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CLINICAL AND BIOCHEMICAL STUDIES OF PATIENTS WITH EPILEPSY

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Abstract: Free radical oxidation is a universal pathophysiological phenomenon in many pathological conditions. Oxygen for any cell, especially neuron, is the leading energy acceptor in the mitochondrial respiratory chain. Binding to the iron atom of cytochrome oxidase, the oxygen molecule undergoes electron reduction, participating in the formation of water molecule. However, under conditions of disturbance of energy-forming processes, incomplete reduction of oxygen results in the formation of highly reactive, and therefore toxic, free radicals or products generating them.

Key words: Free radical oxidation, neurodegenerative diseases, epilepsy.

Introduction. In recent years, oxidative stress is also considered as one of the most significant factors in the pathogenesis of cerebral vascular diseases, neurodegenerative diseases such as Alzheimer's disease and dementias of other types, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy and multiple sclerosis.

A number of publications consider oxidative stress as a possible mechanism in the pathogenesis of epilepsy [2, 3]. In this regard, the reason for the ineffectiveness of epilepsy treatment may be not only the ineffectiveness of antiepileptic drugs, but also a possible underestimation of the pathogenetic mechanisms of the disease, including oxidative stress [1,4]. Studies conducted in recent years indicate that the administration of antioxidant drugs to epileptic patients along with antiepileptic drugs contributes to the effectiveness of treatment [5]. Modern data of clinical and biochemical studies of epileptic patients testify to the hyperactivity of peroxidative processes in them. Analysis of clinical and experimental data confirms the role of free-radical pathology in epilepsy, which not only genetically predetermines the occurrence of increased seizure activity, accompanies it, but also constantly initiates its manifestation [6]. This conclusion is supported by experimental studies that revealed the activation of free-radical processes in seizures reproduced using various models of epilepsy as a result of bicuculline, pilocarpine, pentylenetetetrazole kindling, lithium-pilocarpine models of status epilepticus in rats, and kainate-induced status epilepticus. There is evidence showing the development of oxidative stress after short seizures. V. Erakovic et al. [11] reported an acute decrease in the regional level of antioxidants in the brain after electroconvulsive shock in rats. They found a decrease in superoxide dismutase (SOD) and glutathione peroxidase activity in the hippocampus and frontal cortex 2 h after a single electroconvulsive shock. S. Arnaiz et al. [12] observed an increase in lipid peroxidation (LPO) after seizures induced by 3-mercaptopropionic acid in rats. An increase in POL of up to 40% was noted in the first 3-6 min after seizure onset. The induced seizures can be partially prevented by treatment with antioxidants such as SOD-mimetics, melatonin and vitamin C [13].

Catalytic antioxidants can reduce oxidative damage in animals with epilepsy, although they do not reduce seizure duration or the length of interictal periods [14].

Markers of oxidative stress (carbonyl groups in proteins, thiobarbituric acid reactive substances, glutathione and glutathione disulfides) were studied in experimental models as a result of kainic acid action in the cerebral cortex, hippocampus, cerebellum and basal ganglia. Similar changes in oxidative stress indicators were found in all brain regions, except for glutathione, which plays an important antioxidant role in the cerebral cortex but not in the hippocampus [15]. Partial mitochondrial SOD

deficiency in mice leads to severe complications due to chronically increased mitochondrial superoxide formation. Normal at birth, these mice subsequently develop age-dependent oxidative stress and seizures. As a result of increased susceptibility to kainate-induced seizures, hippocampal cell death was observed [8]. It is suggested that H2O2, formed in excess in the presence of superoxide, may oxidize glial glutamate transporters and lead to a decrease in their expression. Disturbance of glutamate balance leads to increased neuronal excitability and may be responsible for epileptogenesis in this animal model.

Evidence is emerging to support that oxidative stress is a consequence of brain damage after the first epileptic seizure and may subsequently be responsible for epileptogenesis [6]. The first epileptic seizure causes excitotoxicity, neuroinflammation and oxidative stress [7]. During brain damage as a result of seizures in rodent models, there is a significant increase in neuronal glucose uptake and metabolism [8]. Cerebral blood flow is increased during this process, leading to the accumulation of lactate. As shown in rodent models, recurrent seizures can also lead to overproduction of mitochondrial superoxide radicals, which can be converted to hydroxyl radical [9]. The hydroxyl radical in the presence of Cu2+ and Fe2+ ions readily oxidizes proteins, lipids and DNA, resulting in changes in protein function, membrane permeability and gene expression, respectively. This leads to increased neuronal excitability and decreased seizure readiness threshold.

