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MODERN APPROACHES TO THERAPY OF PATIENTS WITH STATUS EPILEPTICISM.

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Annotation. Significance of the problem: In 2019, William Kaelin, Gregg Semenza, and Peter Ratcliffe received the Nobel Prize for their discoveries related to hypotoxicity. HIF-1α (Hypoxia-dependent factor 1-alpha) plays an important role in the adaptation of cells and control of metabolic processes under hypotoxic conditions. An imbalance in the level of HIF-1α can lead to the development of epilepsy and an increase in the number of seizures. The purpose of the study: to study the role of HIF-1α and the effectiveness of the drug Zoresan (zonisamide) in status epilepticus. Materials and methods: 77 patients (20-81 years old) were studied. The level of HIF-1α was measured by biochemical studies, and the results were compared to a healthy control group. Results: HIF-1α level was higher in patients with status epilepticus (598.04±173.86) and decreased in epileptic patients (248.10±54.43) and healthy subjects (140.73±33.92). . Through Zoresan treatment, fibrinogen levels in patients were normalized, which helped to eliminate hypoxia. Conclusion: HIF-1α level and fibrinogen elevation are important as markers of cerebral hypoxia. Zoresan drug is effective for epileptic patients and helps to protect neurons. This drug shows potential to improve long-term treatment outcomes.

Key words: Status epilepticus, HIF-1α, Hypotoxicity, Zoresan, Efficiency, Treatment, Hypoxia, Fibrinogen, Neurology, Biochemical studies.

Relevance: The 2019 Nobel Prize in Physiology or Medicine was awarded to William Kaelin , Gregg Semenza and Peter Ratcliffe for their discoveries related to how cells sense and adapt to changing oxygen levels, i.e. hypoxia. A key role in this process belongs to the protein HIF - 1α (Hypoxia - Inducible Factor 1- alpha). HIF -1 α is a transcription factor that is activated by a decrease in oxygen levels (hypoxia). Under normal conditions, with sufficient oxygen levels, HIF -1 α is destroyed, but in hypoxia it is stabilized, moves to the cell nucleus and activates the expression of genes associated with adaptation to hypoxia, including the gene encoding erythropoietin (EPO) [6,7,8]. Hypoxic-induced factor HIF -1 α is involved in the redistribution of metabolic pathways, switching cells to anaerobic

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respiration when oxygen levels are low - this leads to metabolic disorders and cell death. At high oxygen levels, oxidative stress occurs due to increased production of reactive oxygen species (ROS), which has a destructive effect on tissue cells. It is important to note that the mechanisms of interaction between hypoxia and epilepsy are still being studied. There are suggestions that an imbalance in HIF - 1α may contribute to the development of epilepsy and lead to frequent seizures or worsen the severity of seizures, however, data on this issue are limited [8]. Studies aimed at determining the level of HIF - 1α in the brain of patients with epilepsy may provide information on its role in pathogenesis. Research conducted on the effects of HIF - 1α agonists and inhibitors on epilepsy may demonstrate how these molecules can be used to correct pathological processes [6, 7, 22].

The main goal of AED therapy is to achieve stable and long-term remission, i.e. complete control over epileptic seizures, while minimizing the risk of significant side effects, such as neuropsychiatric and somatic disorders. Another important aspect of treatment is maintaining and improving the patient's quality of life. This includes not only seizure control, but also taking into account the patient's psychological and social well-being, ensuring his social adaptation, and preventing the negative impact of treatment on cognitive functions and general health. AED therapy requires an individual approach, where the choice of drug and its dosage depend on the type of epilepsy, seizure frequency, patient age and other individual factors. An important aspect is also regular monitoring of treatment effectiveness and adjustment of therapy if necessary [3, 4, 9, 10, 11, 16, 19.].

Zoresan (zonisamide) was initially registered in Japan and Korea for adjunctive therapy of refractory focal seizures, with or without secondary generalization, in adult patients. The drug was then approved in the United States and Europe for use as adjunctive therapy or monotherapy for focal and generalized seizures in both adults and children. Over time, studies of zonisamide have confirmed its broader therapeutic capabilities. The drug's efficacy has been confirmed in various types of seizures and forms of epilepsy, including focal and generalized epilepsies, as well as epileptic encephalopathies. Zonisamide has demonstrated its efficacy both as monotherapy and in combination with other drugs, and has been found to be effective in patients of various age groups, including children and adolescents [5, 11, 14, 15, 18, 21]. Zonisamide is indeed of interest in both neurology and psychiatry. Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is a synthetic sulfonamide derivative with anticonvulsant properties that differs in its structure and mechanism of action from other antiepileptic drugs (AEDs). Its multicomponent mechanism of action involves several key aspects[20].

