scored (there is a rating scale for each test). One point is added if the duration of education is <12 years, and two points if its duration is <10 years. The maximum possible result is 30 points. A score of ≥26 points is considered normal. A score of <26 points on the MoCA scale is considered a sign of cognitive impairment. Time to administer the test is 10 minutes.

Registration of CEP P300 was carried out according to the standard method [7, 8] on a 4-channel myographic device "Neuro-MVP-4" (Spectromed, Ukraine).

Presenting in a random sequence "odd-ball paradigm" series of two types of stimuli (clicks): relevant (with a frequency of 2000 Hz, the probability of presentation 30%) and irrelevantt (with a frequency of 1000 Hz, probability of presentation 70%), the stimulus duration 30–50 ms, intensity 75–85 dB, period between stimuli – 1 s, binaural stimulation through headphones, frequency 0.5–50.0 Hz. The patient was in a soundproof and light-insulated room, sitting in a special chair, with his eyes closed. Scalp electrodes were placed according to C3 and C4 coordinates according to the International "10-20%" system, the reference electrode was on the ipsilateral earlobe, the grounding electrode was - on Fpz. The patient pressed joystick button with the dominant hand as soon as he heard a relevant (target) stimulus. The analysis epoch is 500–700 ms, the averaging number is 30–70, separately for relevant and irrelevant stimuli.

The calculation of CEP parameters involved determining the latency and amplitude of the P1-N1-P2 complexes and the following N2-P3-N3, considering the change in the shape of the cognitive response and the interhemispheric asymmetry of indicators. An increase in the latency of CEP P300 compared to the age norm was interpreted as a sign of impaired signal recognition and differentiation processes (similar to cases of detection of dementia, attention deficit disorder, etc.), while a decrease in the amplitude of the P300 was interpreted as a decrease in the amount of short-term memory [7, 8].

Statistical analysis

The results were mathematically processed by comparing groups using the Mann–Whitney (U) test (the distribution of indicators in the groups did not correspond to the law of normal distribution). To compare the frequencies, a contingency table was used to calculate the Pearson chi-squared criterion and the strength of the association(φ or υ). In the case of age dependence of indicators, the upper limit of the 95% interval of the indicator for healthy subjects, calculated by regression equation, was used as the "age norm". Frequency, selection bias, 95% confidence interval (CI), range, median, interquartile range were used to describe the groups. The critical level of significance (p) for testing statistical hypotheses when comparing groups was <0.05.

Results and discussion

In our study, the most significant decline in cognitive functions was found in the attention domain in patients with PCS. These were mostly moderate impairments, characterized by more time than before to perform a mental task, the need for constant checking of the work done, difficulty in comprehending in the presence of interfering factors (TV, radio, phone call, driving a car).

A significant decrease was also found in the memory domain. He was characterized by difficulty in recalling details of current events, frequent use of a notebook or calendar, periodic rereading to follow the plot of the book, repeated payment of bills. Changes in the planning and execution domain were difficulties in performing multi-step tasks, resuming activities after being inerrupted for any reason, for example, due to a phone call. The results of neuropsychological testing of our patients in comparison with the control group are detailed in a previous publication [9].

Fig. 1 is a record of CEP P300 of a healthy person.

As seen in ***Fig. 1***, in the responses to the instruction to respond to relevant stimuli, the peaks of the CEP N2 and P3, which are associated with the processes of recognition and decision-making, are clearly differentiated.

The obtained results of the CEP P300 study were analyzed by independent components ***(Table 1)***.

Binary logistic regression method was used to assess the diagnostic value of the deviation from the norm of CEP P300 indicators in relation to cognitive impairment in patients with PCS. Possible connection of neurophysiological data with indicators of neuropsychological testing according to the MoCA scale was investigated. Binary logistic regression technique allows predicting the probability of occurrence of a certain binary event. A binary is an event that acquires one of two possible values (0 or 1). We considered the presence (<26 points on the MoCA scale) or absence (≥26 points on the MoCA scale) of cognitive impairment in the studied contingent of patients with PCS due to mbTBI as such a binary event.

Analysis of results of binary logistic regression study showed that individuals with changes (compared to the age norm) of CEP P300 indicators, namely a decrease in the amplitude of the P3 peak and an increase in the latency of CEP P300, probably had a higher risk of detecting cognitive impairment ***(Table 2)***.

To assess the influence of the age factor on the results of a neurophysiological study, the main indicators of the CEP were used: the latency and amplitude of the P300 peak ***(Table 3)***.

