Molecular markers of neurodestruction / neuroplasticity and indicators of endothelial dysfunction in assessing the effectiveness of therapy in premature infants with CNS damage - Pavel Bak - Department of Pharmacology and Medical Formulation

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Abstract

It was found that in the development of cerebral insufficiency in children who underwent pre- and perinatal hypoxia are the processes of neurodestruction associated with the activation of transmitter autocoidosis, oxidative and nitrosative stress and impairment of energy metabolism against the background of dysfunction of the myochondria. Experiments and clinics have demonstrated a direct dependence of the concentration of a number of neurospecific proteins and antibodies to them, molecular markers of oxidative stress and mitochondrial dysfunction in the blood of newborns on the severity of the clinical condition. The only neuromolecules that have the ability to resist the mechanisms of neurodestruction are considered to be neurotrophic factors and heat shock proteins, as well as factors induced by hypoxia. Accumulated preclinical and clinical data indicate that dysfunction in the synthesis of nerve growth factor (NGF), brain neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) may promote brain development with impaired neuroplasticity leading to cerebral insufficiency in children who have had pre- and perinatal hypoxia. Preclinical studies also revealed the neuroprotective role of HSP70 and HIF-1a in conditions of cerebral ischemia and hypoxia. A direct relationship was established between the concentration of HSP70, the severity of neurological disorders and the level of specific markers of neurodestruction. It has been shown that low concentrations of HSP70 contribute to the progression of neurodestruction. In addition, preclinical studies have established that cerebral ischemia is accompanied by an increase in bloodinflammatory mediators that increase vascular permeability (IL-1b, NO metabolites, serine proteases, products of oxidative protein modification).There are few data on shifts in the thiol-disulfide system during cerebral ischemia and an increase in blood oxidized intermediates. Currently, there are practically no data on the relationship between the processes of neurodestruction / neuroplasticity and the factors of endothelial dysfunction, which may be involved in the mechanisms of the development of cerebral insufficiency in children who have undergone pre- and perinatal hypoxia. And the results of experimental studies are few and contradictory.

Based on the foregoing, the identification of the relationship between neuromolecular and neurochemical markers of neurodestruction / neuroplasticity and indicators of endothelial dysfunction in children who have undergone pre- and perinatal hypoxia without neuroprotective therapy is relevant and important in the subsequent organization of neuroprotective therapy. We are studying the dynamics of markers of neurodestruction / neuroplasticity and indicators of endothelial dysfunction during the formation of cerebral insufficiency. The relationship between neurodestruction / neuroplasticity and indicators of endothelial dysfunction and clinical characteristics is investigated. The prognostic role of indicators of neurodestruction-neuroreparation, endothelial dysfunction in children with cerebral insufficiency after pre- and perinatal hypoxia in assessing the effectiveness of pharmacotherapy (to restore neurological status) will be determined. In spite of all similarities, ischemic stroke cases representing 80% of the acute cerebrovascular accidents, different steps of platelet activation, coagulation and fibrinolytic cascade are involved in the pathomechanism of the different stroke subtypes. The differentiation of the atherothrombotic, cardioembolic and lacunar forms of acute ischemic stroke is based on the comprehensive evaluation of clinical signs, neuroimaging technics, and diagnostic ultrasound, but also a significant effort was made to characterize the specificities of the underlying processes of the coagulation system by signal molecules, in order to clarify their possible role and to support the diagnostic and therapeutic decisions. The von Willebrand factor was studied as the marker of endothelial injury in 34 acute ischemic stroke patients within 24 hours after the onset of their stroke, and repeatedly 2, 4, and 12 weeks thereafter. To determine the probable source of the von Willebrand factor, usually released not only by endothelial cells, but also by platelets, the authors simultaneously measured the levels of an additional endothelial marker, thrombomodulin, and a platelet activation marker, beta-thromboglobulin. The mean of von Willebrand factor levels measured in stroke patients on the first day was 123%, whereas the mean of the control group 72% ($p < 0.05$). There was no significant difference according to stroke subtype.

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Von Willebrand values determined two weeks later showed a further 60% increase in stroke patients, and after a gradual fall their level remained above the concentration of the control group. The beta-thromboglobulin level measured in stroke group was significantly higher, than in control individuals (171 IU/ml vs. 32 IU/ml, $p < 0.001$). This was characteristic for atherothrombotic and cardioembolic stroke, but not for lacunar infarctions. If measured repeatedly, beta-thromboglobulin levels decreased rapidly in the first two weeks, than somewhat slower. Soluble thrombomodulin was slightly elevated in stroke patients (4.24 ng/ml) compared to healthy subjects (3.81 ng/ml), without statistical significance, and without major differences between subgroups. While early determination of beta-thromboglobulin can contribute to the differential diagnoses of the subtypes of ischemic stroke, the long-lasting elevation of von Willebrand factor may reflect endothelial dysfunction caused by several factors in the microvasculature of the penumbra.

Bottom Note: *This work is partly presented at 27th Annual Summit on Neuroscience and Neurological Disorder at December 01-02, 2021 | Barcelona, Spain*