IMMUNOLOGICAL CHANGES AND CYTOKINES PROFILE IN PATIENTS WITH HIV-INFECTION

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SUMMARY. The article presents the analysis of the profile of cytokines IL-4, IL-10, TNF-α and features of the disease in HIV-infected persons, depending on the level of immunosuppression. Established that the immune status of patients with HIV individuals is characterized by failure of cell compartment with an imbalance ratio of immune cells and increased production of proinflammatory TNF-α and anti-inflammatory IL-10.

***Key words**: HIV-infection, cytokines,cell immunity.*

Отримано 7.11. 2012 р.

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УДК 616.98:578.829.6-06:616.98

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A SHIFT OF THE ENDOTHELIAL DYSFUNCTION MARKERS IN PATIENTS WITH HIV-INFECTION/AIDS UNDER HAART

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On the basis of inspection 127 patients with HIV-infection/AIDS it is set that at this pathology substantially grows concentration of thrombomodulin, and von Willebrand factor, which specifies on HIV-induced of vascular wall defeat. As far as progress of immunogenicity the concentration of all of the noted indexes grows for certain. 3-monthly symptomatic therapy does not influence on the state of endothelia.

***Key words:** endothelial dysfunction, HIV/AIDS.*

Recently, special attention of scientists focused on the role of endothelium in the pathogenesis of HIV infection. Locally, the endothelium forms a wall of hepatic blood capillary – sinusoid to ensure exchange between blood and tissues. In general, endothelial lining of blood vessels of the body is seen as an active independent body that ensures homeostasis of the vascular wall and is an important barrier to the spread and development of infection [1, 2].

Molecules that are produced by endothelium and are markers of its activation and damage are in soluble form in the bloodstream [3]. They can identify qualitative and quantitative laboratory methods. In particular, highly sensitive tests are defined in the peripheral blood content of thrombomodulin and von Willebrand factor levels [4, 5].

Thrombomodulin is a surface glycoprotein of endotheliocytes that involved in the processes of blood coagulation and fibrinolysis [6]. In case of damage endothelial thrombomodulin released into the blood in soluble form, and its concentration in blood correlates with the degree of endothelial damage [7].

Von Willebrand factor is an adhesive glycoprotein which accumulates in the secretory granules of endothelial cells and subendothelial matrix. It regulates the initial adhesion of platelets to subendothelial and plasma levels of coagulation factor VIII. The level of von Willebrand factor in the blood increased by stimulation of endothelial cytokines and in case of it damaged [4].

The aim of the study was to study the content of these markers of endothelial dysfunction in blood of patients with HIV infection, they change depending on the clinical stage of disease and under HAART treatments.

Patiants and methods

The study involved 127 patients with HIV infection who were on ambulatory treatment during 2008-2011 in a regional center for prevention and fight against AIDS of Chernivtsi. Among these patients were 66 men and 61 women aged 19 to 44 years.

Among examined there were 35 (27.6 %) patients with clinical stage I, 60 (47.2 %) – II, 22 (17.3%) – III, 10 (7.9 %) – IV clinical stage.

All patients were divided into two groups: I – 93 persons (47 men and 46 women) aged 19 to 44 years who did not receive HAART; II – 34 patients (19 men and 15 women) aged 21 to 44 years who got first-line HAART (zidovudine + lamivudine + efavirenz). These patients were on HAART for at least 3 months.

Patients with I and II clinical stage HIV-infection/AIDS were combined in the first study subgroup, and from III and IV – to the second subgroup. 21 representative of group II (61.8 %) was in phase II clinical HIV-infection/AIDS, 9 (26.4 %) – in III and 4 (11.8 %) – in IV. Patients with clinical stage II HIV-infection/AIDS made first, and from III and IV – the second subgroup II.

In serum samples of all patients with HIV infection by ELISA quantitatively has been determined von Willebrand factor and thrombomodulin. To identify thrombomodulin used test systems produced by Diaclone (France), and von Willebrand factor – test kits manufactured by Shield Diagnostics (UK). The content of von Willebrand factor calculated as a percentage of standard samples for standard curves [5].

Statistical analysis of digital data had been done by a computer program "Microsoft Excel 2007", using the criterion of Student's and linear correlation coefficient and Pearson. The value of $p < 0.05$ was considered statistically significant.

Results and discussion

Established that significant changes were subjected to all the indicators of endothelial dysfunction. In the representatives of each subgroup thrombomodulin concentration significantly higher than for healthy persons, for I-st and II clinical stages of HIV infection (12,17±0,38) mg/l, while III and IV – (17,38±0,40) mg/l, with normal (4,83±0,35) mg/l ($p<0,02$-$0,005$). Importantly, together with the deepening of HIV significantly increased the concentration of this marker.

