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FEATURES OF THE CORRELATION OF POST-STROKE COGNITIVE DISORDERS

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Abstract: The article presents the main directions, indications and contraindications, methods of using thrombolytic therapy in patients during the acute period of ischemic stroke. The pathogenesis of the development of cerebral infarction is considered, and a comparative description of direct and indirect anticoagulants is provided. The article examines cognitive disorders against the background of ischemic stroke and the relationship after treatment with thrombolytic treatment

Key words: Disability, ischemic stroke, clexane, lipid peroxidation, thrombolytic agents, thrombolytic therapy, cognitive disorders.

In the Uzbekistan, 100 thousand cases of stroke [6]. Incidence of stroke in Uzbekistan is 3.36 cases per 100 people per year, the standardized incidence is 2.39 cases (for men 3.24, for women - 2.24) per 100 people per year. In the structure of morbidity, ischemic strokes (IS) prevail over hemorrhagic ones. AI is one of the leading causes of premature death and permanent bereavement ability to work. The mortality rate from AI in Russia is 1.23 cases per 100 people per year. About a third of patients survivors of AI need outside help in everyday life, and 20% cannot move independently. Only about 20% of patients who survive AI are able to return to previous work activity. Due to significant costs associated with carrying out treatment and rehabilitation measures among patients with IS, providing constant care for patients, the problem of cerebrovascular pathology has become not only medical, but also social significance. IS is a heterogeneous clinical syndrome, including several athogenetic subtypes: arterial damage large caliber (atherothrombotic IS), small caliber (lacunar cerebral infarction), cardiogenic embolism (cardioembolic IS) [9]. In some cases, set a single cause of AI is not possible, its development may be due to rare reasons (vasculitis, arterial wall dissection, gas or fat embolism, etc.). Precise determination of the cause of the first IS in largely determines the effectiveness of measures to prevent recurrent stroke. Research carried out in recent decades in experimental and clinical conditions, have shown lack of identity between acute focal ischemia brain - a potentially reversible condition - and cerebral infarction - morphologically formed focus of necrosis [3]. Irreversible damage develops within 5–6 minutes when blood flow decreases to 10–15 ml/100 g per minute, as a result of which this zone cannot be the object of therapeutic influence [2]. On tissue with an altered functional state remains in its periphery for several hours, without having lost its main structural characteristics and viability - penumbra [4]. Duration of maintenance structural integrity and possibility of restoration the functional properties of this area are determined localization of the ischemic focus, characteristics of blood flow and metabolism, previous episodes of acute or chronic ischemia (ischemic preconditioning) [3]. Characteristic of penumbra is a low level energy and protein metabolism [8]. Extension areas of infarction are observed in areas of minimal local blood flow - less than 45–50% of normal [24]. In most cases, half of the final infarct volume is formed within the first 1.5 hours from the moment of cessation of blood flow, 70–80% - within 5–6 hours. The penumbra zone is the direct target of therapeutic interventions during preserved viability of brain tissue [13], therefore, the first 3–6 hours from the onset of the disease are considered as a “therapeutic window” within which treatment measures can be most effective and safe. Stopping the flow of blood to the brain leads to development of a complex sequence of biochemical and pathophysiological changes – pathobiochemical cascade [4]. Violation of aerobic glycolysis leads to

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the inclusion of glucose metabolism through the oxygen-free pathway, lactic acidosis and the accumulation of calcium ions. Malfunction of ion pumps leads to the entry into cells of sodium, chlorine and water ions – cytotoxic swelling. The role of excess release into the synaptic gap of the excitatory neurotransmitters glutamate and aspartate (glutamate excitotoxicity). If oxygen metabolism is disrupted and it is difficult to utilize free radicals, oxidative stress and a local inflammatory reaction develop [8]. The consequence of these events is apoptosis and expansion of the damage zone [12]. According to the mechanism of apoptosis Cells that have suffered significant ischemic damage and are of questionable viability may suffer. Subsequently, degenerative damage to neurons occurs: demyelination, Wallerian degeneration, reduction of the dendritic field, limitation of the number synapses [2]. Along with the processes of brain damage reparative and regenerative mechanisms are launched: the formation of a new vascular bed, arborization of processes neurons, synaptogenesis. Possible activation of the cortex hemisphere contralateral to the affected hemisphere.

