Prospects in the treatment of ischemic stroke

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Abstract: Stroke is an acute violation of the cerebral blood supply, which leads to ischemia and death of brain cells. According to the National Stroke Registry, 31% of stroke patients are unable to take care of themselves, 20% are unable to move independently and only 8% of surviving patients can return to their previous lifestyle. The ratio of ischemic to hemorrhagic strokes was 5:1, and the average age of stroke development was 66.7 years (63.7 years for men and 69.4 years for women). According to the results of population studies, the incidence of atherothrombotic ischemic stroke is 16%, cardioembolic-29%, lacunar-16%, stroke due to rarer causes-3%, stroke of unknown etiology-36% of cases. The risk of recurrent stroke during the first 30 days of the disease is higher in atherothrombotic stroke compared to other pathogenetic variants. This pathology, due to its prevalence, leads to persistent disability in about 80% of the adult population, so early treatment of acute ischemic stroke is crucial.

Key words: stroke, cerebral circulation disorder, ischemia.

Introduction

At the moment, thrombolysis using recombinant tissue plasminogen activator (rtPA) is the only effective remedy indicated for use during the first six hours after a stroke, as well as

endovascular thrombectomy are still the main methods of revascularization in acute ischemic stroke. It should also be taken into account that intravenous thrombolysis therapy is contraindicated in patients who are in a state of hypocoagulation, given that the half-life of new oral anticoagulants in patients with normal renal function does not exceed 17 hours. In addition, ischemic reperfusion injury after revascularization therapy can worsen neurological symptoms and worsen the prognosis. Also, secondary neuroinflammation after a stroke stimulates further cell damage, which leads to ischemic death of brain cells and, as a result, disability and even death. An early increase in the level of pro-inflammatory cytokines and chemokines from the onset of brain ischemia may be associated with the severity of stroke and, accordingly, a worse prognosis. The presence of this inflammation is diagnosed using computed tomography, but there is no direct connection between these objective indicators and the patient's symptoms, which makes it difficult to treat a stroke. Some studies have reported that higher levels of C-reactive protein and interleukin-6 are associated with a worse prognosis after an ischemic stroke.

Interestingly, the triggering receptor expressed on myeloid cells-1 (TREM-1) is involved in their activation and the formation of innate immunity. TREM-1 is an orphan receptor and is associated with toll-like receptor 4 (TLR4). The TREM-1 receptor is also involved in the development of non-infectious and non-inflammatory neurological diseases, such as cerebrovascular atherosclerosis, ischemia, stroke, and others. It is assumed that during an acute ischemic stroke, endogenous molecules from damaged ischemic brain tissues activate the TREM-1 signaling pathway and trigger the inflammatory process. These data provide a reason for further in-depth study of the role of the post-stroke immune response and the development of a modern optimal method for the treatment of acute cerebral circulatory disorders based on this theory.

No less interesting in recent years is the study of a new promising therapy based on stem cells, which is based on cell replacement and induction of paracrine effects to replace damaged cells, reduce cell death and provide trophic support for host cells. At the same time, it is known that only less than 1% of cells can remain viable for 4 weeks after transplantation due to the harmful effects of damaged tissues. Recent studies have established the connection of paracrine signals with extracellular vesicles, which are produced by all living cells and include microvesicles and exosomes, which in turn play a key role in the regulation of immune responses. Exosomes are released into extracellular fluids and contain proteins, lipids and genetic materials (mRNA, ncRNA, etc.). Updated data showed that exosomes were successfully tested in preclinical models of stroke, myocardial infarction/reperfusion injury and hind limb ischemia. Antitumor treatment methods based on the use of extracellular vesicles have also entered phase II of human clinical trials. The unexpected role of exosomes and their numerous advantages over stem cells in the treatment of ischemic stroke of the brain are of great interest and require further study in order to develop a modern optimal pharmacotherapy for this pathology.

The results obtained

We focused our scientific interest on the role of markers of neuroinflammation, namely, on the relationship of interleukin-6 with the development of acute cerebral blood supply disorders (ischemic stroke). The study group included 32 patients aged from 54 to 72 years: 19 male patients, which was 59%, and 13 female patients, which was 41%. The control group included 10 people, including 5 men and 5 women aged from 54 to 72 years. On the first day after the onset of the disease, the levels of five common inflammatory markers were measured: leukocytes, neutrophils, lymphocytes, C-reactive protein and interleukin-6 (IL-6) in the blood serum. The results were obtained: interleukin-6 increased in patients with stroke compared to the control group. In all 32 patients with acute ischemic stroke, high values of interleukin-6 were recorded, in the control group of 10 people, 1 woman had an increased level of interleukin-6. The average level of circulating interleukin-6 in patients with acute stroke was 27.7 [6.5; 163.4],

which is 6.5 times higher than in the control group of 4.1 [2.2; 5.8] ($p < 0.0001$). The levels of C-reactive protein and interleukin-6, neutrophils and leukocytes were significantly higher in the subtype of atherosclerosis of large arteries, while the number of lymphocytes was significantly higher in occlusion of small arteries. In our study, the level of interleukin-6 was significantly increased in the first 24 hours after the onset of an ischemic stroke. This fact confirms the hypothesis that the production of interleukin-6 is an inflammatory response to acute hypoxic ischemic damage.

After analyzing the results obtained, we can conclude that the levels of pro - inflammatory cytokines (and in our example, this is interleukin-6) increase in patients with ischemic stroke compared to the control group. These results support the evidence that interleukin-6 inhibition may offer a therapeutic approach for the prevention of ischemic stroke.