The concentration of von Willebrand factor also changed significantly in the patients first subgroup (202,65±4,33) % and the second subgroups – (221,11 ±2,57) %, significantly exceeding the level of healthy individuals – (164,50±6,30) % ($p<0.02$). At the same time with the progression of HIV concentration of this parameter significantly increased ($P2\text{-}1<0.05$).

Established a strong inverse correlation between the number of T-helper cells and content thrombomodulin – r=-0,74…-0,91, and between the number of T-helper cells and the concentration of von Willebrand factor – the average inverse (r=-0,43...-0,68).

Elevated thrombomodulin and von Willebrand factor in the patients apparently are the outcome of blood capillary structure and/or increase the expression and release of these factors on endothelial cells as the microvasculature of body tissues. Thus, the findings confirm the hypothesis about the development of endothelial dysfunction in HIV-infection/AIDS.

Damage to endothelial monolayer hypothetically could be the result of pathogenetic links of HIV infection, including virus particles passing through the endothelial barrier and the interaction of immunocompetent cells of the vascular wall. Thus, in the world literature there is evidence of direct infection of endothelial HIV [8, 9], although the direct cytopathic effect of virus in endothelial cells remains to be confirmed.

More proven is a scheme of HIV-induced damage of endothelial cells through a cascade of inflammatory reactions, which is also an important link in the pathogenesis of HIV infection [5]. HIV proteins launch allocation of proinflammatory cytokines such as interleukin-8 (IL-8) and cause endothelial apoptosis [10]. Our studies confirm these data, since overexpression thrombomodulin and von Willebrand factor is a component of the inflammatory response of the vascular wall. In particular, thrombomodulin regulates blood clotting and fibrinolysis has anti-inflammatory and cytoprotective effects, contributing to the maintenance of endothelial integrity. As the release of thrombomodulin that may occur due to inhibition of its formation under the action of cytokines or neutrophils-dependent proteolytic department soluble thrombomodulin of endothelial membrane creates conditions favorable for the development of inflammation. On the other hand, the endothelial monolayer structure violations stimulates excretion of von Willebrand factor, which in turn contributes not only platelet adhesion to bare subendothelium, but adhesion of leukocytes to endothelial cells, also contributing to the development of inflammation [6].

The idea of an important pathogenetic role of persistent activation of endothelium in the progression of HIV infection is confirmed also in studies of the impact of increased expression of biologically active substances such as IL-8 and transforming growth factor в (TGF в), which have stimulating effect on the processes neoangiogenesis [9].

Conclusions

1. In all patients with HIV infection significantly increases the concentration thrombomodulin and von Willebrand factor, indicating that HIV-induced lesions of the vascular wall.

2. The established inverse correlation between the number of T-helper cells and of endothelial dysfunction: the extent of progression of HIV concentration of all these parameters significantly increased.

3. 3-month symptomatic therapy does not affect the state of endothelium.

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ЗМІНИ МАРКЕРІВ ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ У ПАЦІЄНТІВ З ВІЛ-ІНФЕКЦІЄЮ/СНІДом НА ТЛІ ВААРТ

В.Д. Москалюк, В.Д. Сорохан, С.Р. Меленко, І.В. Баланюк

РЕЗЮМЕ. На підставі обстеження 127 хворих на ВІЛ-інфекцію/СНІД встановлено, що при цій патології істотно зростає концентрація тромбомодуліну та фактора Віллебранда, що вказує на ВІЛ-індуковане ураження судинної стінки. У міру прогресування імунодефіциту концентрація всіх зазначених показників достовірно зростає. 3-місячна симптоматична терапія не впливає на стан ендотелію.

Ключові слова: *ендотеліальна дисфункція, ВІЛ/СНІД.*

Отримано 16.01.2013 р.

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УДК 616.98:578.828:614.21:362.147]-036.21(477/87)

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РЕЗУЛЬТАТИ ОЦІНКИ СТАНУ ДИСПАНСЕРИЗАЦІЇ ВІЛ-ІНФІКОВАНИХ ОСІБ В УМОВАХ РЕГІОНАЛЬНОЇ СУБЕПІДЕМІЇ ВІЛ-ІНФЕКЦІЇ/СНІДу В ЗАКАРПАТТІ

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Наведено результати оцінки стану та якості диспансеризації дорослих ВІЛ-позитивних осіб диспансерної групи в Закарпатській області у 2010-2012 рр. Виявлено основні групи причин недосяжності до диспансеризації та відсутності повного охоплення пацієнтів диспансерної групи необхідними медичними послугами в умовах регіональної субепідемії ВІЛ-інфекції/СНІДу в регіоні, де про-