NEW ASPECTS OF THE PATHOGENESIS OF EPILEPSY

Rano Bahodirovna Azizova

Tashkent Medical Academy, Uzbekistan

ABSTRACT

We studied 52 patients with epilepsy with the average age of 36.2 ± 14.7 years old. Of them, 38 patients had idiopathic epilepsy, 14 patients had symptomatic epilepsy. Our study has shown that epilepsy is accompanied with increased levels of autoantibodies to NF-200, GFAP, S100, MBP, DNA, GABA and dopamine receptors, testifying to the important role of autoimmune disturbances in the pathogenesis of epilepsy. More severe attacks are accompanied by worsening of neuroimmune dysregulation. The degree and duration of autoimmune process can serve additional diagnostic and prognostic criteria for epilepsies.

UDC CODE & KEYWORDS

■ UDC: 616.853-092 ■ Epilepsy ■ Pathogenesis ■ Neuroimmune dysregulation

INTRODUCTION

The incidence of epilepsy or seizures is enough high and ranges from 50 to 70 cases per 100,000 population, while the prevalence of epilepsy is 5-10 cases per 1000 population (Engel, 1994; Odinak, 1997; Mukhin et al., 2000; Rakhimbaeva et al., 2009). Moreover, 30% of patients has the attacks and receives anticonvulsants lifelong. There is a clear tendency to increase the number of cases at the age older than 60 years old. This gives the problem medical-social character (Gusev et al., 2006).

Epilepsy is clinically manifested by seizures and cognitive disorders - impaired memory and attention. Cognitive disorders, along with seizures, are the main characteristics of epilepsy patients (Engel, 1994; Nikanorova, 1997; Mukhin et al., 2000). Cognitive defect is believed to be one of the causes of social disadaptation and disability in such patients (Arroyo, 1996). According to studies and practical observations conducted by Choi (1988), Nikanorova (1997), Poletaev (1997, 2004), Gusev et al. (2006) and Prokhorova (2011), medical history of more than 100 generalized tonic-clonic seizures increases the risk of cognitive disorders, which in some cases reach the degree of predementia.

In the 60 years of the last century, Semyonov founded a new direction in epileptology, i.e. the study of the role of autoimmune processes in epileptogenesis (Poletaev, 1995). The study of immunological aspects is associated not only with the question of immunosuppressive effect of many anticonvulsants, but also includes the study of immunopathogenesis of epilepsy with questions predicting disease outcome (Poletaev et al., 2004). Aarli (1993, 2000), Poletaev (1997, 2004), Gusev et al. (2006) and Lusnikova (2008) proved the role of the number of autoantibodies to the proteins S100, GFAP, MR65, NGF, neurotransmitters glutamate, GABA, dopamine, and serotonin. However, in the studied literature, we have found no study devoted to the role of antibodies to proteins NF-200, GFAP, DNA and myelin basic protein (MBP) in idiopathic and symptomatic epilepsies. According to Aarli (1993, 2000), Poletaev (1997, 2004), Gusev et al. (2006) and Lusnikova (2008), neuroimmunogenesis of epilepsy is accompanied by the formation of antibodies to the number of receptors. In this connection, of great interest to study the immunological aspects of epilepsy with prediction of outcomes of different forms of epilepsy, to examine neuropsychological and immunological aspects of idiopathic and symptomatic epilepsies with determination of the role of immunological pathomechanism in development of this disease.

Objective: To evaluate the clinical and immunological aspects of epilepsy with the clarification of its immunological pathomechanism.

Patients and Methods

We studied 52 patients with epilepsy (main group). The average age of patients was 36.2 ± 14.7 years old. The main group was divided into 2 groups: I group – 38 patients with idiopathic epilepsy, II group – 14 patients with symptomatic epilepsy. The control group consisted of 16 healthy subjects matched for age. The patients were followed for 2 years, during which all patients had repeatedly EEG study, investigation of cognitive function by using MMSE scale, test to memorize 5 words, clock drawing test and test for speech activity.

