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THE PERSPECTIVES OF PHARMACOLOGICAL CORRECTION OF DEPRESSIVE DISORDERS AND COGNITIVE DEFICIT AS POST-TRAUMATIC EPILEPSY LEADING SYNDROMES

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Abstract

Traumatic brain injury is the leading cause of symptomatic epilepsy at a young age. Post-traumatic epilepsy (PTE) is the main factor in disabling patients of working age and impairs the quality of life. Comorbid pathology in the form of psychoemotional and cognitive disorders essentially has a single pathogenetic mechanism on the part of traumatic brain disease. There are problems with differential diagnosis between comorbid and direct manifestations of PTE. The above dictates the need to develop modern complex approaches to the treatment of PTE and correction of accompanying and comorbid pathological conditions. Author tries to develop new pathogenetically adequate approaches to the treatment of PTE with correction of the psycho-emotional sphere and cognitive deficit. 44 patients with PTE were examined. The average period of its formation reached 10.3±4.2 years, and the frequency of attacks – 2.4±0.9 per month. Focal attacks prevailed (61.4%). In addition to standard long-term anticonvulsant monotherapy, the main group (32 patients) was prescribed

ethylmethylhydroxyperidine succinate and vortioxetine. The control group (12 patients) received only anticonvulsant therapy.

When using the proposed complex treatment, the number of people with depression decreased from 25 (56.8%) to 10 (22.7%) cases, that is, by 2.5 times ($P < 0.05$). In the main group, from 59.4% to 21.9%, i.e. 2.7 times ($P<0.05$). In the control – from 50.0% to 41.7% ($P>0.05$). 37.5% registered positive dynamics in relation to pathological activity on the electroencephalogram. According to the Luria A. R. test, the average values of the obtained data at all stages of word presentation were probably higher than at the beginning of the study. Indicators of long-term memory changed similarly.

Thus, the proposed treatment approach has a beneficial effect on the main pathogenetic links of the development of PTE, its course and corrects cognitive deficits, psychoemotional layers, which are comorbid conditions.

Keywords: depressive disorders; cognitive deficit; brain injury; vortioxetine; pathogenetic mechanisms; treatment

Introduction. Traumatic brain injury (TBI) is the most common cause of neurological pathology. According to the World Health Organization (WHO), its annual number is 1.8-5.4 cases per 1000 population, and according to forecasts, TBI will become the third leading cause of death and disability in world [9]. The prevalence of TBI in different regions of Ukraine ranges from 2.3 to 6 cases (4–4.2 on average) per 1,000 population [2, 21]. Unfortunately, in our conditions, the level of neurotraumatism continues to grow in connection with the war in the east of Ukraine, therefore, a significant increase in the number of young people who lost their ability to work after a combat injury, which will entail a large number of consequences and final phenomena as a result of TBI, has been registered.

Post-traumatic epilepsy (PTE) is one of the most frequent and dire consequences of TBI. TBI remains the main factor in the development of this type of symptomatic epilepsy at a young age. The term of PTE formation ranges from 3 to 18 months from the moment of injury [2, 11, 24, 32]. PTE is one of the leading causes of disability in patients who are at their best-quality working age, it further worsens the quality of life, developing in 11-20% of people who have suffered a TBI, and its frequency and severity depends on the degree of damage to the central nervous system, the localization of the traumatic focus, the state of the premorbid background, the presence of somatic and the occurrence of comorbid pathology, the state of the autonomic nervous system etc. [14, 20, 29].

Comorbid disorders of the psycho-emotional sphere play a significant maladaptive role in persons with PTE. The prevalence of depressive disorders in patients with epilepsy ranges from 4.1 to 32%, with an overall prevalence in the population of 13.0% [1, 3]. It has been established that social, personal, and biological factors are involved in the formation of depressive symptoms [18]. At the same time, there is information that the degree and magnitude of damage do not affect the frequency and severity of emotional experiences. The occurrence of depressive and anxiety symptoms is possible when using in the treatment of a traumatic disease medications that affect the mediator exchange of the brain, including induced by anticonvulsant drugs or provoked by the cancellation of the latter [4, 16]. It should be taken into account that depression is also a frequent consequence of TBI. Prevalence rates vary from 14 to 42%, in the population – 2.1% [30].

In addition, depression can occur in up to 32.5% of people with epilepsy for a total population prevalence of 13.0% [31]. Depression affects the course and prognosis of epilepsy, reduces the quality of life and increases the cost of medical care [22, 25].

Difficulties in the diagnosis of emotional disorders in the structure of epileptic seizures are caused by the similarity of emotional and own manifestations of epileptic seizures. At the same time, the leading role is played by the limbic-reticular complex – an integral part of the development of this kind of disorders, atrophic disorders, which quite frequently develop in the hippocampus (regulator of the cognitive sphere) with the subsequent development of hippocampal sclerosis [8, 12].

