Prokhorova Anna Vladimirovna,
MD, assistant professor of Nervous diseases of the Tashkent Medical Academy
E-mail: mbshakur@mail.ru

Azizova Rano Bakhodirovna,
Assistant of the Department of Nervous Diseases of the Tashkent Medical Academy
E-mail: bahodirovna1983@mail.ru

Pathogenetic role of immune reactivity of neurotropic auto antibodies and neural mediators at symptomatic and idiopathic epilepsy

Abstract: We detected intensification of immune reactivity represented by a change of neurotropic antibodies level to proteins and receptors of neural mediators participating in epilepsy genesis and formation of aberrant plasticity in patients with symptomatic and idiopathic epilepsy.

Keywords: epilepsy, pathogenesis, immune reactivity.

Topicality. Recently formed notions of continuous unity of the functions main integrative systems of organism such central nerve system and immune one should serve to be a new impulse to the study of epilepsy immune pathogenesis. On the basis of the data about neural immune interaction new scientific disciplines were formed. These are neural immunology and neural immune pathology [2; 5].

In the modern time, due to researchers who studied immune neural endocrine regulation, it is known that many natural auto antibodies (AB) participate in the regulation of organism general homeostasis and they are reversibly interact with antigens (AG) of own organism. Natural auto antibodies are synthesized in organism of healthy people since fetal period and for the whole life [3, 8].

As a result healthy people of various age and sex have only minimal differences (immune fingerprints) in serum content of some AB. It is established that production, of AB with various specificities is regulated (according to the principle of feedback) by the amount of target-antigens [4]. That proves the presence of powerful mechanisms of physiologic (normal) level of production and secretion of various variants of AB [6]. Part of AB does not have certain organic aiming and interact with AG present everywhere (collagen, DNA, cytochromes, etc). Other part interacts with organ specific antigens (neural specific proteins, organ specific iso-enzymes, insulin, etc.) The aforesaid is relevant to AB interacting with proteins of nerve cells or neurotropic AB (NAAB).

Patients with diseases of nerve system often have alterations of serum content of NAAB. Researchers mostly pay attention to situations characterized by a growth of certain specific NAAB amount which is understood as a pathologic auto immune aggression. Though from the point of view of notions of AB regulatory functions, disorders of serum correlations for various kinds of NAAB can have great significance, and the rise of AB production can have not only pathologic, but also adaptive-compensatory importance [6].

Recently a great attention is paid to participation of common neural immunologic net in the genesis of many diseases [3; 7]. Immunologic aspects of epilepsy are widely discussed in modern literature [2; 8].

Pathogenetic role and diagnostic importance of AB to proteins of brain and receptors of neural mediators demand further study.

Aim of the research: is to study immune reactivity of neurotropic auto antibodies and neural mediators in case of symptomatic and idiopathic epilepsy.

Materials and methods of the research: the level of AAB to neurotropic proteins and neural mediators was determined in blood serum of 59 patients with epilepsy. For the performance of immunologic analysis we formed the following clinical groups: I group — 17 patients with idiopathic epilepsy; II group — 42 patients with symptomatic epilepsy.

16 clinically healthy people served to be the control.

All patients underwent a thorough preliminary anamnesis and clinical selection, which was performed by means of stratification randomization method using criteria of inclusion and exclusion. Criteria of patients' inclusion into study: adults, epileptic seizures at the moment of hospitalization or in anamnesis, idiopathic and symptomatic epilepsy. Criteria of exclusion: children, cryptogenic epilepsy, pseudo epileptic attacks, psychogenic reactions, conversion attacks (hysteria).

Quantitative definition of serum immune reactivity of antibodies to receptors of neural mediators (glutamate, GABA, dopamine, serotonin and cholin receptors) and neural specific proteins (NF200, Gfap, S100 and CBP) was performed with the help of solid-phase immune enzyme method ELI-N-Test and same name test-sets produced by MIS «Immuneculus» (Russia). AAB Immune reactivity value from 80 to 140 R. U. was considered to be normal, and immune reactivity index AB1/AIAB2 from 0.8 to 1.2 [9, 16].

Analysis of the achieved values was performed with the help of «SPSS for Windows» and «STATISTICA» Microsoft Excel with processing of variation statistic methods. Reliability of the achieved results was evaluated by pair method according to Student's t-criterion. Differences were considered to be reliable with $p<0.05$.