Immunological studies were conducted with ELI-Neuro-test 12 by immunoenzymatic analysis by method of Poletaev (1997, 2004). We studied the level of neurotropic autoantibodies to NF-200, GFAP, S100, MBP, voltage-dependent calcium channels, glutamate receptors, GABA, dopamine, serotonin and n-choline receptors, as well as to DNA and $\beta 2$ glycoprotein. The data obtained were processed using methods of variation statistics. The significant difference was established at $P < 0.05$.

Results and Discussion

Epilepsy is manifested by not only seizures and cognitive disorders, but also impaired memory and attention. Along with seizures, cognitive disorders are the main characteristics of epilepsy patients (Engel, 1994; Nikanorova, 1997; Mukhin et al., 2000). We studied dependence of form of cognitive disorders on type of seizure. Table 1 show that the significant

changes in cognitive sphere (average score was less than 27 on the MMSE scale) were observed in patients with secondary generalized and simple partial seizures. This trend was observed also on the other tests (test to memorize 5 words, clock drawing test and test for speech activity).

Table 1: The ratio of form of cognitive disorders and type of seizure

Type of seizure	MMSE (<27 points)	Test 5 words (<4)	Clock drawing test (<8)	Test for speech activity
Secondary generalized seizures (n=30)	24 (80%)	21 (70%)	12 (40%)	10 (30%)
Complex partial seizures (n=13)	4 (31%)	4 (31%)	–	–
Simple partial seizures (n=9)	7 (77.7%)	6 (66.6)	3 (30%)	2 (22.2%)

Source: Author

The study of immunological aspects involves the study of the immunopathogenesis of epilepsy with questions predicting disease outcome. According to Lusnikova (2008), Rakhimbaeva et al. (2009), Rashidova (2009) and Prokhorova (2011), neuroimmunogenesis of epilepsy is accompanied by the formation of antibodies to the number of receptors. In order to clarify the immunopathogenic mechanisms of epilepsy we carried out neuroimmunologic study, results of which are presented in Table 2.

Table 2: The levels of neurotropic autoantibodies in patients with idiopathic and symptomatic epilepsies, CU; M±m

Index	I (n=38)	II (n=14)	Control (n=10)
NF-200	22.0±6.7*#	11.4±3.4#	3.3±2.6
GFAP	11.8±6.2#	13.9±7.9#	-17.3±6.9
S 100	54.3±10.3#	39.4±10#	5.8±1.3
MBP	14.9±4.9*#	2.6±4.3	8.0±4.7
Vd Ca-channels	-20.8±3.2#	-19.6±4#	-3.8±1.3
Choline-receptors	-20.0±6*	0.6±11.5	-16.0±4.4
GABA-receptors	22.6±3.5#	21.9±3.9#	1.5±0.9
Dopamine-receptors	19.7±3.9#	18.9±2.1#	1.5±0.2
Serotonin-receptors	10.9±3.3	5.1±3.7	12.3±1.4
DNA	2.4±1.7*	25.3±13#	-3.8±1.3
β2 glycoprotein	-12.9±3.9	-10.6±4.9	6.5±5.1

Notes: * - significant differences between I and II groups, # - significant differences to control group