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The aim of the study was to study the role of hif -1 a and the effectiveness of the drug zoresan in patients with status epilepticus.

Materials and methods of the study. We conducted a study of 77 patients. At the time of the research work, the patients were aged from 20 to 81 years. In terms of age category, by gender in the main group, women accounted for 17 (51.5%), and men - 16 (48.5%), in the comparison group men - 12 (60%) and women - 8 (40%). By age category among women in the main group was the age - over 80 years 1 patient (3%), female patients dominated, among the age group of 60-80 years - 7 (21.2%), and men accounted for - 3 (9%). Among the age group of 40-60 years, women accounted for - 5 (15.1%), and in the group of 20-40 years - 4 (12.1%). In the general group among men in the category of 20-60 years in groups there were 12 patients (36.2%). Biochemical blood tests (coagulation factor fibrinogen, Antithrombin III **).** The study included quantitative determination of the level of HIF -1 alpha , as well as in healthy people who formed the control group (n = 20) . The Sanwich - ELISA principle was used as a research method . Blood and the " Human HIF -1α (Hypoxia Inducible Factor 1 Alpha)" from Elabscience (USA).
Standard (MS Excel 2002, Statistica 6.0) and specially developed programs were used for statistical calculations. The assessment of differences in quantitative indicators in the studied groups was carried out parametrically (calculation of the M-weighted arithmetic mean, average error (m), standard deviation (σ), reliability of differences in average values according to Student's t-criterion).

Results and discussions. When studying the anamnesis data of patients of different age categories (from 20 to 81 years of life), the onset of pathology was diverse and different. In terms of age category, by gender in the main group, women accounted for 17 (51.5%), and men 16 (48.5%), in the comparison group men - 12 (60%) and women - 8 (40%) (diagram 1).

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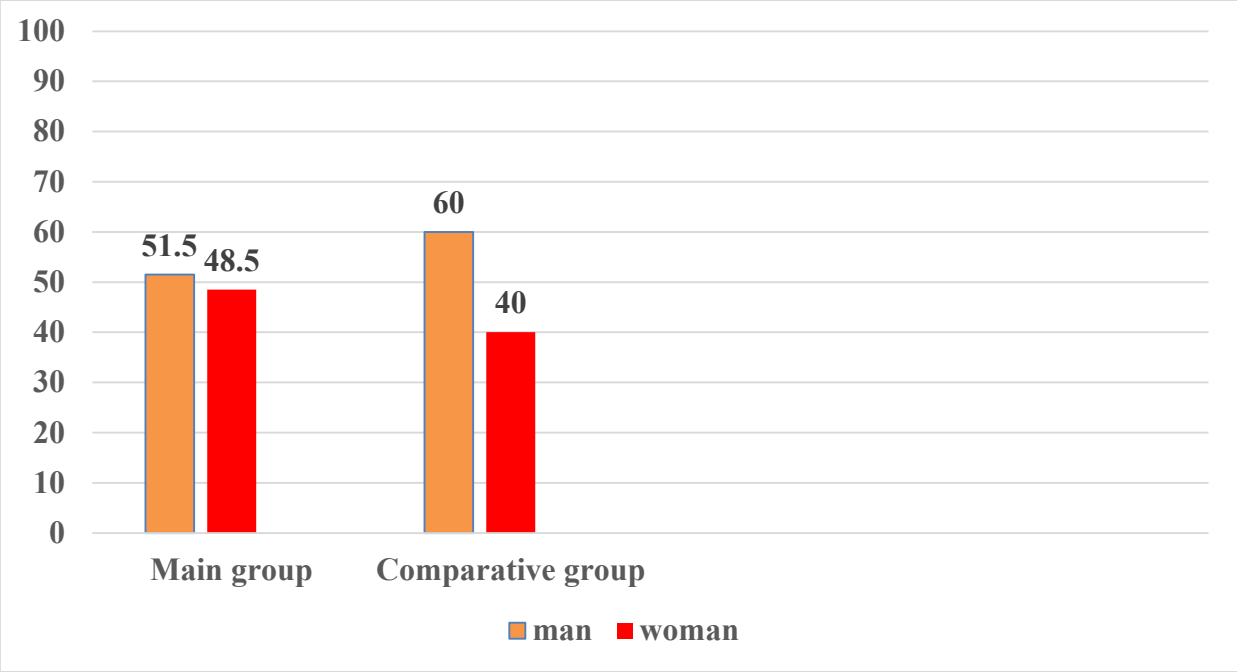