The value of the Fisher criterion F is less than the critical value for a given number of observations. In order to determine the age norms of the latency of CEP P300, we analyzed the works of the authors [10], indicating the presence of a narrow range of the slope of the regression line of P300 latency depending on age - from 1.07 to 1.8 ms/year. In the case of the control group, the regression equation takes the form: LP300 = 277 + 1.07 x Patient age (p = 0.05, 95% CIb: 252 - 302; 95% CIp300: 0.04 - 2.1), in the group of patients with PCS – LP300 = 311 + 1.4 x Patient age (p = 0.005, 95% CIb: 276 - 346; 95% CIp300: 0.4 - 2.3). Thus, there is an increase in the growth rate of the latency indicator by 1.3 times (the process of "cognitive aging" is 30% faster), as well as an increase in the constant by 11%, or, in terms of years, with a change in latency of 1.4 ms/year – "cognitive aging" as a result of trauma is accelerated by 24 years. Accordingly, the upper limit of the normal value of the latency indicators of CEP P300 components in patients with PCS was calculated, using the regression equation for the upper limit of the 95% confidence interval of the control group (const = 302; b = 2.1). Under these conditions, the P 300 latency index exceeded the age norm in 31 examined patients with PCS aged 18-45 years,.

It was found that exceeding the upper limit of the age norm of P300 latency is statistically significantly associated with the presence of cognitive disorders according to the data of the MoCA scale (χ^2 = 6.4; φ = 0.2; p = 0.01).

One of the main tasks of clinical neurophysiology is an objective assessment of brain dysfunction. Therefore,to objectify the presence and severity of cognitive disorders typical for PCS in the domains of attention and memory, we chose the P300 method of examination. From a physiological point of view, attention is associated with increased processing of relevant (important, essential) sensory information and suppression of irrelevant information; these amplification/suppression operations

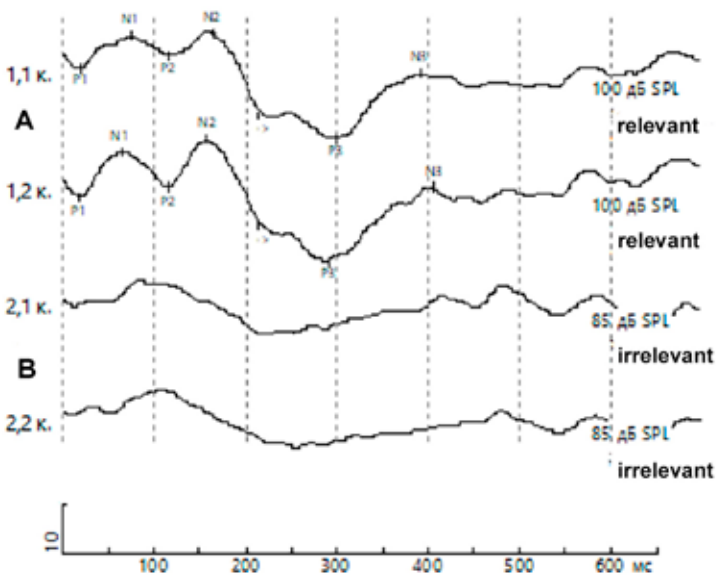

Fig. 1. CEP P300 in a healthy 30-year-old man (A). On the abscissa axis is the time interval from the moment of presentation of the auditory stimulus. Negative peaks are marked N1, N2, N3, positive peaks are marked P1, P2, P3. A - two button-press responses to relevant stimulus (infrequent). B – two responses to irrelevant stimulus (frequent)

Table 1. Latency and amplitude of CEP P300 components in patients with PCS and in the control group

Latency, ms	Study group, n=41		Control group, n=30	
	Right	Left	Right	Left
P1				
Me	79	79	38	37
Range	29–149	31–152	18–63	24–63
IQR	54–100	55–101	34–54	34–56
N1				
Me	122	117	94	95
Range	60–202	67–202	42–129	44–137
IQR	103–148	101–148	77–108	76–119
P2				
Me	183	182	175	172
Range	115–268	124–279	110–213	111–229
IQR	159–204	157–204	156–185	161–188
N2				
Me	251	249	226	239
Range	190–347	21–354	151–281	152–282
IQR	222–282	225–285	210–254	212–254
P3				
Me	354	350	303	305
Range	249–469	147–469	249–339	254–337
IQR	335–379	334–378	295–308	292–308
N3				
Me	424	419	385	386
Range	303–538	303–548	344–451	335–449
IQR	396–458	396–461	373–397	372–397
Amplitude N2/P3, μV				
Me	4,3	4,6	11,1	10,8
Range	1,6–51,0	1,6–52,0	4,1–17,5	3,9–18,5
IQR	3,2–6,5	3,3–7.0	9,3–14,4	9,2–14,6

Notes. Negative peaks are marked N1, N2, N3, positive - P1, P2, P3; Range – range from minimum to maximum value; Me - is the median; IQR - is the interquartile range.

