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WILLIBRANT'S FACTOR AS THE INDICATOR OF ENDOTHELIAL DYSFUNCTION AT PSORIASIS ON THE BACKGROUND OF METABOLIC SYNDROME

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ФАКТОР ВИЛЛИБРАНТА КАК ПОКАЗАТЕЛЬ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ ПРИ ПСОРИАЗЕ НА ФОНЕ МЕТАБОЛИЧЕСКОГО СИНДРОМА

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SUMMARY

Для изучения эндотелиальной дисфункции была произведена оценка активности фактора Виллебранта в плазме крови у больных псориазом на фоне метаболического синдрома. Обследовано 74 пациента мужского пола с крупнобляшечным псориазом: без клинико-лабораторных симптомов метаболического синдрома - 1 группа (n=36), с метаболическим синдромом – 2 группа (n=38). Контролем служили 28 здоровых доноров мужского пола в соответствующем возрастном диапазоне. Исследования проводились в возрастном диапазоне от 18 до 70 лет; Активность фактора Виллебранта определяли по ристомицин-индуцированной агрегации формалинизированных тромбоцитов в плазме крови. Установлено, что в сравнении с группой здоровых лиц, у больных псориазом уровень активности ФВ статистически значимо нарастает по мере развития инсулинорезистентности. Выявлено, что наличие метаболического синдрома у больных псориазом характеризуется развитием глубокого дисбаланса в фибронектин-опосредованной системе, в системе гемокоагуляция/фибринолиза в сторону преобладания гиперкоагуляционных сдвигов на уровне очага воспаления, за счет нарушения фибринолитической активности ФВ, что является показанием для коррекции синтеза активаторов и ингибиторов фибринолиза, направленных на восстанавление функциональных свойств эндотелиоцитов – как одного из патогенетических факторов системного воспаления псориатической болезни.

ФАКТОР ВІЛЛІБРАНТА ЯК ПОКАЗНИК ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ПРИ ПСОРІАЗІ НА ТЛІ МЕТАБОЛІЧНОГО СИНДРОМУ

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РЕЗЮМЕ

Для вивчення ендотеліальної дисфункції була виконана оцінка активності фактора Віллебранта в плазмі крові у хворих на псоріаз на тлі метаболічного синдрому. Обстежено 74 пацієнта чоловічої статі з крупнобляшковим псоріазом: без клініко-лабораторних симптомів метаболічного синдрому – 1 група (n=36), з метаболічним синдромом – 2 група (n=38). Контролем служили 28 здорових донорів чоловічої статі у відповідному віковому діапазоні. Дослідження проводились у віковому діапазоні від 18 до 70 років. Активність фактора Віллебранта визначали за ристоміцин-індукованою агрегацією формалінізованих тромбоцитів у плазмі крові. Установлено, що в порівнянні з групою здорових осіб, у хворих на псоріаз рівень активності ФВ статистично значимо наростає по мірі розвитку інсулінорезистентності. Виявлено, що наявність метаболічного синдрому у хворих на псоріаз характеризується розвитком глибокого дисбалансу в фібронектин-опосередкованій системі, в системі гемокоагуляція/фібринолізу в бік переважання гіперкоагуляційних зрушень на рівні осередка запалення, за рахунок порушення фібринолітичної активності ФВ, що є показанням для корекції синтезу активаторів і інгібіторів фібринолізу, направлених на відновлення функціональних властивостей ендотелиоцитів – як одного з патогенетичних чинників системного запалення псоріатичної хвороби.

Key words: psoriasis, Willibrant's factor, hemocoagulation, metabolic syndrome.

Last two decades a traditional paradigm «psoriasis – it is disease of epidermal cells first of all» has been replaced by the new scientific model including keratinocyte-mediated factors, mediators of inflammation and vascular mechanisms [1, 2, 3].

Morphological changes of vessels at level of derma participating in formation of dysregenerative disturbances an essential place occupy in psoriasis pathogenesis [4, 5, 6]. The pathogenetic «vascular» component of psoriasis includes also imbalance in vascular, endothelial and thrombocyte growth factors (TGFβ, PDGF, VEGF) systems [7, 8]. The specified growth factors are revealed and in synovial fluid of patients with psoriatic arthritis [2,9,10].