Experimental studies have shown that the return of blood to the ischemic area through a revascularized section of the artery does not always lead to complete normalization of local cerebral blood flow. Even just 5 minutes after the onset of ischemia, in the “ischemic penumbra” zone, gradual disturbances in the perfusion of cerebral tissue occur: in the first minutes - hyperemia (or “luxurious perfusion”), then post-ischemic hypoperfusion, which is the result of severe microcirculation disorders caused by the release of from ischemic tissue vasoactive and proinflammatory metabolites. The longer the pre-reperfusion period, the less chance to quickly normalize microcirculation in the ischemic area and the higher the risk of additional reperfusion damage to cerebral tissue: oxidative, caused by the inclusion of oxygen in the processes of free radical oxidation, and osmotic, caused by the increase in cytotoxic edema due to excess water and osmotically active substances. The feasibility of therapeutic reperfusion remains within 3 – 6 hours, then with its use the risk of not only reperfusion damage, but also hemorrhagic complications increases significantly. Thus, reperfusion should be early, active and short-term if possible [7].

The nature of reperfusion therapy is determined by the pathogenetic variant of stroke development. In case of occlusion of medium- and large-caliber arteries, the effectiveness of therapeutic measures is determined by the achievement of early recanalization of the vessel. Monitoring of cerebral blood flow using transcranial Dopplerography showed that with complete early recanalization of an occluded vessel, in 75% of cases there is a significant improvement in the patient’s condition during the first day of the disease (a change in the NIHSS scale by 4 points or more, which corresponds to a significant regression of focal neurological disorders). With partial restoration of blood flow, such a “dramatic” improvement occurs in almost half of the patients, while in patients with no early recanalization of the affected vessel, significant clinical improvement does not occur within the first 24 hours. Moreover, in the long-term period, 3 months after a stroke, a significantly better recovery of impaired neurological functions is observed in patients with complete early recanalization of the occluded artery and rapid (within the first day) regression of focal symptoms.

It has been established that the severity of positive clinical dynamics depends on the speed of thrombus lysis: the best restoration of neurological functions occurs with rapid (almost instantaneous) thrombus lysis. The rate of thrombus lysis varies in different pathogenetic variants of stroke. The most rapid and complete lysis occurs in cardioembolic stroke, which is accompanied by a significant improvement in stroke outcome and functional recovery of the patient. Slow recanalization is more often observed with atherothrombotic artery disease and may not be accompanied by a significant improvement in clinical dynamics. Spontaneous recanalization of an occluded artery is observed in

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approximately 10% of patients with IS. Carrying out early ultrasound examination (transcranial Doppler ultrasound) increases the frequency of possible recanalization to 20%.

For most occlusions of medium and large arteries, the treatment of choice is thrombolysis, which provides early recanalization in 30–40% of cases. Currently, 5 generations of thrombolytics have been developed [8]. At the same time, recombinant tissue plasminogen activator is recommended for use in the first 180 minutes after the development of IS caused by occlusion of an artery of medium and large diameter, in the absence of a hemorrhagic component in the ischemic focus and an area of extensive hypodensity on CT - MRI of the brain, exceeding 1/3 of the territory of the middle cerebral arteries, with systemic blood pressure values not exceeding 180/110 mm Hg. Art. A dose of 0.9 mcg/kg should be used, maximum 90 mg/day; 10% of the dose is administered intravenously, the remaining 90% is administered intravenously by drip over 60 minutes.

