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The role of immunological mechanisms in the progression of disease in patients with chronic ischemia of the brain against the background of hypertension and atherosclerosis

Abstract: The study of chronic brain ischemia pathogenesis showed that in cases of CBI of hypertonic genesis the levels of proinflammatory cytokines were significantly increased, particularly IL-6.

Keywords: chronic brain ischemia, proinflammatory cytokines, atherosclerotic and hypertonic genesis.

In our days the brain vascular diseases remain to be the focus of attention of the society due to highly alarming epidemiological situation in relation to morbidity rate of stroke in Uzbekistan as well as due to catastrophic consequences of various forms of cerebrovascular pathology for physical and psychical health of nation [1]. The multiple large-scaled investigations showed that arterial hypertension (AH) and atherosclerosis of the cerebral vessels appeared to be the main cause and the most important factor of chronic brain ischemia (CBI) [3; 8; 9]. They occupy the key role in the vascular dementia [1; 5; 7]. Many examinations indicated about participation of inflammation in the atherogenesis and development of chronic brain ischemia [4; 9]. Even at the relative functional preservation in the patients with CBI the autoimmunization develops to the structural components of the nervous tissue which depends both on the antigens released out of hematoencephalic barrier and on damaged complex regulation of the nenuroimmune system, determining immune homeostasis [6; 10]. However, the role of immune connecting inflammatory process as potential universal ingredient of the CBI pathogenesis of various genesis seems to be unspecified.

Purpose. To study proinflammatory cytokines IL-1β, TNF-α and IL-6 in the peripheral blood serum of the patients with CBI with regard to its genesis (hypertonic and atherosclerotic), as well as to AH stage and duration.

Materials and methods. We have studied some proinflammatory cytokines, that is, IL-1β, TNF-α and IL-6 in the serum of peripheral blood from 84 patients with CBI according to its genesis (hypertonic and atherosclerotic). All studied patients were divided into 2 groups in relation to pathogenesis of CBI. Group 1 included 53 (63,1%) patients with CBI, developing predominantly at the basis of AH. According to the classification of arterial hypertension by the level of AP and to the Guidelines of the Russian Society on arterial hypertension and All-Russian Scientific Society of Cardiologists (the 3 revision, 2008) [2] we divided patients of group 1 into 3 subgroups: 21 patients with AH Stage 1,22 patients with AH stage II and 10 patients with AH stage III. The arterial hypertension was divided according to the duration: AH stage I — to 5 years of duration in 10 patients, more than 5 years — 11 patients; AH stage II with duration to 5 years — 12 patients, more than 5 years — 10 patients. Group 2 comprised of 31 (36,9%) patients with CBI developing predominantly associated with atherosclerosis. Control group consisted of 29 practically healthy donors with purpose to compare the immunological characteristics. Measurements of the contents of cytokines (IL-1β, TNF-α and IL-6) in the serum of peripheral blood were performed with method IFA — assays with commercial test-systems (Vector-Best), Novosibirsk, RF, 2013. Statistic processing was made on the PC "Pentium-4.

Results and discussion. Comparative analysis of the level of proinflammatory cytokines in the patients with CBI in the both groups revealed presence of reliable difference with parameters of control group. The content of IL-1β in the blood serum of patients with CBI was reliably increased by 1,51 times (P<0,05) and 1,28 (P<0,05) times, in comparison with practically healthy persons, respectively, in group 1 and 2. It being interested that high content of IL-1β was diagnosed in the patients of group I: increased by 1,18 (P<0,05) times in comparison with characteristics of the patients with CBI of atherosclerotic genesis: in group I the content of IL-1β accounted for 14,9±0,86 pg/ml, while in group 2–12,71±0,58 pg/ml.

According to the literature data IL-1β is multifunctional cytokine with wide spectrum of effects, plays key role in the development and regulation of non-specific body defensive system and specific immunity, one of the firsts is included into the body defensive response during exposure to pathogenic factors. The macrophages and monocytes as well as lymphocytes and fibroblasts are the main producers of IL-1β. The