Communication of nervous-vascular disturbances and the increased synthesis of proinflammatory substances in the focus of psoriatic inflammation at various types of injuries (traumatism) of derma (the concept of transformation of injuring stimulus in immunopathologic answer) is discussed also [5].

Characteristic pathogenetic peculiarity of psoriasis is excessive growth of capillary network in limits of papillary derma. Angiopoietines 1 and 2, Tie2-receptors of vessels, vascular endothelial growth factor and growth factor of fibroblasts actively participate in this process. Essential increase of angiopoietine 2 and Tie2 in cultures of cells of capillaries endothelium of patients with psoriasis is revealed [11, 12, 13].

Essential increase of plasma levels of endothelin 1 and 2 in patients with psoriasis is revealed. Dysfunction of endothelium in patients with psoriasis is revealed and in researches of Trevisan G. and et al. (1994) [14], Cecchi R. and et al. (1994) [15], Zachariae H. and et al. (1996) [16], Yildiz L. and et al. (1997) [17], Su Y. and et al. (1997) [18], Sochorova R. and et al. (2000, 2003, 2004) [19], Zhang Y. and et al. (2005) [20].

Summarizing the aforesaid, it is possible to confirm that continuation of scientific search in decoding of various aspects of endothelial dysfunction in patients with psoriasis is represented an actual scientific direction.

Developing this thought, it is necessary to mention that at inflammation procoagulative activity of endothelium cells is shown in stimulation of synthesis and an expression on a surface of endothelium of the tissue factor, which is the initiator of alternative depending on endothelium of coagulation way. So, the tissue factor catalyzes activation by the VII factor of IX factor bounded with a wall of vessel. Formed factor IXa transforms the factor X (bounded with endothelium) in Xa, which transforms prothrombin into thrombin. On the classical internal mechanism of coagulation the factor IX is activated in plasma by factor XIa of a contact phase of thrombogenesis. An alternative way – it is that effective mechanism, which conducts to occurrence of small amounts of thrombin still insufficient for coagulation of fibrinogen, but specifically activating endothelium cells, thrombocytes and leucocytes. Stimulation of synthesis and expression of the tissue factor on a surface of endothelium underlies of thrombotic reactions in the focus of inflammation. Along with these processes on a surface of the damaged endothelium there is an activation of a contact phase of coagulation [21].

Using scientific analogy, it is necessary to mention research of Herve P. et al. (1998) [22], in which at chronic diffusive diseases of a liver the endothelium-associative possible connection between systemic endotoxinemia and development remodelling vascular system is surveyed.

The initial attachment and splitting of thrombocytes on subendothelium regulates synthesized by endothelium cells protein of Willibrant's factor serving by cofactor of thrombocytes adhesion to subendothelium of arteries and vessels of microcirculation, and also a carrier of the factor VIII of fibrillation. At inflammation remission of Willebrant's factor from the activated cells is broken: the mediator of inflammation IL-1 released by monocytes reduces level of mRNA, the coding Willibrant's factor (WF), and accordingly level of this protein in all compartments [23].

A series of definition methods in peripheral blood of substances synthesized in cells of vascular endothelium and allocated in the circulating blood, carry out marked role in definition and estimation of degree of expression of endothelial dysfunction. As such markers are used the tissue activator of plasminogen, thrombomodulin and a fibronectin [23].

At the same time the most informative method of studying of endothelial dysfunction is definition of Willibrant's factor (WF) having high enough (concerning endotheliocytes) cellular specificity. WF is one from components of VIII factor of coagulating system of blood and represents multimeasured glycoproteid, which presents in plasma, megacaryocytes, in granules of thrombocytes can collect in cellular organellas of endothelial cells – little bodies of Weibel-Palade [24].

Synthesis WF is carried out with some excess, and this excess is collected in endothelial cells and if necessary can be quickly mobilized. Presence of subendothelial depot of WF is one of the major conditions providing effective adhesion of thrombocytes and hemostasis in case of injury of endothelial layer of a vascular wall. WF concentration in plasma makes approximately 10 mkg/ml with a half-life period of 18 hours. It is established that increase of WF free occurs in reply to action of different stimulus, including a mechanical trauma, endotoxin, IL-1, fibrin, thrombin, histamin, a membrane-attack complex of a complement, antibodies to DNA, oxidative stress.

