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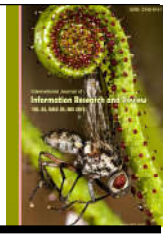

Research Article

THE VALUE OF ENDOTHELIAL DYSFUNCTION IN THE GENESIS OF DEVELOPMENT RHEUMATOID ARTHRITIS

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune, systemic disease that affects the joints. In RA, the body's immune system destroy body's tissue for a foreign invader. This leads immune system to attack the protective cushion of tissue and fluid between the joints. The result is swelling, stiffness, and pain in the joint. The body's misfiring immune system also may go after the body's soft tissues, like cartilage, and organs such as the heart, eyes, and veins. According to the literature, the number of publications on the study of dysfunctional disorders of the endothelium in patients with RA is limited.
Methods: Retrospective analysis representing in this article was performed through 68patients with RA who was received inpatient treatment in the Department of Rheumatology 3-clinic Tashkent Medical Academy (TMA) in period from November 2014 to January 2016. Authors analyzed spreading spectrum of endothelium dysfunction degree in RA patients via verified laboratory data. Authors studied the age and gender characteristics of patients with dysfunction that occurred after RA and the degree and severity of endothelial dysfunction.
Results: The observation of the dysfunction of endothelial cells of blood vessels was accompanied by impaired synthesis of nitric oxide, which was reflected in a decline in the content of nitric oxide in the blood serum of the surveyed people. In patients with RA anemia syndrome with negative H. pylori infection, this indicator counted to an average of 1.48±0.12 g/ml. In the third group of patients, the studied parameter, has reached a level of 1.24±0.09 g/ml, which is 49% lower than healthy individuals (PL 0.05). The content of Willebrand factor in patients with RA without anemia was, on average, 98.41±7.64, which was 17% higher than in healthy individuals.
Conclusion: Endothelial dysfunction is the link between microbes and autoimmune disease. It is possible the mechanism of iron capture by bacteria in the stomach and reduce gastric levels of ascorbic acid, which can lead to the development of anemia.

INTRODUCTION

Rheumatoid arthritis (RA) - chronic systemic connective tissue disease with lesions of the joints according to the type of symmetrical erosive and destructive polyarthritis and various extra-articular manifestations. The development of multiple systemic manifestations determines the severity and poor prognosis of the disease. After 20 years of onset 60-90% of patients, suffer permanent disabilities. Disability in these patients may be not only due to the progressive destruction of the joints, but also due to severe visceral lesions. Pathology of the gastrointestinal tract diagnosed in 13-62% of patients suffering from RA. The nature of the pathological changes of digestive organs in patients with RA is due not only to the manifestation of systemic rheumatoid inflammation at the base, which are immune disorders, but and damaging effects of H. Pylori infection. Altered immune response and inflammatory reactions underlie rheumatoid vasculitis, which promotes the development of endothelial dysfunction and disturbance of tropism of the gastrointestinal mucosa. According to the literature, the number of publications on the study of dysfunctional disorders of the endothelium in patients with RA is limited.

Objective: to study the role of endothelial dysfunction in the development of RA and their relationship with Helicobacter pylori infection.

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MATERIALS AND METHODS

The study included 68 patients with true RA, who was hospitalized in the Rheumatology Department, 3-clinic of TMA from November 2014 to January 2016. The inclusion criteria of patients in the study were reliable diagnosis of RA, the absence of severe concomitant pathology of internal organs with functional impairment. The following exclusion criteria were

considered unreliable for the diagnosis of RA, presence of severe concomitant pathology of internal organs with functional impairment. Activity of RA was assessed by DAS-28 indicators, the level of erythrocyte sedimentation rate, C-reactive protein and white blood cell count. The number of patients studied in 56 patients the disease duration was from two years and within five years, 12 patients the duration of the articular syndrome did not exceed 18 months from the appearance of the first clinical signs of articular syndrome. The study included 16 patients suffering from RA without anemia (Hb 120 g/l) - group I patients, 20 patients (group II) RA with anemic syndrome with Helicobacter pylori infection. As controls 14 healthy persons of both sexes.

Laboratory tests, General blood analysis, General urine analysis, quantitative determination of C-reactive protein, rheumatoid factor in the serum, the presence of H. pylori infection was determined using ELISA method and the urease test. The content of desquamated endotheliocytes in blood plasma was determined by the method of Hladovec. J.(1972). The percentage factor of Willebrand investigated by the method of G. V. Mikhailov (1986).

Indicators	Healthyperson index n=14	group I RA patients without anemia syndrome n = 16	RA patients with anemic syndrome II group without H. Pylori n = 20	RA patients with anemic syndrome group III with H. Pylori n = 32
Desquamated endothelial cells of blood plasma $1x10^4$/ml	1.24 ± 0.09	8.23 ± 0.63	5.02 ± 0.34	2.91 ± 0.17
Nitric oxide in the blood serum g/ml	2,43 ± 0,15	2,01 ± 0,14	1,48 ± 0,12	1,24 ± 0,09
Willenbrand factor (%)	84,3 ± 5,56	98,41 ± 7,64	104,5 ± 7,91	127,8 ± 6,14
The amount of active forms of platelets (%)	11,93 ± 0,71	29,41 ± 2,13	31,14 ± 3,12	38,4 ± 3,01
The content of thrombomodulin ng/ml	4,64 ± 0,21	4,01 ± 0,18	3,54 ± 0,16	2,14 ± 0,17
Annexin A5 ng/ml	0,85 ± 0,09	1,44 ± 0,11	3,96 ± 0,21	6,02 ± 0,39

Note: *- reliability of differences (PL 0.05).