Results of the research: Results of the performed researches demonstrated that clinically healthy people (control group) had natural AAB to the studied neurotropic proteins which in certain limited titers were normal components of

blood serum of almost healthy people. In relation to that, in compliance to the recommendations of test systems' manufacturers it was indicated as "an inner standard serum".

In the evaluation of the results of immunologic study it was detected that both groups of patients differed from the control group, both in the level and degree of immunologic values distribution.

For the revealing possible pathogenetic peculiarities we performed analysis of neural immune Interrelations in both groups in comparison with the control one. As a result it was determined, that in the group of patients with SE the levels of AAB to all neural specific proteins reliably exceed the values not only of "inner standard serum", but also analogue values of patients with IE. So, the highest AAB among the studied ones in both groups was AAB to S100, and in the patients with SE that value exceeded normal values 1.6 times ($P<0.01$), and in the patients with IE 1.9 times ($P<0.05$). At the same time there was reliable rise of AAB in the group with IE in comparison with the group with SE (150.3±11.8 r. u. versus 124.1±4.6 r. u. $P<0.05$). That kind of AAB rise to protein S100, which is Ca-conjugating protein, can prove the hypothesis that one of the parts of epileptic seizures pathogenesis is increase of neuron membrane permeability for Ca2+ ions with increase of its concentration in intercellular space.

Analysis of AAB level to protein NF200 also showed reliable rise of its titers in the patients of the both groups (average 1.7 times with SE and 1.3 times with IE correspondingly, $P<0.05$). At the same time there was notable reliable prevailing of AAB level to NF200 in the patients with SE (121.8±8.2 r. u. versus 97.6±8.9 r. u. $P<0.05$), indicating excessive plasticity, evidently promoting preserving of more stable pathologic links of epileptic system in the patients with SE.

The level of serum AAB to neural specific protein CBP also reliably exceeded the values of "Inner standard serum" in both groups (average 1.7 times in the patients with SE ($P<0.01$) and 1.3 times in the patients with IE correspondingly, ($P<0.05$)) with simultaneous exceed of these values in the patients with SE average 1.3 times in comparison with the patients with IE (102.4±8.0 r. u. versus 78.8±7.7 r. u., $P<0.05$).

The level of serum AAB to GFAP was approximately at the same level with AAB to CBP and in patients with SE it was 102.5±8.3 r. u., and in the patients with IE — 80.4±7.2 r. u., reliably exceeding the values of the control group average 1.8 ($P<0.01$) and 1.4 times ($P<0.05$) correspondingly. Comparative analysis between the groups also revealed statistically significant rise of AAB to CBP among the patients with SE in comparison with the patients with IE 1.3 times ($P<0.05$).

As a result of that analysis we revealed positive correlation link between the duration of epilepsy and the levels of AAB to all studied neurotropic proteins, the most expressed one in the patients with SE in comparison with the patients with IE. Similar direct link was determined between the level of AAB and the frequency of seizures in the checked patients. And that interrelation did not depend on etiologic factor of epilepsy.

Thus, clinical-immunologic analysis revealed accurate rule of antibodies content to neurotropic proteins dependently on the etiology, term and progress of SE and IE. The rule of detected rise of neurotropic AAB in close relationship with each other and frequency of seizures was a proof of deterioration of neural immune misregulation with the growing severity of clinical progress in the patients with epilepsy.

Disorder of permeability of brain immune barriers leads to formation of AAB to neurotropic proteins, intensifying the deficiency of trophic supply to brain and progressing of damaging processes. Differentiation of the achieved results dependently on the form of epilepsy revealed that the greatest sensitizing of immune competent cells to neural specific antigens NF200, GFAP and CBP was observed in cases of SE, and it, in its turn, was a reliable reflection of a destructive process and pathologic permeability of HEB in this group of the patients.

In the correlation of the values of the patients with IE and SE with the data of "inner standard serum" we detected reliable one-direction rise of an individual level of serum immune reactivity of AAB to the receptors of all studied neural mediators.

In our opinion, quite interesting data were achieved in the examined patients in relation to the level of AAB to cholin receptors. Particularly, in the group of patients with IE the AAB level to that neural mediator was 162.9±5.3 r. u., 4.8 times exceeding the values of "inner standard serum" ($P<0.01$), and 3.5 times the similar values in the patients with symptomatic epilepsy (46.7±4.9 r. u., $P<0.05$).