Theoretical data suggested that an anticoagulant, in particular heparin, should be effective in IS. However, international studies (International Stroke Trial Collaborative Group) have shown that when treating patients with IS with heparin, the high risk of early hemorrhage exceeds the positive effect of therapy. Only a subgroup post-hoc analysis proved the feasibility of using anticoagulant therapy with heparin in the first days of progressive atherothrombotic stroke, as well as in cases of confirmed cardiogenic embolism and surgical interventions on cerebral vessels. Heparin is prescribed during the first 3–5 days of the disease in a daily dose of up to 10–15 thousand units under the control of laboratory parameters, primarily activated partial thromboplastin time (aPTT), which should not increase more than 2 times. 1 - 2 days before the end of the course of heparin treatment, it is advisable to gradually reduce its dose with the prescription of indirect anticoagulants, which continue to be taken for the next 2 - 3 weeks. The most effective use of warfarin is in a dose of 2 – 5 mg/day, especially with long-term previous therapy with heparin, in the presence of atrial fibrillation, after heart valve replacement or concomitant myocardial infarction. In the absence of concomitant cardiac pathology, it is possible to prescribe phenyline in a daily dose of 0.03 - 0.06 g. It should be remembered that treatment with indirect anticoagulants must also be carried out under strict laboratory monitoring of coagulogram parameters. The biological activity of heparin depends on the plasma protease inhibitor antithrombin III. Therefore, in case of antithrombin III deficiency in patients with increasing thrombosis of the main or internal carotid artery, it is recommended to administer blood plasma simultaneously with heparin (100 ml 1–2 times a day) [9].

Thus, the prescription of heparin in the first days of AI can only be used according to strict indications. At the same time, it has now been shown that, in contrast to conventional heparin, low molecular weight heparins (LMWHs) with a molecular weight of 400–5000 daltons (clexane, fraxiparin, fragmin) have predominantly anti-Xa activity, and they inhibit even those factor Xa molecules that have already contact the platelet surface [4] . The advantage of LMWH is also: their less binding to the vascular endothelium and plasma proteins, which leads to better digestibility of these drugs and their rapid absorption from subcutaneous fat depots (after subcutaneous administration, 90% of LMWH is “absorbed” and only 15 - 30% of conventional heparin); a longer half-life (possibly their subcutaneous administration 1-2 times a day and less frequent laboratory monitoring); lower affinity for von Willebrand factor, which helps to weaken the effect of these heparins on the cellular component of hemostasis (platelets) and significantly reduce the risk of developing “heparin thrombocytopenia/thrombosis”, as well as better predictability of anticoagulant effects even when using high doses of drugs. Hemorrhagic complications with the use of LMWH are generally rarer and less severe than with treatment with conventional heparin. It is important that

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these drugs prevent the risk of developing deep vein thrombosis and pulmonary embolism - one of the most dangerous complications of the acute period of stroke.

However, it is very important that, despite the possibility of restoring impaired functions, cognitive deficit in a patient who has suffered a stroke, is steadily progressing. This is confirmed by the results of a large number of studies. If after 6 months after a stroke, 45–80% of patients experience moderate cognitive decline and 10–18% – dementia [8,9], then 5 years after a stroke the frequency of dementia reaches 20–25%. According to other observations, the incidence of post-stroke dementia reaches 30% in surviving patients, increasing by 7% 1 year after stroke, by 10% after 3 years and by 48% after 25 years [10]. , in most cases, cognitive impairment is multiple, which is associated with diffuse vascular lesions affecting various brain structures. Clinical manifestations will be very diverse, but the unifying link will be dysfunction of the frontal lobes, manifested impairment of attention, neurodynamic characteristics and executive functions. The main factors determining development vascular dementia is the total volume of damaged brain tissue, while the number of lesions Of less importance is the localization of lesions in strategically important areas, the presence of white matter lesions and bilateral lesions. If the patient has repeated strokes that led to the formation of severe cognitive deficiency, they speak of multi-infarct dementia. At it is possible that the patient has only one clinical episode of stroke, but, according to neuroimaging, multiple ischemic lesions that were asymptomatic. Cognitive disorders include significant focal cortical abnormalities corresponding to the , in most cases, cognitive impairment is multiple, which is associated with diffuse vascular lesions affecting various brain structures. Clinical manifestations will be very diverse, but the unifying link will be dysfunction of the frontal lobes, manifested impairment of attention, neurodynamic characteristics and executive functions. The main factors determining development vascular dementia is the total volume of damaged brain tissue, while the number of lesions Of less importance is the localization of lesions in strategically important areas, the presence of white matter lesions and bilateral lesions. If the patient has repeated strokes that led to the formation of severe cognitive deficiency, they speak of multi-infarct dementia. At it is possible that the patient has only one clinical episode of stroke, but, according to neuroimaging, multiple ischemic lesions that were asymptomatic. Cognitive disorders include significant focal cortical abnormalities corresponding to the localization of ischemic foci, memory loss and impairment are often noted executive functions. It is also common for patients the presence of severe focal neurological symptoms. The course of multi-infarct dementia, usually with acute onset and further slow stepwise progression, which is determined by development strokes and plateau formation.ocalization of ischemic foci, memory loss and impairment are often noted executive functions. It is also common for patients the presence of severe focal neurological symptoms. The course of multi-infarct dementia, usually with acute onset and further slow stepwise progression, which is determined by development strokes and plateau formation. And of course, it is very important whether there was a cognitive deficiency before stroke development. The presence of significant cognitive impairment before stroke may indicate about the worst prognosis for the restoration of damaged functions. Even in cases of post-stroke dementia stroke can be considered as immediate the cause of dementia in only 50% of patients [11]. Results interviews with relatives suggested the presence pre-stroke dementia in 26% of patients, and pre-stroke cognitive impairment in 75% [10]. One of the main reasons for cognitive decline in this case is decompensation or activation of a previous neurodegenerative process, most often of the Alzheimer's type. Therefore, detection from data neuroimaging of atrophic changes, especially in the hippocampal region, is a significant predictor of cognitive decline. One of the most important areas allowing reduce the risk of progression of cognitive deficits, is secondary prevention of stroke, including correction of vascular risk factors and antiplatelet therapy. Arterial ypertension is the most common

