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STATE OF NEUROTRANSMITTERS (GLUTAMATE AND GAMMA-AMINOBUTYRIC ACID) IN PATIENTS WITH WILSON'S DISEASE

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СТАН НЕЙРОТРАНСМІТЕРІВ (ГЛЮТАМАТУ ТА ГАММА-АМІНОМАСЛЯНОЇ КИСЛОТИ) У ПАЦІЄНТІВ З ХВОРОБОЮ ВІЛЬСОНА — КОНОВАЛОВА

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СОСТОЯНИЕ НЕЙРОТРАНСМИТТЕРОВ (ГЛЮТАМАТА И ГАММА-АМИНОМАСЛЯНОЙ КИСЛОТЫ) У ПАЦИЕНТОВ С БОЛЕЗНЬЮ ВИЛЬСОНА — КОНОВАЛОВА

The research objective was studying of condition inhibitory excitatory neurotransmitter in patients with Wilson's disease (WD). The content of excitatory neurotransmitter glutamate and inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been defined in blood serum of 40 patients with WD. It was shown that WD clinical course is accompanied by the raised emission of excitatory neurotransmitter glutamate and decrease emission inhibitory neurotransmitter GABA. The overexcitation of brains structures is a consequence of this double factor. This fact should be considerate in carrying out medical-rehabilitation actions.

Keywords: Wilson's disease, neurotransmitters, glutamate and gamma-aminobutyric acid.

Метою дослідження було вивчення стану гальмівних і збуджуючих нейротрансмітерів у пацієнтів з хворобою Вільсона — Коновалова (ХВК). У 40 хворих з ХВК було визначено у сироватці крові вміст збудливого нейромедіатора глютамата і гальмівного нейромедіатора гамма-аміномасляної кислоти (ГАМК). Показано, що перебіг хвороби Вільсона — Коновалова супроводжується підвищеним викидом медіатора збудження глютамата і зниженням рівня гальмівного нейромедіатора ГАМК. За рахунок цього подвійного чинника йде перезбудження структур головного мозку. Даний факт необхідно враховувати під час проведення лікувально-реабілітаційних заходів.

Ключові слова: хвороба Вільсона — Коновалова, нейротрансмітери, глютамат, гамма-аміномасляна кислота

Целью исследования явилось изучение состояния тормозных и возбуждающих нейротрансмиттеров у пациентов с болезнью Вильсона — Коновалова (БВК). У 40 больных с БВК было определено в сыворотке крови содержание возбуждающего нейромедиатора глютамата и тормозного нейромедиатора гамма-аминомасляной кислоты (ГАМК). Показано, что течение болезни Вильсона — Коновалова сопровождается повышенным выбросом медиатора возбуждения глютамата и снижением уровня тормозного нейромедиатора ГАМК. За счет этого двойного фактора идет перевозбуждение структур головного мозга. Данный факт необходимо учитывать при проведении лечебно-реабилитационных мероприятий.

Ключевые слова: болезнь Вильсона — Коновалова, нейротрансмиттеры, глютамат, гамма-аминомасляная кислота

Wilson's disease (WD) is a serious, chronic, progressive disease with a genetically determined autosomal recessive inheritance of copper metabolism disorders. The development of disease is defined by gene ATP7B, which is located on the long arm of chromosome 13 and encodes a transmembrane protein P-type ATPase. At the present moment there are identified more than 350 mutations in this gene. This protein embeds the molecule of copper into apoceruloplasmin and performs the elimination of copper into bile [4, 13, 15].

The defect of ATPase leads to the fact that free ions of copper, after "overflowing" the liver buffer systems, begin to enter into the bloodstream and accumulate excessively in the brain, particularly in its basal ganglia [5, 11].

As far as copper accumulates in the brain structures, the pre neurological stage of disease transfers into the neurological stage with development of various neurological and psychopathological syndromes.

Neurological stage of Wilson's disease acquires chronic neurodegenerative remitting nature. It should be noted that today the problem of early, timely and adequate definition of the neurodegenerative process in the brain with the help of biological markers is highly relevant, but not completely solved [1, 3, 16].

Much attention in this regard is paid to determination of neurotransmitters levels and GABAergic exchange indicators in the cerebrospinal fluid and blood. Glutamate and gamma-aminobutyric acid (GABA) are the main synaptic neurotransmitters in the brain. GABA is the major inhibitory neurotransmitter in the central nervous system. It is a biogenic substance and it is involved in neurotransmitter and metabolic processes in the brain. It was shown in the experimental studies that brain energetic processes are activated significantly under the influence of GABA: respiratory activity of the tissue is increasing, brain glucose utilization and blood circulation of the brain are improving [7, 12]. As it was shown by clinical studies, GABA reduces the effects of stress, it is an important mood modulator, and it improves concentration. An excessive amount of GABA leads to the excessive relaxation and calm, that makes difficult the normal response of the body. Insufficient amount of GABA contributes to the development of fear, neurosis, depression and development of seizures and epilepsy [8, 10].

Glutamate is the one of the major excitatory neurotransmitter. It is associated with learning and memory. Molecule of glutamate plays an important role in the processes of cellular metabolism and an important role in the development of epileptic seizures. Excessive amounts of glutamate are toxic to neurons and cause the development of neurodystrophic processes in the brain. Insufficient amounts of glutamate contribute to poor memory and learning ability [9, 14].

