Evaluation of Doppler and electroencephalographic changes in patients with postconcussion syndrome due to mild blast traumatic brain injury

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Mild blast traumatic brain injury (mbTBI) often remains undiagnosed and untreated due to lack of treatment of patient, imperfect screening tools, unclear diagnostic criteria, and lack of means to objectify or visualize the injury.

Objective: to investigate Doppler and electroencephalographic changes in patients with postconcussion syndrome (PCS) due to mbTBI and the possibility of their use to objectify the injury.

Materials and methods. The study involved 115 male participants of hostilities in the East Ukraine (main group) with a diagnosis of “PCS after previous mbTBI” and 30 healthy individuals (control group). Patients were in the long-term period of injury (from 6 months to 3 years). After collecting complaints and history data, the neurological status and the state of cognitive functions were examined. Neuropsychological testing according to the Montreal cognitive assessment score was carried out. Ultrasound duplex scanning with color Doppler mapping of neck and head vessels and transcranial duplex scanning were performed. Quantitative electroencephalography was performed according to standard parameters (sensitivity - 70 μV / cm, time constant - 0.1 s, filter - 40 Hz).

Results. In patients with PCS after mbTBI, transcranial duplex scanning can detect changes in vascular resistance in the intracranial vessels of both the carotid and vertebrobasilar basins (mostly reduced resistance values), as well as signs of venous discirculation in the basal veins of the brain, quantitative electroencephalography – changes in the frequency and topic of the α-rhythm, a decrease in its amplitude, frequency-spatial inversion, the presence of signs of dysfunction of nonspecific brain structures, according to spectral analysis – a decrease in α-power, an increase in β-power, activity in θ- and δ-bands.

Conclusions. Detected Doppler and electroencephalographic changes may persist in the long-term period of mbTBI. They should be taken into account in the differential diagnosis of post-traumatic stress disorder.

Key words: mild blast traumatic brain injury; postconcussion syndrome; cognitive impairment; quantitative electroencephalography

Introduction

In modern military conflicts, blast traumatic brain injury (TBI) is the most common injury among military personnel [1]. According to American researchers using combat material in Afghanistan and Iraq, only 2.8% of the injured suffered severe injuries, whereas in the majority of cases a mild TBI was diagnosed. Mild blast traumatic brain injury (mbTBI) often remains undiagnosed and untreated due to lack of treatment of patient, imperfect screening tools, unclear diagnostic criteria, and lack of means to objectify or visualize the injury [2]. Russia-Ukraine war is characterized by the use of the full range of modern weapons (artillery, missile and small arms, rocket grenades and land mines). This has led to an increase in the number of victims of blast injuries who need effective care and rehabilitation [3].

The clinical picture of mbTBI is characterized by variability. Typical symptoms include headaches, fatigue, tinnitus, irritability, neuropsychiatric and cognitive impairments. Cognitive impairment after mbTBI may persist for a long time (years) and permanently [4, 5]. This has led to the allocation of postconcussion syndrome (PCS) as a separate nosological unit. The diagnosis of PCS is made by a history of severe head injury resulting in loss of consciousness, and at least three of the following signs: 1) complaints of pain (including headache) and discomfort (dizziness, general malaise, excessive fatigue or noise intolerance, 2) emotional changes such as irritability, emotional lability or some degree of depression and / or anxiety, 3) subjective complaints of difficulty concentrating and performing mental tasks, memory problems without clear objective...
findings, 4) insomnia, 5) reduced alcohol tolerance, 6) concern about the above symptoms and fear of persistent brain damage up to hypochondria and acceptance of the role of the patient [6].

One of the biggest problems in diagnosis and treatment of PCS due to mbTBI is the possible presence of concomitant psychiatric disorders, including post-traumatic stress disorder (PTSD). Complaints, neurological and cognitive manifestations of these disorders may be similar, which significantly complicate their differential diagnosis. Its importance is growing given the different approaches to treating both conditions. PTSD therapy implies mainly normalization of stress response through psychological and pharmacological correction, whereas the treatment of mbTBI should take into account structural and molecular biological changes to prevent their impact on the severity and duration of neurological deficit [7, 8]. This leads to the relevance of the diagnosis and objectification of clinical signs of PCS with the help of modern instrumental methods of examination used in clinical practice, in particular ultrasound, neurophysiological and neuroimaging.

Objective: to investigate Doppler and electroencephalographic changes in patients with postconcussion syndrome as a result of mild blast traumatic brain injury and the possibility of their use for the objectivization of the injury.