In addition, the frequency of attacks, antiepileptic drugs administration (AEDs) also affect emotional and, especially, intellectual-mnestic functions [17]. And cognitive deficit is also comorbid to TBI and PTE, due to organic damage to brain structures, neurotransmitter imbalance. There is an opinion that the "mental" and "cognitive" components of neurological disorders are, in fact, a single whole from the point of view of neuroanatomy and pathophysiology either at the level of neural networks or at the level of neurotransmitters [26, 27].

Accordingly, the requirements for the selection of AEDs are increasing, taking into account their impact on the emotional and cognitive spheres [23]. There are certain criteria when choosing an anticonvulsant capable of minimizing the deterioration of cognitive deficits in PTE [5].

In addition, for adequate therapy of PTE, correction of mediator exchange, strengthening of neuroplasticity and implementation of the necessary neuroprotection,

influence on the central mechanisms of regulation of the somatic sphere, depressive-anxious stratifications, and manifestations of ANS dysfunction are necessary.

It is also known that taking AEDs can lead to the manifestation of toxic and other side effects, affect biological processes, often inhibit mental activity, especially taking into account already existing cognitive and intellectual-mnestic disorders as a result of encephalopathy in the framework of TBI, vascular pathology of the CNS and comorbid accompaniment this pathology. It is necessary to develop new approaches to treatment that can maximally influence the leading links of the pathogenesis of TBI, PTE, and comorbid pathological conditions.

The aim of the work is to develop new pathogenetically adequate approaches to the treatment of PTE with correction to both psycho-emotional sphere and cognitive deficit.

Materials and methods

44 patients with PTE were examined (32 – main group, 12 – control). The average age was 32.3±6.1 years. The average period of PTE formation was 10.3±4.2 years, and the frequency of attacks was 2.4±0.9 per month. Focal attacks prevailed (61.4%).The Hospital Anxiety and Depression Scale (HADS) were used to diagnose depression [33]. The Luria A.R. test was used to study short-term and long-term memory [19]. The bioelectrical activity of the brain was studied – electroencephalography (EEG) according to the method of L.R. Zenkov [10] and Magnetic resonance imaging (MRI) – MR tomograph "Hitachi AIRIS II" by Hitachi Medical systems America, Inc. (USA) with a voltage of 1.5 T in T1W, T2W, FFE, FLAIR mode.

In addition to the standard long-term anticonvulsant monotherapy of first-line PEDs, which are normotimics, the main group was prescribed *ethylmethylhydroxyperidine succinate,* intravenously 300 mg 1-2 times a day, 10 days, after which – 200 mg intramuscularly once, 10 days, and then 125 mg 2-3 times for 4-6 weeks; simultaneously with intramuscular administration, *vortioxetine* was prescribed at 10 mg 1 r/day throughout the study and further for at least 6 months.

The control group received long-term anticonvulsant first-line AEDs monotherapy.

Results

MRI analysis with a history of PTE revealed damage to the CNS as a result of TBI, depending on the severity of the brain damage in the history, they increased. Bone defects (6.8%), cicatricial atrophic lesions (27.3%), post-traumatic cysts (20.4%) and hematomas (11.4%), expansion of subarachnoid spaces (61.4%), ventricular system (21.9%) external

(29.5%) and internal hydrocephalus (40.9%), increased or decreased density of brain matter of various localization (34.1%).

EEG was an important addition to the diagnosis of PTE. In the period between attacks, 15.9% of patients showed no signs of seizure activity on the EEG.

In the vast majority of cases, the electroencephalogram showed signs of a non-specific nature in 56.8%, including with disorganization in the structure of basic rhythms, frequency, modulation and waveform, as well as a tendency to hypersynchronization.

In 75.0% of patients, regardless of the type of attacks, a decrease in the α-rhythm index, a predominance of low-amplitude polyform activity, and an increase in the high-frequency index were found.

In the presence of generalized attacks, 61.4% of patients have registered diffuse changes of varying severity, while slow-wave activity was detected in 36.4%, with sharp waves – in 34.1%.

Focal epileptiform activity was registered in 29.5%. In 9.1% of this kind of "focus" is determined in the frontal lobes. In 22.7% – in the temples. The main electroencephalographic changes in the cell were "sharp-slow wave" and "peak wave" complexes, regional sharp waves and their slowing down.

At the same time, the average frequency of attacks was equal to 0.9±0.1 months, which shortens the interparoxysmal period by 2.3 times compared to the average duration in the population of examined patients, which was 2.1±0.5 months ($p<0.05$). The phenomenon of epileptic activity was manifested more often in the presence of a higher frequency of epileptic attacks.

The presence of psycho-emotional layers and dysfunction of the central nervous system primarily affected the decrease in α-rhythm activity. In addition, the regularities associated with the reduction of damage to the central nervous system are preserved, which further affects the reduction of the modulation amplitude.