Approximately 15,0 % WF of blood are in thrombocytes, where it passively gets at a stage of lacing out of thrombocytes from megacaryocytes, in which there is synthesis of WF. Thrombocytic WF does not render essential influence on concentration of the factor in blood plasma. By numerous researches it is proved that increased level of WF in peripheral blood is immediately caused by injury of vascular endothelium [24].

Thus, use of estimation of WF activity in blood plasma as high informative integrated indicator of presence and degree of expression of endothelial dysfunction at psoriasis is represented quite correct biological model.

Purpose: to estimate activity of Willibrant's factor in blood plasma in patients with psoriasis on the background of metabolic syndrome.

MATERIAL AND METHODS

For the decision of tasks 74 patients male with big-plaque psoriasis are observed, who were subdivided into 3 groups. The 1-st group has made 36 patients with psoriasis without clinical-laboratory symptoms of metabolic syndrome. 38 patients with psoriasis with metabolic syndrome have entered into the 2-nd group.

As control 28 healthy male donors were in a corresponding age range.

Researches were spent in an age range from 18 till 70 years; the greatest number of patients with psoriasis is registered by us at the age of 18 – 30 years in 1-st group and in 2-nd – patients from 41 till 60 years.

Activity of Willibrant's factor defined on ristomycin-induced aggregation of formalinized thrombocytes in blood plasma [23]. Considering that WF level in blood is extremely low, for its definition high-strung immunologic methods are used with application of specific antibodies and different ways of registration of an antigen complex formation – antibody (radio-immune, immuno-enzymatic, immuno-chemoluminescent) [24].

Use of the basic indirect method of definition of WF level is based on structural complement of antibiotic ristomycin (ristocetin) to some membranous receptors of thrombocytes and active domains of WF molecule. Ristomycin is capable to cause of thrombocytes aggregation, and degree of expression of the last is directly proportional to maintenance of WF in reactive medium [24]. In particular, the micro-method of ristomycinum-induced aggregation of formalinized thrombocytes in plastic plane-table with the subsequent registration of results by means of a plane-table photometer [23] is used.

RESULTS OF RESEARCH AND DISCUSSION

Results of research of level of WF activity in blood plasma in norm and in patients of the 1-st and 2-nd groups testify that in comparison with group of healthy persons, in patients with psoriasis level of WF activity statistically significant increase in process of development of insulin-resistance.

Maintenance of WF in group of healthy persons has made 111,58 ± 1,89 %. In patients of the 1-st group WF activity has made 131,87 ± 1,65 %, in the 2-nd group – 151,47 ± 2,72 %. It is necessary to notice that WF indicator in the 1-st group is increased on 18,2 % ($p<0,001$), in patients of the 2-nd group – on 35,8 % (p and p1 <0,001) in comparison with control group (table 1).

Table 1

Level of WF activity in blood plasma in patients of the 1-st and 2-nd groups, %

Group	Statistical indicator	WF
1st group	M ± m n p	131,87 ± 1,65 36 < 0,001
2nd group	M ± m n p p1	151,47 ± 2,72 38 < 0,001 < 0,001
Healthy persons (control group)	M ± m n	111,58 ± 1,89 28

Note: p – reliability of differences calculated in comparison with group of healthy persons;
p1 – reliability of differences calculated in comparison with the 1st group of patients.

CONCLUSIONS

It is revealed that presence of a metabolic syndrome in patients with psoriasis is characterised by development of deep imbalance in a fibronectin-mediated system, in system haemocoagulation/ fibrinoliz towards prevalence of hypercoagulative shifts at level of the inflammation focus at the expense of disturbance of fibrinolytic activity of WF that is the indication for correction of synthesis of activators and the fibrinolysis inhibitors referred on recovery of functional properties of endotheliocytes – as one of pathogenetic factors of systemic inflammation of psoriasis.

Thus, the systemic inflammation at psoriasis can prove to be prove by markers of activity of thrombocytes – Willibrant's factor and can serve as a biomarker of gravity monitoring of psoriasis in patients on the background of a metabolic syndrome.

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