
Research Article**A comparative clinical and encephalographic study on manifestation of the choline and dopamine deficiency syndromes in consciousness recovery after severe traumatic brain injury****M. V. Chelyapina –Postnikova¹, E. V. Sharova¹, O.S. Zaitsev²**¹Institute of Higher Nervous Activity and Neurophysiology of RAS, Russia²Federal State Autonomous Institution “N.N. Burdenko National Medical Research Center of Neurosurgery” of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract:**Purpose:** to describe and compare the severity of clinical signs of choline and dopamine deficiency and their EEG manifestation in consciousness recovery of patients with sTBI.**Material and methods:** The data of dynamic and clinical EEG studies of 98 patients (68 men, 30 women) with severe traumatic brain injury were analysed. The patients were aged13 to 57 y.o. (mean 31 ± 12 y.o). The observation period ranged from 3 weeks to 20 months after trauma. The analysis assessed the neurological status and mental activity in patients, including EEG studies with a dynamic pattern assessment.**Results:** the EEG pattern of dopamine deficiency syndrome featured emerging synchronised beta activity at 13-14 Hz with a significant rise in the frontal and anterior temporal regions, concurrent with a general decrease of biopotential amplitude, EEG flattening and smoothing differences between zones, as well as more or less pronounced theta rhythms. In patients with choline deficiency syndrome, alpha activity of 7–8 sec (no matter how unstable, disorganized and slow) came to be most characteristic, even in cases of deeply depressed consciousness (coma). Alpha activity was combined with an increased diffuse fast activity or polymorphic (rhythmic) groups of theta-delta waves in the EEG pattern during a general disorganization of biopotentials.

Keywords: dopamine deficiency syndrome, choline deficiency syndrome, cholinergic system, dopaminergic system, EEG, severe traumatic brain injury.**Introduction:**

Severe traumatic brain injury (sTBI) is one of the essential medical and social problems, as it often causes disability and mortality in young people [1].

This pathology is associated not only with damage to morphological structures and functional cerebral connectivity, but also with a failure in key cerebral neurotransmitter systems. In the acute stage of sTBI, a so-called “neurotransmitter storm” occurs, i.e. a sharp rise in dopamine, acetylcholine, noradrenaline, glutamate, serotonin in the cerebrospinal fluid (CSF) followed by long-decreased neurotransmitter levels in the CNS [2, 3]. Neurochemical systems suffer from both direct damage to the anatomical structures containing cholinergic and dopaminergic neurons, and secondary edema and hypoxia [4; 5; 6; 7]. Some previous studies described clinical signs (symptoms) of post-traumatic dysfunction of each of those systems separately [8,9,10]. We also identified the EEG correlates of clinical syndromes of dopamine and choline deficiency in sTBI [8,9]. There have been no dynamic comparative studies of those clinical and EEG syndromes as manifested in traumatic disease comparatively so far.

Purpose:

The study aims to describe and compare the severity of

clinical signs of choline and dopamine deficiency and their EEG manifestation in consciousness recovery of patients with sTBI.

Material and research methods

The data of dynamic and clinical EEG studies of 98 patients (68 men, 30 women) with severe traumatic brain injury were analysed. The patients were aged 13 to 57 y.o. (mean 31 ± 12 y.o). The observation period ranged from 3 weeks to 20 months after trauma. In all the patients, CT and MRI scans found a complex brain damage at different levels.

The dynamic and detailed assessment of the state of consciousness [11,12] was conducted on the Glasgow coma scale [13]. The data from the acute stage of trauma featured a coma lasting from 3 to 39 days. Just before the study started, the level of consciousness in patients was different: coma in 16, vegetative status in 16, akinetic mutism in 7, mutism with speech understanding in 23, speech disintegration in 6, amnesic confusion in 9, severe cognitive deficiency in 3. In neurological examination, patients were assessed for personality changes and the severity of rigidity and tremor on the Unified Parkinson’s Disease Rating Scale scales [14], changes in muscle strength on the Muscle Strength Grading Scale of 0 to 5 [15; 16]. Autonomic disorders were assessed on scales for abnormal salivation and hidrosis [17]. The presence of oral automatism, convulsive seizures, oculomotor

disorders was considered, and the presence of attention was measured using eye-tracking and fixation.

Concurrently with the neurological examination, each patient underwent a dynamic EEG study. It included 18-channel monopolar registration of biopotentials using indifferent ear electrodes with a bandpass of 0.5-35 Hz as reference points (Nichon Kohden EEG machine). Then the coherent spectral analysis was applied to the artifact free EEG-segments of the resting state with eyes closed for at least 60 seconds, using MBN-Neurokartograph software (Russia). Coherent spectral quantitative EEG parameters were calculated over the ranges of normal frequencies (delta, theta, alpha1-3, beta1-2).