target cells, such as immunocompetent, endothelial, epithelial cells, fibroblasts and others. IL-1β initiates and regulates inflammatory, immune processes, activates neutrophils, T- and B-lymphocytes, stimulates synthesis of the acute phase proteins, cytokines (IL-2, —3, —6, TNF-α), molecules of adhesion (E-selectines), procoagulants, prostaglandins. It increases hemotaxis, phagocytosis, hemopoiesis, vascular wall permeability, cytotoxic and bactericide activity, provides pyrogenic effect and others. Endothelial cells of the human vessels under effect of IL–Iα and β secrete polypeptides similar to thrombocytary growth factor. These polypeptides stimulate cellular migration and proliferation and induce releasing of vascular mediators of inflammation that in significant increase of these cytokines may result in disseminated vascular blood coagulation. The observed increase in level of IL-1β in the our studied patients, evidently, is connected with stimulation with use of ligand CD40, processing of pre-IL-β and releasing of biologically active cytokine in the endothelial cells and cells of arteries, consequently showing both on the mechanism of ICE-activation in the inflammatory process at atherogenesis and other pathological states and on the new mechanism of activation of IL-1β in the vascular cells.

It is established that Th1-cells produce powerful cytokines having proinflammatory effect such as IL-β, TNF-α and others [6; 8]. Th2-cells secrete proinflammatory cytokines, such as IL-4, which stimulate predominantly humoral chain of immunity. Disturbance of the balance in the production of cytokines Th1/Th2 has the important significance in the immunopathogenesis of the development of CBI and its progressing. On the basis of above-said we studied the content of cytokine IL-6 in the blood serum of the patients with chronic brain ischemia.

Analysis of the IL-6 content in the serum of peripheral blood in the patients with CBI allowed to reveal reliable increase in all studied groups in comparison with control. Thus, in group 1 the level of IL-6 increased 2,65 times (P<0,001), in group 2–2,02 times (P<0,001), in comparison with control, accounting for 9,06±0,54 pg/ml and 6,94±0,34 pg/ml, respectively. As it may be seen from the data presented, in CBI of hypertensive genesis the changes at the IL-6 level are more marked and reliably increase parameters of the patients with CBI of atherosclerotic genesis 1,31 times (P<0,01).

It should be noted that IL-6 induces synthesis of the acute phase proteins, in this connection (as IL-1β and TNF-α) IL-6 may be concerned to the cytokines of inflammation. According to the literature data IL-6 induces significant increase in level of mRNK c-sis gene (β-chain) in the cultivated human endothelial cells, that may be good reason for inflammatory vascular effects.

TNF-α is another cytokine responsible for development of the inflammatory processes. Measurement of its level in the patients with CBI of different genesis showed reliable increase in all patients. Thus, it is established that the serum level of TNF-α in the group of patients from group 1 an 2 was increased 2,56 times (P<0,001) and 1,76 (P<0,001), respectively, in relation to values in control group, according for 11,70±0,64 pg/ml and 8,04±0,36 pg/ml in group 1 and 2, respectively, at control values 4,58±0,81 pg/ml. We revealed significant increase in levels of NTF-α in groups of patients with CBI on the background of AH, in group 1 of patients the level of TNF-α was increased 1,45 times in comparison with parameters from group 2. Consequently, we revealed considerable increase of serum TNF-α in the both groups of patients with CBI, that may be served as criterion for presence of inflammatory process in CBI.

It should be noted that in group of factors of tumor necrosis TNF-α and β (lymphotoxin) are included. TNF-α is a product of monocytes/macrophages, endothelial, mast and myeloid cells, LAC, neuroglia cells, and in some cases –activated T-lymphocytes. The latter are main producers of TNF-β, which is produced later (2–3dat after activation), than TNF-α, under the effect of antigens and mytogens on the T-lymphocytes. There are three main directions of TNF: cytotoxic, directed to the cells of tumor or cells damaged by viruses; immunomodelling and anti-inflammatory, induced by activation by macrophages, neuttophils, eosinophils and endothelial cells; besides effect on metabolism, leading to hyperglycemia, bone resorption and increase in myogenic glycogenolysis, that is, cachexia, observed in some parasitic infections.

The TNF releasing results in capillary permeability, lesion of the vascular endothelium and occurrence of the development of intravascular thrombosis. Especially TNF-α plays important role in the development of vascular inflammatory lesions. The excessive contents of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, promotes to maintenance of the inflammatory process in the body on whole and may intensify the blood coagulation.

We showed that from studied proinflammatory cytokines the highest level was determined in IL-6, in relation to control. However the intensification of these changes was different.