Diagram 1

Age category of the studied patients

By age category among women of the main group, age - over 80 years 1 patient (3%), and also female patients dominated among the age group of 60-80 years - 7 (21.2%), and men accounted for - 3 (9%). Among the age group of 40-60 years, women accounted for - 5 (15.1%), and in the group of 20-40 years - 4 (12.1%). In the general group among men in the category of 20-60 years 12 patients (36.2%) (diagram No. 2). Patients with epileptic status of the main group amounted to - 24.2%, in which the history of the pathology was 1-5 years, and patients with a history of 10-20 years - 27.3%, 20-30 years accounted for - 30.3% of patients and 30-40 years 18.2% of patients, with a history of pathology of 5-10 years with epileptic status were not identified. In the comparative group, the history of pathology of 1-5 years was in 10 % of patients, with a history of 5-10 years was observed in 5%, 10-20 years - 25%, 20-30 years accounted for 40% of patients, 30-40 years was in 20% of patients the history of pathology (diagram 3.).

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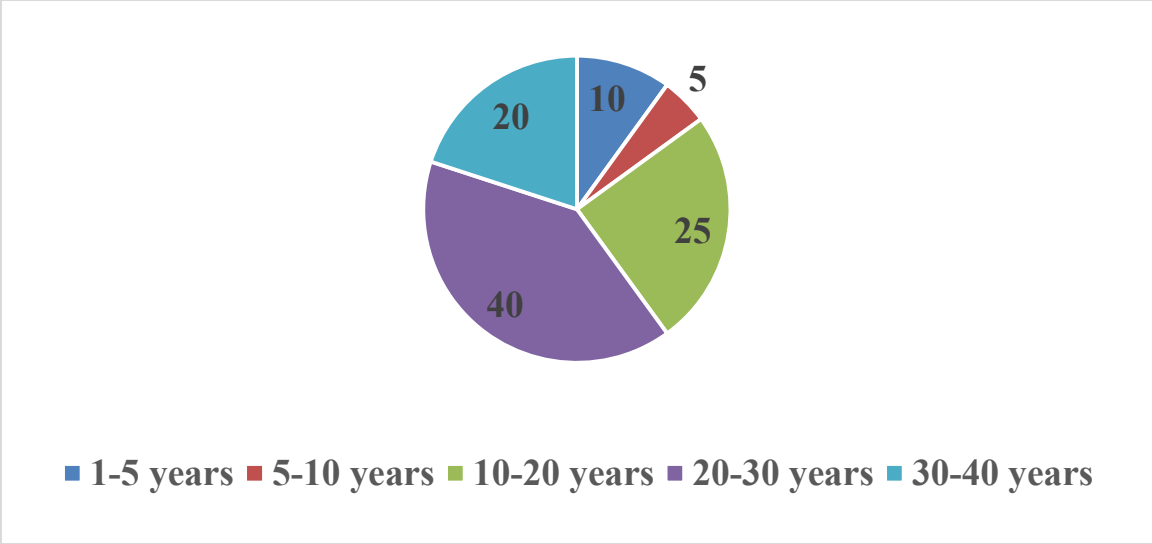

Diagram .3.

Duration of pathology in patients in the comparative group

The classification of epileptic seizures has a multi-level structure and is important for more accurate determination of the type of disease, diagnosis and selection of adequate treatment.