Materials and methods
Study participants
The study involved 115 men male participants in hostilities in the East of Ukraine (main group) and 30 healthy individuals (control group). All patients of the main group were diagnosed with ”PCS after previous mbTBI” by the special military medical commission of the Ukrainian Military Medical Academy based on the history and clinical data and accompanying medical documentation. Patients were in long-term period of injury (from 6 months to 3 years).

All patients of the main and control groups gave informed and voluntary written consent to participate in the study and subsequent processing of the information obtained. The study was approved by the Committee on Ethics and Bioethics of the Institute of Neurosurgery named after acad. A. P. Romodanov, Ukraine (Minutes №1 dated 16.01.2018).

Inclusion criteria:
1) participants of hostilities who suffered a mild TBI as a result of mine explosion;
2) age 18–45 years;
3) no history of previous TBI, cerebrovascular disorders, surgery on the central nervous system.

Exclusion criteria:
1) previous TBI;
2) any cerebrovascular accident;
3) alcohol abuse;
4) addictive substance abuse;
5) psychiatric observation.

Characteristics of the group
Of the 115 surveyed, 103 (89,6 ± 5,6%) had higher education, 11 (9,6 ± 5,4%) had incomplete higher education, and 1 (0,9 ± 1,7%) – had secondary education.

Study design
After collecting complaints and medical history data, the neurological status and the state of cognitive functions were studied. A questionnaire ”Cicerone” was used, neuropsychological testing according to the Montreal Cognitive Assessment Score (MoCA) was carried out. The Hospital Anxiety and Depression Scale (HADS) was also used and the Asthenic State Scale (ASS)- to objectify asthenic disorders. The results of neurological and neuropsychological testing are presented in a previous publication [9].

Ultrasound duplex scanning with color Doppler mapping of the main arteries of the neck and head and transcranial duplex scanning (TCDS) were performed using diagnostic systems "Sonoline G-S60" ("Siemens", Germany) and "Toshiba Aplio MX" (Japan) according to standard methods [10, 11]. Extra- and intracranial portions of the vertebral artery, extracranial portions of the carotid arteries (common, internal, external), internal jugular veins, proximal cerebral arteries (middle, anterior and posterior), basilar artery were studied. When imaging extracranial vessels, the diameter, anatomical course, state of the vascular wall (thickness and nature of the intima-media complex), the presence and structure of atherosclerotic plaque, the degree of lumen stenosis according to the recommended ECST and NASCET protocols were assessed. Quantitative assessment of hemodynamic parameters (linear blood flow velocity, indices of vascular resistance) in the studied vessels was carried out.

Quantitative electroencephalography (EEG) was performed using a 24-channel "BRAIN-TEST" electroencephalograph ("DX system", Ukraine) according to standard parameters (sensitivity - 70 μV / cm, time constant - 0.1 s, filter - 40 Hz). The electrodes were placed according to the standard scheme ”10-20%”, monopolar lead, with reference ear electrodes A1 + A2. Computer EEG analysis was performed using spectral analysis and power mapping.

Statistical analysis
Statistical data processing was performed using StatPlus software (version 7.0 Microsoft). The normality of data distribution in comparison groups was determined by the Kolmogorov-Smirnov criterion. Data are presented as the median and interquartile range between the 25th and 75th percentiles (Q3 – Q1). The results were compared using the criterion χ². The results were considered statistically significant with a null hypothesis probability p <0.05. The diagnostic value of deviated EEG findings for objectification of cognitive impairment in PCS after mbTBI was assessed using the binary logistic regression method.

Results and discussion
Ultrasound duplex scanning did not reveal structural changes in the vascular wall of the carotid arteries in the control and main groups. Velocity blood flow rates in extracranial vessels and resistance indices (pulsatility indices (PI) and peripheral vascular resistance (RI)) did not differ statistically significantly in the study groups. According to TCDS data, peak and mean linear blood flow velocity indices in cerebral arteries and segments of the vertebral basilar basin (VBB) in the control and main groups were not statistically significantly different, but
in patients with PCS, statistically significant increase in the frequency of deviations from the norm was noted, mainly in the direction of decreased intracranial vascular resistance indices, which is not typical for men of this age group. Thus, the proportion of patients with PI less than or below the lower limit of normal in the intracranial segments of the carotid basin was 30.4%, in the control group – 6.6% ($\chi^2 = 7.1$, $p = 0.01$). The frequency of such changes in VBB was 39.1% compared with 16.6% in the control group ($\chi^2 = 5.3$, $p = 0.02$). An increase of vascular resistance indices in intracranial vessels was registered mainly in the VBB. It was not statistically significant (15.6 and 13.3%, respectively). In general, the average PI values in the middle cerebral arteries in patients with PCS was: on the right – 0.79 (0.69–0.86), on the left – 0.78 (0.69–0.85), in the control group – 0.83 (0.80–0.87) and 0.82 (0.79–0.86) ($p < 0.05$) respectively. PI values in VBB in patients with PCS and control group did not differ statistically significantly, probably due to different changes in vascular resistance: PI in the intracranial vertebral artery in the main group on the right – 0.82 (0.71–0.9), on the left – 0.83 (0.74–0.91), in the control group – 0.84 (0.80–0.89) and 0.83 (0.78–0.87) ($p > 0.05$).