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of all studied risk factors in patients with stroke (more than 90% of cases). The PROGRESS study demonstrated a 19% reduction in the risk of developing cognitive impairment and dementia by 34% during antihypertensive therapy. Not less relevant is the correction of cardiac disorders (arrhythmias, heart failure, coronary heart disease), glucose and lipid levels blood, affective disorders, exclusion of alcohol and quitting smoking, regular physical and mental activity. Considering the frequency, severity and high risk of progression of cognitive impairment after stroke, It seems advisable to use drugs with a neuroprotective effect. One of these drugs is citicoline (Ceraxon), which is a natural endogenous compound that is an intermediate metabolite in biosynthesis phosphatidylcholine - one of the main structural components of the cell membrane - and consists of two the main molecules are cytidine and choline. The study showed that 42 (53%) Stroke patients develop cognitive impairment. In most cases, they were moderate in nature, even in the absence of pronounced motor restrictions. During the year of observation, the condition cognitive functions had a fluctuating nature with the difference is that in the main group the cognitive status was restored to normal, i.e. had no negative dynamics, and in the control group there was a clear tendency towards the progression of cognitive deficit. In the late recovery period, stabilization of the cognitive status was observed among patients of the main group, and neuropsychological test scores in the control group continued to deteriorate. The positive effect of cortexin on the restoration of motor and cognitive functions can be explained by improved microcirculation, interneuronal and interhemispheric transmission, acceleration of metabolism and replenishment of neurotransmitter deficits. The improvement in long-term memory is explained by the influence of cortexin on the neurotransmitters of the nervous system, and, accordingly, also on neurodynamic and regulatory cognitive functions. Thus, the drug Cortexin is promising in the treatment of cerebral stroke, capable of protecting affected neurons and normalizing metabolism of damaged tissues, and as a result, slow down the growth of the infarct damage zone. Early administration of the drug promotes faster positive dynamics in the neurological status, increasing the patient's functional independence, and repeated courses of Cortexin help stabilize and restore cognitive functions. In the acute period of damage to cells of the nervous system, cortexin provides cytoprotection, in the early recovery period it improves cell metabolism and promotes the restoration of intercellular contacts, in the late recovery period and during chronic pathological processes of the brain it helps maintain the metabolism of nerve cells and the process of remyelination. This study shows the effectiveness neuroprotector of the polypeptide nature of cortexin in acute, early and late recovery periods AI, as well as with long-term use throughout recovery period. Repeated 4-fold course Cortexin treatment for a year (courses of 10 days) has a significant preventive effect against post-insulin cognitive impairment. It is advisable to use the recommended treatment regimen for patients undergoing AI to achieve full daily independence.

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