As it may be seen from the Fig.1, the most increase was characteristic for IL-6 and TNF-α. Thus, in patients with chronic brain ischemia of hypertonic genesis the level of these cytokines exceed values of IL-1β and TNF- α 1,76 (P<0,01) and 2 (P<0,001) times, respectively. In the patients with CBI of atherosclerotic genesis this increase accounted for 1,59 (P<0,01) and 1,37 (P<0,05) times, respectively, in comparison with cytokines IL-6 and TNF- α. On our opinion, this is connected with development of inflammatory vascular effects under influence of IL-6 and TNF-α: increase in capillary permeability, endothelium impairment and development of intravascular thrombosis.

Then we studied the state of proinflammatory cytokines in relation to stage of AH in patients with CBI of hypertonic genesis. It was established, that the serum level of IL-1β in the patients with stage 1 AH was 11,39±1,17 pg/ml, stage II AH — 15,95±0,98 pg/ml (P<0,01). Stage III AH — 20,27±2,26 pg/ml (P<0,01). It is interesting that the contents of IL-1β in stage 1 AH had only tendency to the rise, while during hypertension intensification, the changes gain statistically significant

character, increase by 1,61 (P<0,01) times in stage II AH and by 2,04 (P<0,001) times in stage III AH in comparison with controls. The difference between groups showed that the level of IL-1β was increase by 1,4 (P<0,01) times in patients with stage II AH and by 1,78 (P<0,01) times in the patients with stage III AH in relation to group stage I AH.

In comparison with parameters of IL-1β the content of IL-6 increased more markedly in the serum of peripheral blood of the patients. Thus, in the patients with stage I AH the level of IL-6 increased statistically significant by 2,1 (P<0,001) times and 2,85 (P<0,001) times — in stage II AH and by 3,54 (P<0,001) — in Stage III AH in relation to controls. At the same time IL-6 in group of patients with stage I AH accounted for 6,89±0,82 pg/ml, with stage II AH — 9,75±0,61 pg/ml, while in group of stage III AH — 12,12±1,29 pg/ml. In comparison with parameters of patients with stage I AH, in the patients with stage II AH the level of IL-6 increased by 1,42 (P<0,01), and in patients with stage III AH this rise was 1,76 (P<0,01). The data presented showed that the contents of IL-6 increased progressively during deepening of the pathological process.

Analysis of the level NTF-α in the blood serum of patients with AH showed its progressive rising. Thus, in the patients with AH I, AH II, and AH III stages the level of this cytokine was increased by 1,98 (P<0,001); 2,76 (P<0,001) and 3,32 (P<0,001) times, respectively, in relation to values in the control group. We found significant increase in the level of TNF-α in group of patients with stage III AH. In comparison with parameters of group of patients with stage I AH, the parameters of TNF- α increased by 1,4 (P<0,05) times in group of patients with stage II AH and by 1,7 (P<0,01) times — in the patients with stage III AH.

Thus, the investigations performed showed progressive increase in contents of studied cytokines during increase in stage of AH. The most changes are characteristic for stage III AH, particularly IL-6 and TNF- α.

Then we studied contents of the proinflammatory cytokines in relation to duration of AH in patients of group 1. Comparative analysis showed that serum level of IL-1β in the patients with stage I AH to 5 years was 6,26±0,62 pg/ml and 7,59±1,60 pg/ml, exceeding norm values by 1,83 (P<0,001) and by 2,2 (P<0,001) times, respectively. Differences between groups were statistically insignificant. The level of TNF- α in group of patients with stage I AH to 5 years and more 5 years was 8,15±0,71 pg/ml and 10,08±1,86 pg/ml, respectively, exceeding norm values by 1,78 (P<0,01) times and 2,2 times, respectively, in relation to control. Differences between groups were statistically insignificant.

The data obtained showed that differences in the contents of proinflammatory cytokines in relation to duration of hypertension were insignificant and not reliable.

The level of IL-1β in group of patients with stage II AH to 5 years accounted 14,7±1,36 pg/ml, and in group with stage II AH more than 5 years — 17,15±1,38 pg/ml, exceeding norm parameters by 1,48 (P<0,05) and 1,73 (P<0,01) times. Differences between groups have statistically insignificant character. The content of IL-6 in group of patients with stage II AH to 5 years was 9,36±0,81 pg/ml, and in group with stage II AH was more than 5 years — 10,15±0,94 pg/ml. These findings exceed statistically significantly the parameters of practically healthy persons by 2,74 (P<0,001) and 2,97 (P<0,001) times. However, differences in the parameters between groups with regard to duration of disease we did not reveal. The content of TNF-α in group of patients with stage II AH to 5 years was 11,89±1,07 pg/ml, and in group with stage II AH more 5 years — 13,36±1,23 pg/ml. These parameters statistically significantly exceed parameters of practically healthy persons by 2,6 (P<0,001) and 2,92 (P<0,001) times. However, differences in the parameters between groups in relation to duration of disease we did not reveal.