In the studies of S. Gurgul et al. [10] also studied the level of free radicals (hydroxyl and nitroxyl) in the brain tissue of Wistar rats after a single epileptic seizure. A significant increase in free radical levels was determined 60 min after the seizure, but not immediately after the seizure (1 min and 15 min). The increase in free radicals was significantly lower when animals were treated with melatonin 1 h before seizure induction. Moreover, in accordance with the results of the study, melatonin in high doses may exhibit proconvulsive effects by contributing to the reduction of GABA levels in the brain. At the same time, low doses of melatonin have anticonvulsant activity by increasing the level of GABA in the hippocampus and cerebral cortex [11].

During status epilepticus, reactive oxygen and nitrogen species are produced, leading to mitochondrial dysfunction and damage to mitochondrial DNA. This in turn affects the synthesis of various enzyme complexes involved in the electron-transport chain. As a result, processes including POL, reactive gliosis, hippocampal neurodegeneration, and reorganization of neuronal networks are observed during epileptogenesis. These factors predispose to the development of spontaneous, recurrent seizures with further formation of epilepsy. The obtained results of experimental studies are consistent with the data of clinical studies [12]. A significant increase in the level of O2- and 8-oxo-deoxyguanosine (the predominant form of free-radical DNA damage) in epileptic patients confirms the relationship between chronic seizures and free-radical damage to the nervous system.

Decreased levels of glutathione reductase in epileptic patients contribute to a fall in the level of reduced glutathione, resulting in an impaired ratio of reduced and oxidized glutathione concentrations [13].

S. Hamed et al. [4] reported high levels of POL markers (malonic dialdehyde and thiobarbituric acid reactive substance) and low levels of total antioxidant activity in patients with epilepsy. The results of in vivo and in vitro studies have shown that the biological effects of free radicals are controlled by a wide range of antioxidants such as vitamins E, C, A, uric acid, glutathione and enzymatic antioxidants including glutathione reductase, glutathione peroxidase and SOD, which can be evaluated by measuring total antioxidant activity.

K. Sudha et al. [15] studied oxidative stress parameters such as POL, SOD, glutathione peroxidase, glutathione reductase, catalase, and levels of antioxidant substances (vitamins C, E, A, and ceruloplasmin) in epileptic patients and healthy controls. The activities of POL and plasma ceruloplasmin were significantly higher in patients with epilepsy compared to controls. The plasma concentrations of vitamins C and, A were significantly lower in patients with epilepsy. After treatment with antiepileptic drugs, the antioxidant status of patients with epilepsy improved, suggesting the involvement of free radicals in the pathogenesis of epilepsy [15].

Low activity of cytosolic SOD was revealed in patients with progressive myoclonic epilepsy. In contrast to healthy individuals, mitochondrial manganese-containing SOD is inhibited in the cerebral cortex in patients with epilepsy. Some authors believe that reduced levels of SOD1 activity are associated with recurrent seizures, and SOD1 deficiency in cerebrospinal fluid (CSF) may be a predictor of pharmacoresistant epilepsy [8].

The level of POL products (diene conjugates and schiff bases) as well as total lipids is significantly increased in CSF of epileptic patients, and they come from the brain, not from the blood. It is significant that POL activation is both a consequence of an epileptic seizure and a link in the mechanism of its generation. Therefore, during a convulsive seizure, the amount of POL products increases sharply, and the total antioxidant activity of brain tissue decreases. G.N. Kryzhanovsky [9] describes hereditary deficiency of antioxidant systems of the brain as one of the prerequisites for idiopathic epilepsy.