Source: Author

Patients with epilepsy marked increase in neurotropic autoantibodies that reflects the course of disease, i.e. more severe attacks are accompanied by worsening of neuroimmune dysregulation (Prokhorova; 2011). Thus, we observed a significant elevation of antibodies to protein S100 in both subgroups, greater in idiopathic epilepsy, compared to the control (54.3±10.3; 39.4±10 and 5.8±1.3 CU, respectively, $p<0.001$). There is evidence that these antibodies lead to depolarization of the cell membrane, thereby, increasing the spiking activity of cells on EEG (Aarli, 1993, 2000). This may indicate a violation of glial relationships and their role in the pathogenesis of epilepsy, especially in idiopathic one. The levels of autoantibodies to MBP were high in the first group (14.9±4.9 CU, $p<0.001$), while in the second group were low (2.6±4.3 CU), in comparison with control (8.0±4.7 CU). This is evidence of pathological processes in nerve fibers, including demyelinating processes. The observed increase in the level of autoantibodies to GFAP, which was higher in symptomatic epilepsy (13.9±7.9 CU, $p<0.001$), may indicate affection of the barrier function of the hematoencephalic barrier and significant neuronal loss, as GFAP is the main structural component of intermediate filaments of astrocytes. Elevated levels of autoantibodies to NF-200 in patients with epilepsy suggest the role of this neurotrophin in the regulation of plasticity and are evidence of its biological activity in the cells of the immune system in patients with epilepsy. Patients with idiopathic epilepsy had higher (22.0±6.7 CU) levels of NF-200 vs. patients with symptomatic epilepsy (11.4±6.4 CU) ($p<0.001$). Our results coincide with the data of Lusnikova (2008).

Study of the levels of autoantibodies to neurotransmitter receptors revealed significant increase of autoantibodies to GABA receptors (22.6±3.5; 21.9±3.9 and 1.5±0.9 CU, respectively groups, $p<0.001$) that is evidence of GABAergic system disturbance both in idiopathic and symptomatic epilepsies. Choi (1988) reported that GABA increases the neurotoxic effect of glutamate on one hand and inhibits antiepileptic system structure on the other. We have identified high levels of autoantibodies to dopamine receptors (19.7±3.9; 18.9±2.1 and 1.5±0.2 CU, respectively groups, $p<0.001$) and low levels to serotonin receptors (10.9±3.3; 5.1±3.7 and 12.3±1.4 CU, respectively groups, $p<0.001$) in the patients examined, confirming the close relationship with the glutamatergic system dysregulation of biogenic amines, which ultimately leads to neuronal death and as a result has epileptogenic effect on the brain. Furthermore, in the second group of patients we observed increased levels of autoantibodies to double-stranded DNA, which in this case can be regarded as characteristic of the autoimmune process in the CNS (non-specific inflammatory process).

Thus, our study showed that epilepsy is accompanied by immune dysregulation resulting from increase of neurotrophic autoantibodies. In idiopathic epilepsy, we observed more significant elevation of antibodies to protein NF-200, S100, MBP, GABA and dopamine receptors, testifying to the role of degenerative and demyelination processes, as well as apoptosis, emotional dysfunction, GABA and dopaminergic disturbances in such patients. In symptomatic epilepsy, we found elevated levels of autoantibodies to GFAP, GABA and dopamine receptors, as well as to DNA and reduced levels to serotonin receptors, indicating GABA, dopamin and serotonergic disturbances, proliferation of astroglial cells (gliosis) and barrier

dysfunction of the hematoencephalic barrier, as well as non-specific immunoactivation, possibly, connected with non-specific infectious-inflammatory process.

Thus, our clinical-immunological study confirms the greatest role of autoimmune disturbances in the pathogenesis of epilepsy. More severe attacks are accompanied by worsening of neuroimmune dysregulation that are similar to studies by Arroyo (1996), Lusnikova (2008), Rashidova (2009) and Prokhorova (2011). The changes observed may indicate the presence of different mechanisms of realization of brain plasticity in patients with idiopathic and symptomatic epilepsies.

Conclusion

Patients with complex partial seizures are more likely to develop cognitive impairment than patients with secondary generalized and simple partial seizures.

Autoimmune disturbances play the important role in the pathogenesis of epilepsy. More severe attacks are accompanied by worsening of neuroimmune dysregulation, manifested by increased levels of autoantibodies to NF-200, GFAP, S100, MBP, DNA, GABA and dopamine receptors. The degree and duration of autoimmune process can serve additional diagnostic and prognostic criteria for epilepsies. Along with appropriate antiepileptic drugs, timely correction of autoimmune aggression and local inflammation, considering investigated markers of neuroimmune dysregulation, should be recommended in treating epilepsy patients.

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