By the type of localization in the age category from 20 to 40 years, 1 patient (3%) had focal seizures, generalized seizures - 5 (15.1%), by etiology, cryptogenic seizures were observed in 6 patients (18.1%) , idiopathic seizures in 3 patients (9%), and symptomatic seizures were not detected at this age. In this group, the patients had primary seizure types - generalized clonic seizures - 9 (27.3%), absences - 1 (3%), and myoclonic seizures were not detected. Among patients aged 40 to 60 years, they mainly suffered from generalized seizures - 7 (21.2%), focal and cryptogenic seizures were equally detected in 5 patients (15.1%), and idiopathic and symptomatic seizures, respectively, in 3 (9%) and 4 (12.1%) patients. In the age group from 60 to 80 years, the same was observed - generalized and cryptogenic seizures in 6 (18.1%), focal seizures were noted in 4 (12.1%) patients, idiopathic and symptomatic seizures, respectively, in 1 (3%) and 2 (6%) patients. By age, cryptogenic and generalized types of epileptic status are observed at all ages

In the examined patients, the frequency of epileptic status varied from several times a year to several times a month and even several times a week. In the main group of patients, seizures occurred 2-3 times a month in 15 (45.4%) patients, in 10 (30.3%) patients 1-6 times a week, in 7 (21.2%) patients seizures occurred from 7 to 12 times a year and only in one (3%) patient every day (diagram 3).

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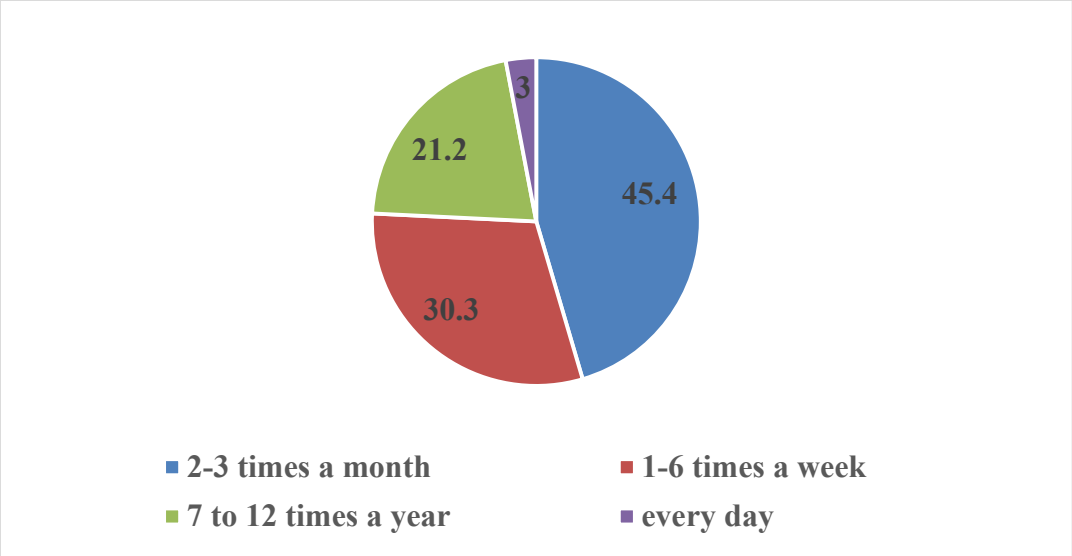

Diagram 3.

Frequent occurrence of seizures in patients of the main group, %

In the comparative group, the highest frequency of seizures was in 11 (55%) patients once every 3-4 years, in 6 (30%) patients once every 2-5 years, in 2 (10%) patients once every 4 years and in one (5%) patient seizures are repeated once a year. Thus, women dominated by gender in the patients, among the age group of 60-80 years - 21.2%, and men, summing up the same indicator for the general group from 20-60 years old was - 36.2%. By the duration of pathology, epileptic status occurred in patients with a history of 20-30 years - 30.3%, 10-20 years in patients - 27.3% and in 24.2% it was - 1-5 years, and patients with a history of 30-40 years were - 18.2% of patients. The peak of development of generalized seizures by age category was among patients from 40 to 60 years (21.2%), and among patients in the group from 20-40 years by etiology, cryptogenic seizures were found in 18.1% of patients. According to the frequency of occurrence of periodic epileptic seizures in patients of the main group - 45.4% were observed 2-3 times a month, in 30.3%) patients 1-6 times a week, and in the comparison group seizures were in 55% of patients once every 3-4 years, and in 30% of patients once every 2-5 years.

According to the examination results, frequent relapses of epileptic seizures lead to a hypoxic state of the brain. According to our study, a decrease in hemoglobin in the peripheral blood was observed in all 100% of patients and was manifested by varying degrees of hypochromic anemia (Table 1).

Table 1.