Consequently, in the patients with stage II AH changes of parameters of all studied cytokines did not depend on the duration of hypertension.

Thus, intensity of changes in the content of proinflammatory cytokines in the patients with CBI of hypertonic genesis in relation to duration of disease was not noted.

The established in our work increase in levels of IL-1β, IL-6 and TNF-α in the patients with CBI on the background of arterial hypertension convincingly reflects dynamics of the immunopathological process, correlating with clinical picture and revealed more marked reduction of the parameters of cognitive sphere in this group of patients. The development of cerebrovascular insufficiency is determined in many respects by formation of micro- and macroangiopathies leading to formation of metabolic and hemodynamic disturbances. Diffusive damage of small arteries observed in CBI of hypertonic genesis is accompanied by wide spectrum of changes in the brain. The damage of brain is characterized by gradual accumulation of ischemic and repeated degenerative changes in the brain, due to repeating ischemic episodes in the various vascular basins, first of all, in zones of blood supplying of small penetrating cerebral arteries and arterioles.

It is known that cerebral ischemia results in accumulation of cytotoxic substances which, in turn, leads to activation of microglia, which begins to produce actively cytokines. We suggest that our results obtained confirm established increased levels of proinflammatory cytokines in our research. Besides, the significant increase in production of IL-6 appeared to be marker of activation of the pathological process in atherosclerotic genesis of CBI because it is known, that IL-6 is the mediate cytokine, long activation of which is expressed clinically by body chronization and autoimmunization.

Conclusion. Chronic brain ischemia is characterized by increase in level of proinflammatory cytokines, particularly IL-6. The most changes are noted in the patients with CBI of hypertonic genesis and dynamics of the level changes is under the direct dependence on the stage of AH. The intensity of changes in the content of proinflammatory cytokines in the patients with CBI of hypertonic genesis in relation to duration of disease.

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Surgical treatment by method ligamentotaksisa for fractures of metacarpal bones of the hand

Abstract: Purpose: to improve the results of treatment of fractures of metacarpal bones surgically using the method ligamentotaksisa.

Method: The results of treatment were studied in 36 patients with fractures of the metacarpal bones of the hand between the ages of 18 to 74 years. All patients received surgical treatment method ligamentotaksisa.

Results: The results of treatment were studied in long-term period of 1 year to 4 years. The results of treatment were assessed by an 8-point scale, which takes into account the consolidation of the fracture, the range of motion in the joints, the presence of pain, return to work. Good results are ascertained in 30 (83.3%) patients, satisfactory in 4 (11.1%), poor in 2 (5.6%).The results of treatment is also dependent on the residual displacement of bone fragments. Our results showed that the mixture should not exceed 20°.

Conclusion: Our method of surgical treatment of fractures of the metacarpals with ligamentotaksisa shows for all kinds of intra-articular fractures of the distal end of the metacarpal bones, helps shorten hospital stays and total disability in 2 times.

Keywords: metacarpal bone, the device, surgery, ligamentotaksis.

Introduction: The metacarpal fractures accounts 2.5% of all bone fractures, from them fractures of distal part of metacarpal occurs in 74%. According to different authors, closed fractures of metacarpal I meet from 5 to 40%; Metacarpal II — from 7 to 20%; Metacarpal III — from 5 to 12%; Metacarpal IV — from 8 to 30% and Metacarpal V — from 17 to 56% of all fractures. According fractures localization, closed fractures of metacarpal bones are distributed as follows: in the shaft — in 30–50% of patients, in the base — at 12–20%, in the head — from 4 to 6%. In 36,5–42,0% of patients occurred subcapital fractures of II–V metacarpal bones in the so-called metacarpal neck [1; 2,]. Treatment of brush injuries is a complex and important section of hand surgery. So far, there is no consensus on the choice of treatment for different types of metacarpal fractures. According to many authors [1; 11] it is become to need