When assessing the indices of venous outflow in cerebral veins in the main group a statistically significant higher frequency of observations with signs of discirculation in the basal Rosenthal veins (32.2%, in 10.4% of cases - on both sides) was noted compared with the control group (13.3%, $\chi^2 = 4.2$, $p = 0.04$). The linear velocity of blood flow through the vein was 13 cm / s (10–16 cm / s) and 11 cm / s (9–14 cm / s) on the right and left.

Thus, according to TCDS, in patients with PCS changes in vascular resistance in the intracranial vessels of both the carotid basin and VBB were revealed, mainly in the direction of a decrease in resistance indices, as well as signs of venous discirculation in the basal cerebral veins. Such changes are not typical for men of this age group and are statistically significantly different in frequency from those in the control group. In our opinion, these changes are nonspecific and when examining patients with PCS due to mbTBI may play an additional role in a comprehensive assessment of the functional state of the central nervous system.

Among the peculiarities of the EEG in the studied patients with PCS changes in the frequency and topics of $\alpha$-rhythm, a decrease in its amplitude and frequency-spatial inversion, the presence of signs of dysfunction of nonspecific brain structures, especially during exercise stress tests (hyperventilation) were revealed, according to spectral analysis, a decrease in $\alpha$-power, an increase in $\beta$-power, activity in $\theta$- and $\delta$- bands. The lack of specificity of these EEG changes does not exclude the clinical usefulness of such a study, in particular for detecting signs of epileptiform and paroxysmal activity.

The diagnostic value of deviations from the norm of EEG parameters for objectification of cognitive impairment in PCS as a result of mbTBI was assessed using the binary logistic regression method. This statistical method is used to predict the probability of a certain binary event occurring, i.e., one that can take only two values (0 or 1). In our case, it is the presence ($< 26$ points on the MoCA scale) or the absence ($\geq 26$ points on the MoCA scale) of cognitive impairment. It was found [9] that the MoCA scale can be a quick tool for determining cognitive impairment in patients with PCS as a result of mbTBI. It allows assessing such cognitive functions as attention, concentration, executive functions, memory, speech, visual skills, abstract thinking, calculation and orientation [12].

The maximum possible score according to the test results is 30 points. A score of $\geq 26$ points is considered normal, whereas a score of $< 26$ indicates the presence of cognitive impairment. More detailed information on the results of neuropsychological testing of our patients can be found in [9].

Analysis of binary logistic regression study data demonstrated that individuals with changes (as compared to the age norm) in EEG parameters, namely the frequency and topics of $\alpha$-rhythm, a decrease in its amplitude, signs of dysfunction of nonspecific brain structures, especially during exercise stress tests were likely to have a higher risk of detecting cognitive impairment. (Table).

The clinic and diagnosis of mild TBI in the acute period have been studied in detail, whereas the ability of mild TBI, in particular mbTBI, to cause long-term neurological changes is a subject of discussion. It is well known that many patients have long-term symptoms. In such individuals, any subsequent injury or disease to the nervous system is accompanied by a risk of much worse outcomes. However, the detection of long-term neurological disorders in these patients remains a challenge [13].

It is believed that the EEG at rest can be a sensitive method for detecting the long-term effects of mild TBI,

Table. Results of regression analysis * of EEG data of military personnel with postconcussion syndrome after mild blast traumatic brain injury due to the presence of cognitive impairment

<table>
<thead>
<tr>
<th>Neurophysiological indicators</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>Statistical significance level $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HM</td>
<td>BM</td>
<td></td>
</tr>
<tr>
<td>Frequency-spatial inversion of $\alpha$-rhythm, $\alpha$-rhythm frequency change, $\alpha$-rhythm amplitude decrease, $\alpha$-power decrease, $\beta$-power increase, $\theta$- and $\delta$-bands activity</td>
<td>1.07</td>
<td>1.03</td>
<td>1.11</td>
</tr>
<tr>
<td>Dysfunction of nonspecific medial structures, deviation from the norm in the hyperventilation test</td>
<td>1.02</td>
<td>1.0</td>
<td>1.04</td>
</tr>
<tr>
<td>Signs of irritation of the cerebral cortex</td>
<td>1.45</td>
<td>1.01</td>
<td>2.09</td>
</tr>
</tbody>
</table>