Some peripheral blood indices in patients

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	Hemoglobin	red blood cells	Color.indicator
Epileptic status	90.57±3.67	3.50±0.23	0.73±0.05
Epilepsy	80.85±4.63	3.98±0.29	1.08±0.64

In patients with epileptic status, the hemoglobin levels in the blood were below the average value of 90.57±3.67, which was manifested by hypochromic anemia. In the group of patients with epilepsy, the hemoglobin levels in the blood were below the average value of 80.85±4.63 and the color index was above 1.08±0.64 and was manifested by hyperchromic anemia.

In the main group, grade 1 anemia was observed in 17 patients (51.5%), grade 2 anemia in 9 patients (27.3%) and 7 patients (21.2%) had grade 3 anemia. In the comparison group, the following indicators were observed among patients ; grade 1 anemia was in 6 (30%), grade 2 anemia in 10 patients (50.0%) and 4 patients with (20.0%) grade 3 anemia. Various degrees of anemia , as one of the frequently encountered comorbid pathologies, which will provoke a severe course of the underlying disease and lead to severe complications. It is worth noting that long-term anemia leads to oxygen starvation (hypoxia) of the main vital organs and systems, including it is important to note that the most sensitive organ to hypoxia is the brain, which reacts to weak decreases in hemoglobin. Hypoxia aggravates metabolic processes in neurons and can lead to instability of electrical activity and increased seizure readiness, and this is directly related to hypoxia-induced protein (HIF) (Hypoxia Inducible Factor). HIF-1α mediates the expression of many genes that are involved in neurogenesis, angiogenesis, cell proliferation, erythropoiesis and cellular metabolism, enhancing the adaptation of nervous tissue to ischemic stress and, therefore, exerting a neuroprotective role [6,8]. Other studies have reported a detrimental role of HIF-1α in ischemic brain injury, including the inflammatory response and disruption of the blood-brain barrier (BBB) integrity after ischemic stroke. This indicates that HIF-1α is likely a mediator of neuroinflammation and a factor determining BBB permeability [17]. Modern concepts of the role of the specific regulatory protein HIF-1a (hypoxia-induced factor-1 alpha) in the mechanisms of adaptation of the body to a state of hypoxia. In our study , an increased level of hypoxia-induced factor-1 alpha was observed in all groups (Table 2).

Table 2.

Some biochemical immunological indicators

	HIF-1a	Fibrinogen

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Epileptic status	598.04±173.86	5.63±0.44 *
With epilepsy	248.10±54.43 *	6.53±0.32 *
Without epilepsy	140.73±33.92 *	6.69±0.26

Note: *- p < 0.05

In the study of HIF -1α (Hypoxia Inducible Factor 1 Alpha) in the blood of patients with status epilepticus (598.04±173.86), as well as with epilepsy (248.10±54.43) were higher than the reference values than in patients without epilepsy (140.73±33.92). In the main group it was 588 pg / mL (range - 146.3-1835.5 pg / mL), the comparison group with epilepsy - 250.91 pg / mL (range - 124.35-590.89 pg / mL) and the control group without epilepsy - 140.41 pg / mL (range - 35.244-270.75 pg / mL). As can be seen, the highest value of the HIF -1 alpha level was noted in patients with epileptic status, followed by patients with epilepsy, and the lowest level of HIF -1 alpha was found in patients in the control group. HIF -1 α plays a key role in understanding and treating diseases associated with cerebral hypoxia . Long- term hypoxia in the body leads to an increase in hypercoagulation changes and promotes compensatory enhancement of anticoagulant and fibrinolytic activity. It is accompanied by hypercoagulation , signs of thrombinogenesis and a decrease in anticoagulant activity, which indicates a prethrombotic state [22].

CONCLUSIONS. Thus, the mechanisms of adaptation processes of hypoxia of the body are of great importance, the increase of HIF-1a (hypoxia-induced factor-1a) and fibrinogen in the blood plays a key role. Based on the above, it is worth noting that the indicator of high fibrinogen levels in epilepsy is a significant diagnostic predictor of cerebral hypoxia [5]. The effectiveness of polytherapy in 100% of patients was manifested in the form of a decrease in fibrinogen in the blood. Normalization of fibrinogen levels in the blood simultaneously eliminates hypoxia in brain tissue. Our own research data correspond to the data of foreign studies, show the effectiveness of the drug zoresan in epileptic status, helps protect neurons and makes it valuable in the treatment of patients suffering from recurrent seizures. This also indicates the possibility of using this drug to improve the outcomes of long-term therapy.

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