The amount of active forms of thrombocytes were determined using morpho-functional method proposed by A. S. Shitikovoy (1988). The content of thrombomodulin in patients with RA was assessed by ELISA using the test system "Diagnostic" company "Biochemmak" (Russia). The content of soluble apoptosis marker Annexin A5 in plasma was determined by enzyme immunoassay using test systems company "Biochemmak" (Russia). The norm we have taken averages of the parameters studied in 14 healthy men of the same age and sex, as in the main group of patients. The research results were processed by variation statistics method on a personal computer using standard programs for correlation analysis with calculation of average arithmetic size (Kalachev A. M., 1999). The significance of differences of mean values of compared parameters was evaluated by ± student's t test. The differences were significant at the 0.05 PL.

RESULTS AND DISCUSSION

As can be seen from the presented research results (table), in patients with RA without anemia when compared with group of healthy persons was significantly increased, on average, 2.3 times (PL 0,05) content of desquamated endotheliocytes in blood plasma. The observed trend of increasing concentration of desquamated endothelial cells was observed in other groups of patients. In particular, in group II RA patients with anemic syndrome without H. pylori it has exceeded the initial level in 4 times, and in group III respondents with a positive H. pylori - 6.6 times (PL 0,05). The observed dysfunction of endothelial cells of blood vessels was accompanied by impaired synthesis of nitric oxide, which was reflected in a decrease in the content of nitric oxide in the blood serum of the examined people. So, in RA patients without anemia syndrome it decreased by 17% when compared with the healthy group. In patients with RA anemia syndrome with negative H. Pylori infection, this indicator amounted to an average of 1.48±0.12 g/ml, 39% below the initial values. In the third group of patients, the studied parameter, has reached a level of 1.24±0.09 g/ml, which is 49% lower than healthy individuals (PL 0.05). The content of Willebrand factor in patients with RA without anemia was, on average, is 98.41± 7.64, which is 17% higher than in healthy individuals. Patients in group II tended to increase the level of factor Willebrand when compared with the original group of 24%, and significant increase of the studied glycoprotein synthesized by endothelial cells when exposed to endogenous factors observed in patients with RA anemia syndrome with positive H. Pylori infection, where the figure exceeded the initial values by 52% (PL 0,05). It is known that platelets strongly adsorbed on plot, devoid of endothelial lining on the background of dysfunction of the endothelial cells, which leads to an increase of active forms of blood platelets.

The observed dynamics of active forms of thrombocytes in patients with RA tended to increase regardless of anemia on average 2.5 times when compared with group of healthy persons. The Anemic syndrome in patients with continent this was accompanied by an increase in the amount of platelets forms on average 2.6 times (PL 0.05). The highest numbers of active forms of thrombocytes were observed in patients with RA anemia syndrome with positive H. Pylori infection, where its value exceeded the initial level of 3.2% (PL 0, 05).

Thrombomodulin, an endothelial membrane receptor and the increase of this index indicates a high protease activity caused by thrombin. As can be seen from the presented results of the study (table.1), only in group III respondents showed a significant decrease in the soluble fraction of thrombomodulin in the blood plasma, on average, 46% (PL 0,05). In recent years, the main attention is paid to the study of biological activity of the proteins belonging to the family of annexins. Annexin A5, like other annexins, does not stand out from normal cells: a source of extracellular annexin A5 are apoptotic and damaged cells. Analysis of the results of the study showed significant increase in the level annexin A5 in all studied groups of patients with RA. So, I group the content of annexin A5 exceeded baseline healthy individuals, on average, by 69%, in group II RA patients with anemic syndrome and a positive H. Pylori infection was 7.1 times (PL 0,05), which is associated with endothelial dysfunction. Markers of endothelial dysfunction in RA patients with concomitant H. pylori infection According to some researchers, in the development of

rheumatic diseases a fundamental role, in addition to genetic and environmental factors in microbial infections. Currently has formed an idea of so-called translocation of bacteria and their antigens and intestinal lumen, as well as their metabolic products. The intercellular permeability is associated with transport between epithelial cells that are associated with the dense contacts, desmosomes and intermediate. They are very dynamic, and their permeability can change in response to external and intracellular stimuli. The intestinal epithelium acts as a selectively permeable barrier, but a number of microorganisms can alter this permeability. These include Helicobacter pylori.

Conclusion

Thus, there are prerequisites that the relationship between intestinal mucosa and H. Pylori may be important in the pathogenesis of rheumatoid arthritis. Therefore, the presence of some correlation between the increase in the level of desquamated endotheliocytes, Willebrand of factors, active forms of thrombocytes and apoptosis factor – annexin A5 in patients with RA with positive H. Pylori infection indicates that when this disease occurs endothelial dysfunction, "run", in turn, Helicobacter pylori inflammation that must be considered when planning adjuvant therapy.

In our view, endothelial dysfunction is the link between microbes and autoimmune disease. It is possible the mechanism of iron capture by bacteria in the stomach and reduce gastric levels of ascorbic acid, which can lead to the development of anemia.

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