Notes: * - binary logistic regression (multivariate regression model); LL - lower limit; UL - upper limit.
with additional advantages such as speed and ease of performance. Prolonged changes in electrical activity in the form of diffuse slowing, detected by EEG, correlate after mild TBI with the duration of loss of consciousness and post-traumatic amnesia [14]. EEG power indicators have been shown to depend on the severity of the injury and retain sensitivity longer than the results of other studies [13].

It has been proved that after severe TBI, impaired consciousness, particularly in vegetative state or state of minimal consciousness, are accompanied by changes in the spectral profile of the EEG [15]. Since mild TBI is also characterized by impaired or altered consciousness, many experts suggest that it may also cause prolonged changes in power indicators. K.D. Cicerone (1996) [16] hypothesized that EEG power indicators may correspond to a state of moderately decreased excitation, which clinically corresponds to attention deficit in patients with mild TBI.

The classic study of EEG changes in mild TBI was the study of quantitative EEG indicators using the discriminant analysis method, conducted by R.W. Thatcher et al. (1989) [17]. Using a comparison of a complex demodulation analysis of coherence, phase and amplitude in 19 standard leads according to the International System “10-20%” in four bands, the authors showed that the main changes in mild TBI in contrast to those without head injuries are: 1) increased coherence in the left frontotemporal area, 2) decreased β-phase in the right dorsofrontal areas, 3) increased asymmetry of α-rhythm amplitude locally in the frontal junctions and between distant frontal and occipital-parietal junctions, 4) suppressed α-power in the posterior hemisphere regions.

It was found that changes in the quantitative indices of EEG at rest are accompanied by clinical manifestations of mild TBI, which persist for a long time. In particular, in patients whose symptoms persist for 6 months after injury, the slowing of frequency characteristics also persists and is localized mainly in areas with disruption of blood-brain barrier [18]. A long-term (up to 2 years) increase in low-frequency power, especially in the prefrontal and right temporal areas is observed in veterans who have sustained mbTBI. This allows differentiating traumatic injury from PTSD, which has similar clinical manifestations, but, according to EEG data, is characterized by a decrease in low-frequency power, mainly in the right temporoparietal area [13]. Other authors found that similar EEG changes persisted in all frequency bands except the α-rhythm for 2.5 years after mbTBI [19]. R.W. Thatcher et al. showed that discriminant analysis method of quantitative EEG indicators can objectively detect the electrophysiological consequences of mild trauma in persons with a history of trauma, even if there are no other signs [17].

The relationship between EEG characteristics and the severity of cognitive impairment according to neuropsychological testing using the MoCA scale in patients with PCS due to mbTBI was studied. The features of EEG changes were found to be changes in the frequency and topic of α-rhythm, decrease in its amplitude and frequency-spatial inversion, the presence of signs of dysfunction of nonspecific brain structures, especially during exercise stress tests (hyperventilation).

Spectral analysis of EEG changes revealed decreased α-power, increased β-power, activity in the θ- and δ-bands. The results obtained are consistent with the data of other authors on changes in electrical activity of the brain in subacute and chronic periods of mild TBI [18-20]. The greater severity of such changes in the presence of post-traumatic amnesia suggests that the increase in power at low frequencies is associated with a temporary block of memory consolidation immediately after injury [13]. In our study using the binary logistic regression method, it was found that the presence of such EEG characteristics was associated with a higher probability of detecting cognitive impairment in the long-term period of mbTBI. Such cognitive changes include mainly disorders of memory, attention, delayed recall and total score on the MoCA scale [9]. Thus, the EEG method can be used to comprehensively objectify cognitive impairment after blast injury. The possibility of such a diagnosis in the chronic period of mbTBI is of great importance. The results of our study of EEG characteristics at rest in such patients suggest the presence of prolonged electrophysiological changes following mbTBI. This assumption is consistent with the findings of D.L Trudeau et al. (1998) [21], who also showed that EEG changes after a combat blast injury are stable and do not depend on whether the patient has previously had a non-combat TBI of any severity. Researchers note that in contrast to blast trauma, craniocerebral injuries with other injury mechanisms are characterized by better gradual recovery. D.L. Trudeau et al. explain this by the fact that blast injury due to the impact of the blast wave causes deeper and possibly irreversible axonal damage in contrast to TBI of other etiologies. The results of our study are consistent with the above-mentioned chronic effects of mild TBI, which may be associated with white matter disruption (axonal damage), resulting in reduced sensory inputs to the neocortex. Pathology of the blood-brain barrier may also play a role, according to findings of increased slow frequency activity after mild TBI, located in the same area where the blood-brain barrier disruption was found [19,20].

