



Some Questions of the Pathogenesis of Ischemic Stroke at a Young Age

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Abstract: The relevance and complexity of the problem of ischemic stroke (IS) in young patients is due to insufficient knowledge of this issue, the complexity of medical and diagnostic aspects, the difference in the causes of strokes from those in older age groups, as well as socio-economic factors associated with the working age of patients.

Key words: young patients, ischemic stroke.

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Epidemiology

The distribution of stroke patients by age was studied in the STEPS study (2007), the results of which showed a high percentage of people under the age of 44 among stroke patients - 11% (rice. 1). Results of an epidemiological study by A. Westover et al. (2007) showed that hemorrhagic strokes prevail in the structure of strokes in patients aged 20 to 44 years (observed in 55% of cases); AI accounts for 45%. On the other hand, IS prevails among patients over 44 years of age - 80% of cases. Population studies conducted in recent years in various countries of Europe and America (B. Kristensen et al., 2007; Halvor Naess et al., 2006; A. Nightingale et al., 2004; K. Lipska et al., 2007), showed that the frequency of IS in young patients is 6.7-17.1 cases per 100 thousand population per year. Differences in the incidence of IS depending on gender and age were revealed. Thus, the incidence of IS in persons aged 18 to 24 years in the general population is 2.5 cases per 100 thousand of the population, and in the age group 35-44 years, this indicator reaches 22.9 cases per 100 thousand [1-6]. In addition, the incidence in men and women under 35, there were no statistically significant differences, whereas after 35 years, the frequency of IS in females exceeded that in males by 32%. According to multivariate regression analysis, in young patients (TH Lee, 2002) the following values of the relative risk for the factors that have the most pronounced effect on the development of IS were established: anomalies of the cerebrovascular system - 25.44; dissection - 21.46; cardiac pathology - 11.15; atherosclerosis - 7.39; hypertension - 5.69; migraine - 3.59; coagulation defects - 2.61; tobacco smoking - 2.16; intracranial tumors - 1.82. However, clarification of the cause of stroke in young patients is associated with certain difficulties. In a study by B. Kristensen et al. (2007) the probable cause of stroke remained unexplained in 21% of cases. Without additional diagnostic information (transesophageal echocardiography - TECG), the number of unidentified cases increased to 37.7%.

Genetic risk factors

IS is a complex multifactorial pathology, the frequency of which increases with an increase in the number of risk factors, including arterial hypertension (AH), smoking and diabetes mellitus. However, in about half of cases, stroke cannot be explained by the presence of risk factors. Despite the fact that classical Mendelian inheritance is determined in less than 1% of cases, studies of twins, familial cases of IS, as well as data from experimental studies on animals indicate that some genetic characteristics are additional risk factors for stroke [7-14]. Probably, the genetic predisposition to cerebral ischemia is realized as a result of the additive effect of several genes (gene-dose effect). Besides, the increased risk of stroke is the result of genotype interactions with external or dynamic factors. Finally, the genetic influence on the risk of developing a stroke depends on age - moreover, it is more significant with the development of the disease at a young age, due to the lack of sufficient time for a significant change in the phenotype under the influence of external influencing and dynamic factors. Studies by A. Pezzini et al. (2005), who studied the interaction of genetic polymorphism - 20210A variant of the prothrombin gene, 1691A variant of the coagulation factor V gene, TT677 methylenetetrahydrofolate reductase genotype, apolipoprotein E gene (the patient's genetic risk score was calculated by the number of these markers) - with modifiable risk factors. The results of M. Grassi et al. (2007) also prove the dose-dependent effect of the studied gene polymorphism on the risk of IS in young people and indicate the presence of a biological interaction between congenital genetic characteristics and modifiable risk factors, which allows substantiating the hypothesis of a synergistic combination of IS risk factors [15-21]. A higher risk of developing IS was associated with a higher genetic score: in particular, the risk of disease increased in the presence of one of the genetic markers, was more pronounced in the presence of more than 2 markers, and significantly increased in the subgroup of individuals who were smokers or suffered from hypertension. Thus, despite the fact that a relationship has been established between the presence of genetic risk factors and the development of IS, the direct independent effect of genetic polymorphism on the risk of cerebral ischemia is limited and becomes of leading importance only in combination with additional factors, which was the basis for the creation of the concept of context dependency (situational dependence) in young patients. The concept of "context dependency" is generally accepted, but only in recent studies has it been proven in young patients. It has been proven that the elimination of modifiable risk factors (normalization of blood pressure (BP), smoking cessation) can reduce the risk of stroke, even in the presence of genetic risk factors). A similar study was carried out by E. Zotto et al. (2004) - it studied the synergistic interaction of polymorphism of the apolipoprotein E gene and tobacco smoking on the risk of developing IS in young people. It was found that the prevalence of the e4 allele and e34 genotype was slightly higher in cases than in the control (0.125 versus 0.071 and 0.242 versus 0.136, respectively). Carriers of the e34 genotype and e4 allele showed an increased risk of stroke in multivariate analysis [22-26]. The risk of stroke was 2.99 (95% CI, 1.64-5.45) for smokers with the e33 genotype, 2.69 (95% CI, 1.25-5.77) for non-smokers with the e34 genotype, 5.39 (95% CI, 1.59-18.30) for smokers with the e34 genotype, compared to 2.27 (95% CI, 1.13-4.56) for non-smokers with the e33 genotype. Similar results were obtained when e4 carriers and non-e4 carriers were compared in the same interaction model. No significant interaction was found between APOE and high blood pressure. Thus, in young APOE 4 alleles and smoking have a synergistic interaction, increasing the individual's propensity to develop IS.