Each patient was assessed for the reliability of differences in the parameters for each scan, as well as deviation from normative data (N = 54) based on a statistical software package and the non-parametric Mann-Whitney test [3 links].

Results and discussion

The neurological examination revealed clinical signs of dopamine deficiency (DD) in 35 patients: increased extrapyramidal muscle tone, resting tremor, hypersalivation, hyperhidrosis, seborrhea, and also decreased voluntary motor and brain activity. These symptoms are characteristic of a number of diseases associated with a hypoactivity of the dopaminergic system [19,20].

An extensive clinical picture of the DD syndrome was matched by EEG changes, such as almost a total lack of the alpha rhythm in EEG pattern and increased synchronised beta activity at 13-14 Hz with a significant rise in the frontal and anterior temporal regions, and concurrent with a general decrease of biopotential amplitude, EEG flattening and smoothing differences between zones, as well as more or less pronounced theta rhythms (Fig. 1a).

This pattern correlated with a certain structure of the power spectrum with dominant peaks in the beta frequency range (Fig. 1b).

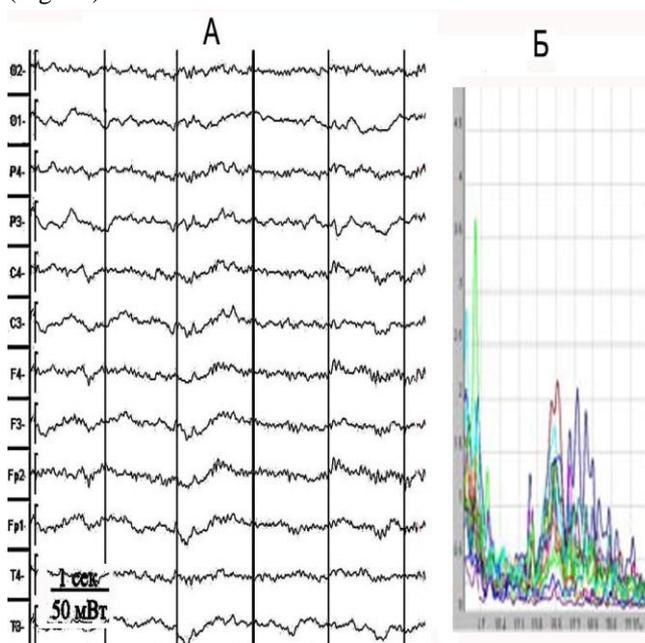


Fig.1 An increase of synchronised beta activity in EEG pattern (A) and its power in the spectrogram (B), characteristic of the

clinical DD syndrome. Patient B. (14 years old) with clinical signs of the DD syndrome and underlying akinetic mutism (1.5 months after trauma)

The amount of theta activity in the EEG pattern, increased in 19 patients, reflected how much the subcortical structures were involved in a pathological process, but did not correlate significantly with damage to any of them in particular.

It is noteworthy how our data on beta activity, as an EEG marker for the post-traumatic DD syndrome, are consistent with other research on dopaminergic system dysfunction. This beta activity, indeed, was described as an early predictor of Parkinson's disease (PD) [21]. The increased power of EEG beta-components compared to the norm was described as characteristic of PD, with moderately increased power in the theta frequency range [22]. Motor disorders in PD are also associated with hyper-synchronization of beta activity in cortical-subcortical neural networks, including basal nuclei [23].

The clinical and EEG manifestation of the DD syndrome was found to be greater at the early stages of mental recovery (vegetative state, akinetic mutism, mutism with speech understanding). A dynamic study (44 to 436 days) detected positive changes in the neurological status of the patients, such as a decreased severity of autonomic disorders (hypersalivation and hyperhidrosis), tremor and rigidity, with significant positive changes ($p < 0.05$) for the latter two.

However, rigidity and tremor did not disappear completely in any of these studies, but only decreased in severity.

The EEG picture of similar neurological dynamics in patients with the DD syndrome showed an increased frequency of beta activity (from 13 to 16 Hz), a decreased amount of the initially slow (theta and delta) activity and normalised power and coherence indicators, but concurrent with a consistent rise in the right hemispheric EEG coherent connectivity compared to the norm, especially in the occipital-temporal cortical regions.

A long-term (up to 5 years) case study found, even in patients with complete consciousness recovery and relative preservation of mental functions, the DD symptoms such as rigidity and tremor, as well as the characteristic features of the EEG pattern.

In 37 patients with sTBI, there were detected neurological (clinical) manifestations of choline deficiency (CHD), such as decreased muscle tone, dryness of mucous membranes and skin, tachycardia, hypotonia of the gastrointestinal tract, oculomotor disorders, decreased voluntary attention. The signs of a depressed cholinergic system were most obvious during organophosphate poisoning [24], and a decrease in its activity was also observed in Alzheimer's disease [25,26].