In our opinion, the found connection between electrophysiological data with the presence of cognitive impairment can help determine the direction and degree of recovery during life, the presence of persistent vulnerability to injuries and diseases of the central nervous system, as well as the need and volume of rehabilitation measures.

One of the biggest problems in diagnosing and objectifying PCS due to mbTBI is the possible presence of concomitant psychiatric disorders. Most often, such patients are diagnosed with PTSD in the long-term period of injury. Both conditions are characterized by memory deficits, fatigue, hypersensitivity to sound and light, insomnia, irritability, decreased concentration and anxiety [22]. Since the complaints, neurological, and cognitive manifestations of these disorders may be similar, it is necessary to differentiate PCS from PTSD. Some patients diagnosed with post-war PTSD may also have some signs of PCS associated with blast injury. If so, it would be important to identify and treat PCS because of its impact on a person's ability to benefit from therapy that involves restoring the processes of
recall, insight, planning, judgment, and other integrative functions [23]. Therefore, it would be interesting to study the possibility of using EEG for this purpose. The reason for this is the understanding that the long-term period of mbTBI is often characterized by a decrease in excitation processes, whereas PTSD by increased alertness. According to the literature, both mbTBI in the chronic period and PTSD, change the power profile, especially at low frequencies (θ- and δ-bands), but in opposite directions [13].

In a publication by L.M. Franke et al. (2016) [13] the idea of possible mechanisms of these electrophysiological changes in blast brain injury was summarized, in particular, it was noted that increased θ- and δ-activity is associated with decreased excitation processes due to various pathological conditions, such as TBI. It is believed that δ-waves reflect the activity of neural circuit of large range. Slow oscillations are effective at long distances in the brain and in modulating local rapid activity associated with perception. Slow and medium frequency oscillations, in particular δ-waves, facilitate coordination between regions of the neural circuit. Excitation to a certain extent blocks these slow oscillations displayed on the electroencephalogram during wakefulness (lower low-frequency power) compared to sleep (higher low-frequency power). Similarly, experimental and pathological deafferentation of the neocortex increases low frequency power. Decreased vigilance and transition to automatic attention are also associated with increased low-frequency power. Based on a study of the relationship between pathological conditions and EEG, it was suggested that slow oscillations are increased after brain damage, when higher functions are impaired. Slow oscillations are associated with conditions where sensory effects are reduced or abnormal, such as sleep and tinnitus, respectively. FMRI-EEG studies at rest have shown that an increase in both δ-activity and θ-activity (but not other frequency bands) is associated with decreased activity in the visual and auditory networks.

According to the results of our study, changes in the bioelectrical activity of the brain can be detected in the long-term period of injury. Their sustainable preservation is consistent with the data of other researchers and differs from disorders due to TBI of other origin. These EEG changes indicate the presence of cognitive impairment in the patient and are useful for differentiation from PTSD. The data obtained are the basis for further study of the possibility of objectifying cognitive impairment in the clinical picture of mbTBI using the cognitive evoked potentials method [24].

Conclusions

1. In patients with postconcussion syndrome after mild blast traumatic brain injury, the method of transcranial duplex scanning allows detecting changes in vascular resistance in intracranial vessels of both carotid and vertebrobasilar basin (reduction of resistance), as well as signs of venous discirculation in the basal veins of the brain. Such changes are nonspecific and may play an additional role in the comprehensive assessment of the functional state of the central nervous system during the examination of patients with postconcussion syndrome.

2. The method of computer electroencephalography allows detecting changes in frequency and topic of α-rhythm, decrease in its amplitude and frequency-spatial inversion, signs of dysfunction of nonspecific brain structures in postconcussion syndrome due to mild blast traumatic brain injury, according to spectral analysis decrease in α-power, increase in β-power, activity in θ- and δ-bands. These changes persist in some of the patients in the long-term period of injury. They should be taken into account in the differential diagnosis of post-traumatic stress disorder.

3. The use of the cognitive evoked potentials method promotes the objectification of cognitive impairments within the postconcussion syndrome after a mild blast traumatic brain injury.

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

The written informed consent was obtained from each patient.

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