Table 2. Results of regression analysis* of CEP P300 data on the presence of cognitive impairment in servicemen with post-concussion syndrome due to mild blast traumatic brain injury

Neurophysiological indicators	Odds ratio	95% confidence interval		Statistical significance level (p)
		LL	UL	
The decrease of P3 peak amplitude	2,6	1,14	5,9	0,003
The increase of CEP P300 latency	1,07	1,03	1,12	0,002

*Notes: * – binary logistic regression (multivariate regression model); LL – lower limit; UL- upper limit.*

constitute "selection operations" ("selective operations") [10,11]. CEP studies suggest the existence of early and late (later than 200 ms from the stimulus onset) stages of information processing, which are differently modulated by attention processes. The early stages are characterized by the so-called "negativity" of choice, while the later by positive components of the CEP (P3a and P3b).

The most common in clinical studies is the use of auditory click stimuli that differ in tone. Evoked brain potentials are considered as indicators of electrical processes in the work of the brain, connected with the mechanisms of information perception and its processing. CEP parameters to a certain extent reflect the higher cortical functions of the brain, namely: recognition of stimuli, memory and thinking processes related to decision-making [10,11]. We selected the main numerical parameters for the analysis of the CEP P300: N2 latency (ms); N2 amplitude as interpeak amplitude P2/N2 (μV); P3(300) latency (ms); P3(300) amplitude as interpeak amplitude N2/P3 (μV) and P3/N3 amplitude (μV); interpeak interval N2–P3 (ms); duration of the P3 wave as the interpeak interval N2–N3 (ms). In the auditory modality, where the oddball paradigm is traditionally used, the phenomenon of inconsistency negativity results from the detection of inconsistency between a deviant stimulus and a memory trace formed by repeated standard auditory stimuli. The first response

Table 3. Latency and amplitude of CEP P300 in age groups

Indicators	Under 30 years old n=6	31-40 years old n=18	Over 40 years old, n=17	Total n=41	Comparisonof groups*
P3 latency on the right, ms					
Me σ	345,33 55,56	360,5 43,02	354,41 42,35	355,76 43,78	F=0,27 p=0,76
P3 latency on the left, ms					
Me σ	354,17 53,77	362,67 43,29	355,24 40,55	358,34 42,78	F=0,16 p=0,85
Amplitude N2 on the right, μV					
Me σ	3,77 1,70	5,80 3,08	7,19 4,59	6,08 3,76	F=2,02 p=0,15
Amplitude N2 on the left, μV					
Me σ	4,01 1,82	5,84 3,03	6,94 4,41	6,03 3,61	F=1,54 p=0,23

* – One-way ANOVA test was used for the comparison.

component (N1) is generated in the area of the primary auditory cortex with a peak latency of about 100 ms, in fact it is the same component for both standard (irrelevant) and deviant (relevant) stimuli. The second component is generated in the associative cortex areas with an amplitude for the deviant stimulus twice as large as the amplitude of the standard stimulus. Finally, P300 (P3a and P3b) are generated in the interval of 250 - 400 ms upon presentation of relevant stimuli [11]. It is the P300 potential (components P3a and P3b), which reflect the activity of the attention system, that is of great importance in the diagnosis of cognitive disorders.

Conclusions

1. Neurophysiological testing using the CEP P300 method allows us to verify the dysfunction of brain activity in the form of attention and memory disorders in patients with PCS due to mbTBI in the long-term period of damage in the presence of cognitive impairment.

2. Exceeding the upper limit of the age norm of P2 and P3 latency components of CEP P300 is statistically significantly associated with the presence of cognitive impairment in patients with post-concussion syndrome.

3. The CEP P300 method can be recommended for the use in the complex diagnosis of cognitive disorders in patients with PCS in the interim and long-term periods of the injury. In the clinical interpretation of latency indicators of CEP P300 components, it is reasonable to focus on standard indicators, including age factor.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed and voluntary written consent to participate in the study was obtained from all patients.

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