In EEG patients with an extensive clinical picture of choline deficiency (CHD), alpha activity of 7–8 sec (no matter how unstable, disorganized and slow) came to be most characteristic, even in cases of deeply depressed consciousness (coma). Alpha activity was combined with an increased diffuse fast activity or polymorphic (rhythmic) groups of theta-delta waves in the EEG pattern during a general disorganisation of biopotentials (Fig. 2). In the power spectrum, this corresponded to a pronounced peak in the alpha

frequency range, though less in power than for the slower (delta and theta) components (Fig. 2B). In patients with a slow EEG pattern, brain damage was more severe, predominantly, of the brainstem structures and the corpus callosum, including diffuse axonal damage.

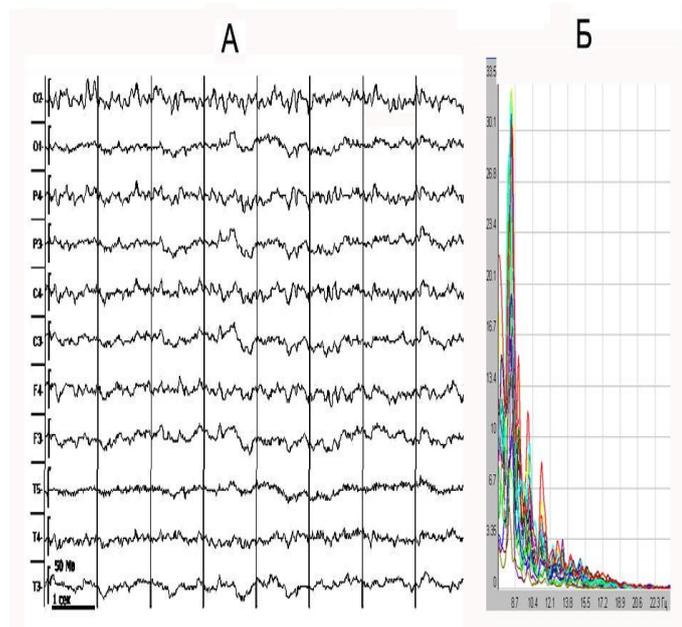


Fig.2 The presence of alpha activity in the EEG pattern (A) and a peak in the alpha band in the spectrogram (B), characteristic of the clinical CHD syndrome.

Patient K. 30 y.o. (40 days after trauma) with akinetic mutism, from a subgroup with predominant alpha and beta activity. More rarely (in 14 patients) both alpha and beta activities were presented in the EEG pattern.

Others' research previously also reported the connection of a pronounced alpha activity and the state of the cholinergic system [27,28]. Dynamic studies showed that the CHD syndrome is more characteristic of the stages from mutism with speech understanding to severe cognitive decline, with 13% of all cases detected in coma. In addition, more pronounced slow components in the EEG pattern were typical for CHD patients at a lower level of consciousness (coma or various types of mutism). Afterwards, the clinical signs of the CHD syndrome regressed, starting with hypotonia ($p < 0.05$) and also autonomic disorders ($p < 0.01$). Oculomotor disorders proved to be most persistent and presented even in patients who returned formally to clear consciousness and had no statistically significant changes. EEG studies showed that regressed components of the CHD syndrome were accompanied by EEG normalisation, such as an increased frequency (from 7-8 to 9-10 Hz), amplitude and regularity of the alpha rhythm, and also restoring its spatial organisation. By the end of the observation period, slow components in the EEG pattern were significantly less pronounced. The most persistent was a pathological increase of EEG coherence, compared to the norm, in the left hemisphere.

Conclusion:

The presented data demonstrate the relevance of identifying

the clinical and EEG syndromes of dopamine and choline deficiency throughout recovery in patients with sTBI. The syndromes differ in terms of neurological symptoms and their EEG correlates: the DD syndrome is associated with specific beta activity; the CHD, with alpha. A comparative assessment of the data provided by neuroimaging methods raises a question on damage significant to a certain morphological structure, or several structures, for the development of each syndrome. In case of the DD syndrome, the basal damage was most characteristic for the group ($p < 0.05$). For patients with CHD syndrome, the thalamic damage was often more significant ($p < 0.05$).

It can be assumed that the manifestation of the slow components in the delta and theta frequency ranges of the EEG pattern is less specific and reflects mostly the degree of brain damage and the severity of illness in patients with TBI. The specificity of the isolated manifestation of each syndrome is defined according to the stages of mental recovery. Distinguishing between posttraumatic DD and CHD syndromes is crucial for personalising therapy. The EEG markers described here can be used as reference points for identifying the syndromes and evaluating treatment efficiency.

Disclosure

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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