According to the Hospital Anxiety and Depression Scale, 34 patients (77.3%) with clinically significant depression were registered. At the same time, in the structure of PTE with depressive experiences, focal forms were more often observed – 15 (83.3%). In our observations, structural damage to the brain came to the fore, i.e. there was a predominance of individuals who suffered a moderate TBI, including severe TBI ($p<0.05$).

The possibility of the influence of depression on the formation of PTE, depending on the degree of severity of primary traumatic brain damage, was analyzed. The average time for

the formation of PTE in the presence of depression was reduced by 0.7 months compared to the general population of the examined persons.

The majority of patients – 93.2% – complained about a decrease in memory, attention, and thinking. It is known that a decrease in motivational-cognitive and other cognitive functions is the leading clinical consequence of TBI. For this purpose, the state of short-term and long-term memory was studied according to the test for memorizing 10 words.

In persons with mild TBI (LTBI), the average values of the test at all stages of word presentation were significantly higher than in groups with a more severe injury, while a violation of selectivity, a narrowing of the volumes of immediate and delayed reproduction was noted. With a severe injury in the anamnesis, there was a tendency to increase the insufficiency of intellectual operations, among which the leading place was occupied by a decrease in the level of generalization. Various dysmnestic disorders were noted.

The productivity of voluntary memorization of verbal material was significantly reduced in comparison with normative data, the volume of direct reproduction in these patients was 2.4 words (TBI; $p<0.05$), while in the case of moderate and severe TBI – 3.2 and 4.8 words, respectively ($p<0.05$).

Discussion

A significant decrease in the volume of long-term reproduction was registered, which indicates a violation of long-term verbal memory. The word learning curve has a “plateau type”, which is especially characteristic of patients with structural brain damage.

The developed comprehensive treatment of the above-described manifestations of PTE is based on the known provisions and personal experience of the authors regarding the possibilities of correction of comorbid conditions in PTE, in particular in the intellectual-mnestic and psychoemotional spheres, which are leading in the structure of symptoms.

Thus, the proposed complex treatment of PTE and comorbid disorders due to the appointment of a combination of ***vortioxetine*** – an innovative antidepressant with a multimodal effect (inhibits the reuptake of serotonin and directly binds to several subtypes of serotonin receptors) with a powerful antidepressant and procognitive effect, a rapid onset of the therapeutic effect [15, 28] and ***ethylmethylhydroxypyridine succinate*** – an antioxidant with noo- and vegetotropic effect, which optimizes cerebral metabolism, membrane protector and stimulator of resistance to brain hypoxia [6, 7, 13].

When using the proposed complex treatment, the number of people with depression decreased from 25 (56.8%) to 10 (22.7%) cases, that is, by 2.5 times ($P<0.05$). In the main group, these values were more pronounced: from 59.4% to 21.9%, that is, by 2.7 times

(P<0.05). In the control group – from 50.0% to 41.7% – insignificant changes: by 8.3% (P>0.05).

37.5% registered positive dynamics in relation to pathological activity: reduction/disappearance of diffuse pathological changes; slow-wave and low-amplitude focal (especially when present in several areas) activity, reduction in the number of sharp and slow wave complexes, restoration of the main rhythm.

In cases of focal epileptic activity, positive changes were registered in 10 22.7%, (P<0.05) mainly in the main group (9 – 28.1%), P<0.05; control – 1 (8.3%). The "focus" of epileptic activity remained in 5 patients (15.6%), while only manifestations of temporal epilepsy were recorded.

According to the test for memorizing 10 words in the main group, in the course of therapy, an increase in the number of responses to the presented words was shown in all presentations. At the same time, the average values of the obtained data at all stages of presentation of words were probably higher than at the beginning of the study. At the same time, their maximum was reached at the moment of the third presentation (7.4±1.2 words), which was probably higher (P<0.05) than at the beginning of the study (6.8±1.3 words). Indicators of long-term memory changed similarly, which on average exceeded the weekend by 8%.

Therefore, the obtained data indicate an improvement in the state of short-term and long-term memory, stability of attention in the process of complex use of adequate anticonvulsants and correctors of autonomic disorders, psychoemotional symptoms and normalization of cognitive functions in patients with PTE.

Conclusions

Taking into consideration all said above, it can be stated, that the proposed treatment approach has a beneficial effect on the main pathogenetic links of the development of PTE. The altering effect of the proposed drugs on the background of PEP leads to a probable reduction of complaints and subjective experiences, as well as indicators of neurological, including cognitive deficits, psycho-emotional layers, which are comorbid conditions. At the same time, a possible effect may be a reduction in the dosage of AEDs, their side effects, prevention of polypharmacy, beneficial effects on the clinical course of PTE with a decrease in the number and severity of attacks with the normalization of brain bioelectrogenesis.

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