Low activity of glutathione peroxidase was found in children with epilepsy. Violation of the regulation of POL processes in patients with various forms of epilepsy and children with seizure syndrome was shown by E.V. Nikushkin and M.M. Bordyukov They found that the greatest increase in the level of POL products is detected in the blood of epileptic patients with a long history of the disease, in patients with generalized seizures, with marked personality changes and with a high frequency of seizures. These manifestations are accompanied by a decrease in the activity of antioxidant system enzymes in the blood of patients: SOD and glutathione peroxidase.

I.P. Drozdova [2] compared the indices of free-radical oxidation in patients with epileptic and non-epileptic (syncope) paroxysms. Both after syncope and after an epileptic seizure, patients had activation of free-radical processes with hyperfunctioning of reactive oxygen species and POL products. This activation was observed in the first hours after the paroxysm and was most pronounced in the case of epileptic seizure.

In the study of M. Pandey [3] studied the content of malonic dialdehyde, one of the end products of POL in 210 patients with epilepsy who had associated mental disorders - psychosis and depression. MDA levels were significantly higher in these patients compared to the control group. Thus, the severity of oxidative stress was significantly higher in epilepsy patients with associated psychiatric disorders [13].

A wide range of studies has provided evidence for the role of oxidative stress in refractory epilepsy [4]. There is no direct evidence for the possible involvement of oxidative stress in refractory epilepsy in patients or animals. However, indirect evidence has been found when studying the ketogenic diet as an alternative therapy for refractory epilepsy. The ketogenic diet has been used for about 80 years for the treatment of refractory epilepsy, although the biochemical mechanisms involved are unknown. D. Ziegler et al. [15] studied the level of POL, activity of catalase, SOD, and glutathione peroxidase enzymes in different brain regions when using a ketogenic diet in Wistar rats. They found no changes in the cerebral cortex, but observed a decrease in total antioxidant defense in the cerebellum with no changes in enzyme activity. In the hippocampus, they observed an increase in antioxidant activity with an approximately 4-fold increase in glutathione peroxidase levels with no change in POL levels. These were the first results to suggest that the high glutathione peroxidase activity in the hippocampus induced by a ketogenic diet may be a defense mechanism against neurodegenerative damage caused by seizure disorders in this structure [14].

The targets of POL products in the body are quite diverse. Scientists have found that POL products have mutagenic effects and are able to break DNA strands by blocking sulfhydryl groups with the formation of autoantigens in the blood and thus support the autoimmune process [6]. In addition, POL products cause depolarization of hyaluronic acid and infiltration of neutrophils in the area of inflammation, which serves as a reason for long-term maintenance of inflammatory processes. Therefore, circulating autoantibodies to the brain and its membranes are detected in the blood of patients with seizure syndrome, especially developed against the background of chronic inflammatory

diseases of the brain and its membranes. Moreover, the level of antibodies in the blood depends on the severity of the disease, i.e., the frequency of epileptic seizures [7].

Another point of application of POL products is arteries involved in the blood supply of the brain. It was found that hydroxyl radicals can increase the synthesis of collagen fibers, which take part in the formation of adhesions formed in the brain. According to morphologic studies, diffuse perivascular round cell infiltrates occur around large and medium cerebral arteries [8]. As the disease progresses, periadventitial connective tissue overgrowths in the form of ring-shaped perivascular couplings, often postinflammatory sclerosis, hyalinosis of arterial walls and obliteration of their lumen are observed. These inflammatory couplings, like a vise, compress the arteries, preventing them from increasing blood flow.

Conclusions: As a consequence, severe ischemic changes in the cerebral cortex develop.The relationship between the frequency of epileptic seizures and the severity of intracranial hypertension was traced, and a direct correlation was found: the more frequent the seizures, the more pronounced the intracranial hypertension. This is due to the influence of the frequency of attacks on the degree of adhesions in the cerebral membranes. In inflammatory sheath processes, this leads to even greater disruption of CSF and hemocirculation. Increased intracranial pressure causes delayed outflow of blood through the venous system of the brain, venous stasis and increased pressure first in the venules, then in the arterioles and small arteries. As a consequence, vascular resistance increases and blood flow decreases. POL products damage the membranes of neurons, which leads to additional opening of ion channels and violation of ion permeability. There is excessive intracellular accumulation of Na+ and Ca2+ ions, which causes spontaneous depolarization of the cell at rest.

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