Gene expression changes throughout life, and specific gene combinations can determine different phenotypes at different periods of life. In young people, genetic factors are more pronounced (since a family history is found significantly more often), external factors are less pronounced and their effect lasts for a shorter time. ... More active smoking cessation and more aggressive treatment of hypertension in patients with a genetic predisposition should be recommended. This will significantly reduce the frequency of IS in this category of patients.

Blood pathology and autoimmune mechanisms of stroke development at a young age

One of the common causes of IS in young people is hematological disorders. These include diseases characterized by hypercoagulability: Primary: deficiency of antithrombin III, fibrinogen disorder, resistance to activated protein C, violation of the fibrinolytic system, homocystinuria, the presence of lupus anticoagulants or anticardiolipin antibodies in the blood, deficiency of protein C and S;

Secondary: pregnancy and the postpartum period, taking oral contraceptives, ovarian hyperstimulation syndrome, nephropathic syndrome and other diseases. Antiphospholipid syndrome (APS) is an autoimmune non-inflammatory disease in which the production of antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulants) is noted, accompanied by coagulation disorders (immunologically mediated coagulopathy) and a number of intrauterine fetal death in women caused by thrombosis of the placental arteries. Antiphospholipid antibodies are a heterogeneous group of antibodies determined by enzyme immunoassay and radioimmunoassay methods. Another method for determining antiphospholipid antibodies is coagulation. It is based on the ability of antiphospholipid antibodies to interfere with phospholipid-dependent coagulation reactions, that in vitro causes an increase in blood clotting time, which is not corrected by mixing with an equal amount of donor plasma [27-30]. The antibodies detected in this way are called "lupus anticoagulant", since they were first detected in systemic lupus erythematosus. The development of thrombosis is due to the ability of antiphospholipid antibodies to react with the components of the coagulation cascade, phospholipids of the vascular endothelial membranes and platelets, which determines the tendency to hypercoagulability due to a decrease in prostacyclin production, a decrease in the activation of the natural anticoagulant, protein C, inhibition of the fibrinolytic function, inhibition of the antithrombin system, inhibition of the antithrombin. The antibodies detected in this way are called "lupus anticoagulant", since they were first detected in systemic lupus erythematosus. The development of thrombosis is due to the ability of antiphospholipid antibodies to react with the components of the coagulation cascade, phospholipids of the vascular endothelial membranes and platelets, which determines the tendency to hypercoagulability due to a decrease in prostacyclin production, a decrease in the activation of the natural anticoagulant, protein C, inhibition of the fibrinolytic function, inhibition of the antithrombin system, inhibition of the antithrombin. The antibodies detected in this way are called "lupus anticoagulant", since they were first detected in systemic lupus erythematosus. The development of thrombosis is due to the ability of antiphospholipid antibodies to react with the components of the coagulation cascade, phospholipids of the vascular endothelial membranes and platelets, which determines the tendency to hypercoagulability due to a decrease in prostacyclin production, a decrease in the activation of the natural anticoagulant, protein C, inhibition of the fibrinolytic function, inhibition of the antithrombin system, inhibition of the antithrombin.

Additional clinical and laboratory manifestations that are present in some patients, but are not included in the international diagnostic criteria for APS, include cytopenia, livedo, renal syndrome, heart valve damage, chronic leg ulcers (L.A. Kalashnikova, 2008).

Distinguish between primary APS, which is not combined with any known autoimmune diseases, and secondary APS, which most often develops in systemic lupus erythematosus. In secondary APS, it is coagulopathy, not vasculitis, that is the main cause of IS.

Cerebral circulation disorders in APS, as a rule, are associated with disorders of arterial circulation, usually arechemic in nature, although isolated cases of hemorrhagic stroke have been described, presumably caused by "fragility" of blood vessels and platelet dysfunction. Repeated transient ischemic attacks and IS can be combined with impaired blood circulation in the arteries of the eye, headaches, epileptic syndrome, chorea, encephalopathy. In young patients with cryptogenic ischemic stroke, antiphospholipid antibodies were determined according to the data of different authors with a

frequency of 2.4 to 46% of cases (S. Miyakis, 2006). Strokes with APS have a number of characteristic features:

- more frequent development in women;
- damage to the intracerebral, not the main arteries of the head;
- good regression of symptoms;
- tendency to relapse in the absence of secondary prevention (35-70%). Repeated AIs are accompanied by the development of larger cerebral infarctions.

It should be emphasized that the diagnosis of APS as a cause of IS in young patients is impossible without the detection of high or moderately elevated titers of antibodies to isotype G cardiolipin and / or a lupus anticoagulant of moderate or high activity (E.N. Aleksandrova, 2004; M.K. Ustyuzhanina, 2007). Prevention of repeated disorders of cerebral circulation in APS includes the constant intake of indirect anticoagulants and antiplatelet agents (L.A. Kalashnikova, 2008).

Thus, stroke in young patients is a multifactorial problem that requires a multidisciplinary approach to early diagnosis, timely (within the therapeutic window) prescribing therapy and comprehensive medical and social rehabilitation. Despite the significant variety of etiological causes of IS, the pathogenetic links of the disease in young and elderly patients remain similar. According to the European guidelines for the management of patients with IS and TIA (2008), there is no neuroprotective program that has demonstrated a significant improvement in the outcome of the disease. The results of recent randomized controlled trials on the efficacy of free radical traps and magnesium sulfate have been negative. A phase III randomized, placebo-controlled study of antioxidant therapy with uric acid administered after systemic rtPA thrombolysis is ongoing; Phase II of this clinical trial has shown the safety of this therapy. A meta-analysis of research results revealed moderate efficacy of citicoline (A. Davalos, 2002); clinical studies of the effectiveness of this drug are ongoing.

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