However, despite the fact that glutamate and GABA are the major synaptic neurotransmitters in the brain, there are almost no works in the literature that covered the questions of functional state of these neurotransmitters in patients with Wilson's disease. Also, their influence on the formation of various disease manifestations and their role as biomarkers of disease nature and outcome is not discovered.

We have examined 40 patients with Wilson's disease, among them: women — 16 persons, men — 24 persons. For the period of appeal to the clinic of the Institute the average age of the patients was 30.8 ± 7.2 years. The age of patients ranged from 20 to 49 years. The average age of patients from the onset of first symptoms through to the final diagnosis, and therefore the beginning of etiopathogenetic therapy, was 2.6 years and ranged from 1 to 7 years. Duration of disease was from 1 year to 15 years and the average was 9.5 ± 2.4 years. The diagnosis of Wilson's disease was determined or confirmed in the clinic of the Institute on the basis of reduction of ceruloplasmin amount in serum below 20 mg/dL, the increase of copper excretion in the urine of more than 100 mg/day and the presence of Kayser-Fleischer rings.

Analysis of the clinical picture in the surveyed patients revealed polymorphic, varying severity of neurological and psychopathological symptoms. Depending on the key symptoms according to the classification of Konovalov (1960), the patients were distributed as follows: the greatest number of patients had tremor (15 individuals) and akinetic-rigid form (15 individuals), rigid-arythmo-hyperkinetic form was in 4 patients, extrapyramidal-cortical — in 3 patients and abdominal form also in 3 patients.

The control group was composed of 16 persons who had no symptoms associated with damage of the central nervous system. Age of the control group was within 27—38 years and in average it was of 29.11 ± 9.6 years.

For the determination of glutamate and gamma-aminobutyric acid in the serum of patients and individuals of control group we used the method of high-voltage electrophoresis with subsequent quantitative analysis of selected fractions by spectrophotometric method. We used a standard set of Sigma-manufactured in our research.

The results of these studies showed that in the serum of patients with Wilson's disease the level of inhibitory neurotransmitter of gamma-aminobutyric acid was significantly ($p < 0.05$) lower than in the control group, and respectively, was 3.57 ± 1.02 and 7.5 ± 1.04 mmol/l. At the same time the level of excitatory neurotransmitter glutamate was higher than in the control group and respectively, was 150.85 ± 10.25 and 124.85 ± 12.95 mmol/l.

While conducting a gender analysis, we did not find significant differences in content of GABA in the serum of women and men (3.54 ± 0.95 and 3.68 ± 1.01 mmol/l, respectively). However, there is a tendency towards a higher content of glutamate in women compared with men (158.1 ± 12.35 and 138.0 ± 10.11 mmol/l, respectively).

In our researches we found no reliable correlation between forms of Wilson's disease and the content of glutamate and GABA in serum. However, there is a tendency of glutamate increasing in the serum of patients with marked emotional lability and anxiety. The rate of glutamate in these patients was on average 167.0 ± 11.32 mmol/l. GABA index among them was slightly lower than the average for the group (3.49 ± 0.09 and 3.57 ± 1.02 mmol/l, respectively).

According to earlier studies, almost half of the patients with Wilson's disease have increased indexes of seizure activity on EEG [2]. Therefore, we carried out a comparative analysis of serum glutamate and GABA content in serum, depending on the nature of the bioelectric activity of the brain. It was found that in patients with severe convulsive readiness on EEG there was higher glutamate indexes than the average for the group of patients IOO (165.2 ± 11.32 and 150.85 ± 0.96 mmol/l, respectively). Indicator of GABA in the group of patients with increased convulsive readiness almost did not differ from that of the total group (3.48 ± 0.93 and 3.57 ± 1.02 mmol/l, respectively).

We investigated the levels of glutamate and GABA in patients with Wilson's disease in the dynamics before and after the modern pathogenetic treatment aimed at linking ions of toxic free copper and removing them from the body by using chelating agents (cuprinol), as well as comprehensive symptomatic restorative treatment. As the analysis has shown, the level of gamma-aminobutyric acid in blood serum had significantly ($p < 0.05$) increased after complex chelate and symptomatic recovery treatment (respectively 3.11 ± 0.61 and 4.73 ± 0.07 mmol/l) and the content of glutamate had decreased (134.86 ± 11.84 and 114.91 ± 10.53 mmol/l, respectively).

Thus, the results of the researches allow us to make the following conclusions. The course of Wilson's disease is accompanied by an increased release of excitation neurotransmitter of glutamate and reduction in the level of the inhibitory neurotransmitter GABA, and due to this dual factor the extra excitation of brain structures takes place.

Evidently, it contributes to the development of neurological and psychopathological symptoms and syndromes such as trembling, hyperkinesis, increased muscle tone, neurotic state, fears, and increased seizure activity.

According to the literature and our data, Wilson's disease is a lifelong, chronic relapsing disease and the neurodegenerative process develops in the brain of these patients. This process is caused by a cascade of metabolic disorders and therefore therapeutic and rehabilitation measures should be directed not only to the normalization of copper metabolism, but also on the patronage of the brain and in particular on the normalization of neurotransmitter metabolism.

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