The further analysis of neural immune interrelations in the patients with epilepsy revealed a reliable high level of AAB to glutamate and voltage-dependent Ca channels among the other studied AAB. Thus, in the group of patients with SE these values were equal to 73.8±5.3 and 98.5±7.0 r. u. correspondingly, exceeding the values of "inner standard serum" average 1.3–2 times ($P<0.05$), and in the group with IE — 98.1±8.8 and 78.6±6.4 r. u. correspondingly, exceeding the normal values average 1.7–2 times ($P<0.01$). In the patients with IE we revealed a reliable rise of AAB to glutamate not only in relation to the control values, but also those of the patients with SE (98.1±8.8 and 73.8±5.3 r. u. correspondingly, $P<0.05$). That significant rise of AAB to glutamate among the patients of both groups proves actual disorders of excitement processes as a result of membrane neural-transmitter receptor and mechanisms of glutamate excite toxicity. At the same time the results of the performed immunologic studies prove, that more significant disorders of glutamate ergic system were noted in cases of IE. The achieved data were interpreted as a proof of significant misbalance in glutamate ergic system mostly in the patients with IE, and it was trigger moment for the start of neuronal sprouting process.

The levels of AAB to GABA, dopamine and serotonin in the examined groups also exceeded normal values and were approximately at the same level. And the reliable differences

from the "inner standard serum" in that case were detected only in the patients with IE (AAB GABA 71.8±4.7 r. u., P<0.05; AAB DA 74.4±4.2, P<0.01; AAB SER 76.9±3.4 r. u., P<0.05). Among the examined patients with SE reliable differences were detected only in relation to AAB to dopamine (62.6±5.0 r. u., P<0.05).

High level of auto antibodies to GABA is the proof of disorders in the work of GABA-ergic system, intensifying neurotoxic effect of glutamate on the one hand, and inhibiting structures of anti-epileptic system on the other (Gusev Y. I., Gekht A. B., 2009). In particular, reliable rise of AAB to this neurotransmitter in the patients with idiopathic epilepsy can prove deep misbalance in glutamate-ergic system and expressed exhaustion of GABA-ergic system in that group of the patients, and it serves to be a trigger for the processes of neuronal sprouting. The presence of high levels of AAB to dopamine and serotonin in the patients with IE and a reliable difference from the values of "inner standard serum" proves a close link of glutamate-ergic system with the system of biogenic amines, misregulation of which leads to destructive effect on neurons and has pro-epileptic effect. In that case that kind of correlation of AAB can be interpreted as a proof of expressed auto immune reaction from the side of nerve tissue, which, in its turn, promotes maintenance of pathologic epileptic system in the patients with IE.

Thus, the rise of AAB to ligand-binding site of neural mediators' receptors (Glu-R, GABA-R, Dop-R, Ser-R and Chol-R) indicates changes in the corresponding systems of neurons. The higher serum level of AAB to receptors of neural mediators can indicate the presence of various mechanisms of neural mediation and neural plasticity realization in the patients with IE and SE.

Conclusion. The total sum of the achieved data, relevant to immunologic aspect, testify that inadequate reaction of immune system can lead to formation of pathologic convulsive activity. In other words, immune pathologic mechanisms, including those which are manifested by abnormal alterations in the production and serum content of neurotropic AAB, are involved to epilepsy pathogenesis.

One of the leading mechanisms of pathogenesis of epilepsy is complex reconstruction of neural-immune interrelations, manifested by one-direction rise of the level of auto antibodies to neural specific proteins S100, GFAP, NF-200, CBP and neural mediators glutamate, GABA, dopamine, serotonin and voltage-dependent Ca channel. And the key part in the pathogenesis of idiopathic epilepsy is neural mediator misbalance, and in the pathogenesis of symptomatic one — rise of AAB level to GFAP and CBP.

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Saydaliev Saydimurat Saydiganievich,
Ministry of Health the Republic of Uzbekistan
Tashkent, Uzbekistan
E-mail: mmm.karimjon@mail.ru

Prevention of polio, results and achievements

Abstract: Regularly by independent experts of the World Health Organization, evaluates the quality of immunization and surveillance for acute flaccid paralysis in the Republic of Uzbekistan.

Due to the high level of immunization coverage against polio, as well as the absence of polio cases during at the appropriate level of surveillance for acute flaccid paralysis, the Republic of Uzbekistan for 12 years, retains the status of a "territory free of wild polio."