ENDOGENOUS PATHOLOGICAL FACTORS AS THE REASON OF SYSTEM INFLAMMATORY REACTION DURING 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 destroys 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 endogenous pathological factors as the reason of systematic inflammatory reaction in patients with RA is limited.

Methods: Retrospective analysis representing in this article was performed through 68 patients with RA who were received inpatient treatment in the Department of Rheumatology 3-clinic Tashkent Medical Academy (TMA) in period from 2013 to 2015. The activity of rheumatoid arthritis was estimated on DAS-28 indicators, the erythrocyte sedimentation rate (ESR) levels and quantity of leukocytes. The research included 16 patients suffering from RA without anemia (Hb>120g/l) – the first group of patients, 20 patients (second group) of RA with anemia (Hb<110g/l) and without helicobacter pylori infection and 32 patients (the third group) of RA with anemia and positive helicobacter pylori infection. For control group, 14 almost healthy people of both sexes were chosen.

Results: Cytokine attack to endotheliocytes cause “oxygen explosion” of a cell which is also associated with the increase pool middle molecular weight (MMW) on average by 1.6 times in plasma of blood and by 1.8 times in erythrocytes in patients with RA without anemia. An increase of malondialdehyde in blood erythrocytes for 25% was noted. The hepatocellular answer is shown by production and release of proteins of a sharp phase, i.e. the increase of C-reactive protein by 1.7 times and fibrinogen by 1.4 times [PL 0.05] in RA patients without anemia. Tumor necrosis factor level in patients of the III group exceeded the initial level of healthy people by 2.9 times [PL 0.05]. The cascade of anti-inflammatory cytokine at this group of patients starts the main mechanism of development of disease where IL-6 stimulates development of proteins of inflammation's sharp phase in liver, in particular C-reactive protein and fibrinogen whose contents exceeded reference values respectively by 2.9 times and by 1.9 times [PL 0.05]. Conclusion: Several endogenous pathological factors such as TNF-α, C-reactive protein, fibrinogen, malondialdehyde were determined as the reason of systematic inflammatory reaction in rheumatoid arthritis.

KEYWORDS: TNF-α, C-reactive protein, malondialdehyde, pool middle molecular weight, endothelium, IL-6.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic disease which is characterized by development of inflammatory process of a synovium and formation of bone-destructive changes of joints; and in its pathogenesis the significant role is played by activation of lipid peroxidation processes, disorganization of anti-radical protection and development of an oxidative stress.[1, 4] Activation of processes of free radical oxidation leads to accumulation
of toxic substances, which are related to endotoxins, i.e. molecules of average weight. It is said that during an inflammation, disorder of integrity of cell membranes during RA is observed; thus, endogenous pathogens while being molecules of protein leave from cytosol to the intercellular environment, a lymph circulation and blood. These molecules of average weight possess neurotropic activity, oppress the processes of biosynthesis of protein, separate oxidation and phosphorylation processes, change movement through membranes, erythropoiesis, phagocytosis, microcirculation, etc.\[2\]

Quite large number of the scientifically based data has been collected by now, the data testifying that a Helicobacter pylori infection, as well as any other, has got not only local, but also systematic effects (inflammatory and autoimmune), causing the corresponding reactions from some organs and systems.\[3\] Meanwhile, the ways of activation of LP system during a systematic inflammation during with H. Pylori infection associated RA and the importance of this universal mechanism in development of an endotoxemia are not clear. The purpose of current research was studying of a role of endogenous intoxication during with H. Pylori infection associated RA.

**MATERIALS AND METHODS**

The research included 68 patients with authentic RA who were on stationary treatment in the Department of Rheumatology, third clinic of Tashkent Medical Academy.

The criteria of inclusion of patients in research were the authentic diagnosis of RA and the absence of severe concomitant diseases of internal organs with functional impairment.

Criteria exceptions were the doubtful diagnosis of RA, existence of severe concomitant diseases of internal organs with functional impairment.

The activity of rheumatoid arthritis was estimated on DAS-28 indicators, the erythrocyte sedimentation rate (ESR) levels and quantity of leukocytes.

From total of the examined patients, 56 patients had duration of a disease from two and more years within five years, 12 patients had articulate syndrome for not more than 18 months from emergence of the first clinical signs of an articulate syndrome. The research included 16 patients suffering from RA without anemia (Hb>120g/l) – the first group of patients, 20 patients (second group) of RA with anemia (Hb<110g/l) and without helicobacter pylori infection and 32 patients (the third group) of RA with anemia a positive helicobacter pylori infection. For control group, 14 almost healthy people of both sexes were chosen.

The haemogram on the analyzer with an assessment of the erythrocyte indices was investigated in all patients during receipt to the clinic. Concentration of C-reactive protein was defined on biochemical semi-automatic analyzer “Mindray” and using sets of the firm “Human” (Germany). A level of a tumor necrosis factor was investigated on the automatic IFA-analyzer by method of the solid-phase immune-enzyme assay with the use of the “Biochemmak” set (Russia). The content of middle molecular peptides was judged on the basis of direct spectrometry of the protein-free supernants received after sedimentation of proteins TCHU solutions at the given waves of 254 nm and 250 nm.

The factor of a tumor of a necrosis was determined on the automatic IFA-analyzer by method of the solid-phase immune-enzyme assay with the use of the “Biochemmak” set (Russia). Concentration of C-reactive protein was defined on biochemical semi-automatic analyzer “Mindray” and using sets of the firm ‘Human’ (Germany). The level of a malondialdehyde (MDA) in erythrocytes was determined by coloring of the malondialdehyde with thioarbiturates (U.M. Vladimirov et al. 1972). The level of molecules of average weight (MAW) was investigated by a method of N. I. Gabrielyan et al. (1984) on a photometer in the ultraviolet range on lengths of waves with 220 to 300 nm. Level of a middle molecular pool for plasma and erythrocytes was estimated by means of an integrated indicator of optical density.

Statistical processing was carried out with use of a “Statistics for Windows” package. Distinctions in groups were considered significant at probability of the faultless forecast of 95% [P<0.05].

**RESULTS AND DISCUSSION**

The scientific development executed in the general rheumatology allowed drawing a conclusion that a prelude of development of multiple organ failure during rheumatoid diseases is the syndrome of the system inflammatory answer. Its cornerstones are the effects of a number of biologically active agents developed by immune competent cages and the subsequent activation of cytokine in response to the damaging factor, emission of cytokine in a blood-groove system, which are activated by various blood cells and the hormonal status, and development of acute phase reaction and generalization of inflammatory reaction. The complex of biochemical and immunological damages is followed by changes of the level of a middle molecular pool in plasma and erythrocytes.

It is apparent from the received results of research, presented in table 1, that rheumatoid arthritis without anemia is followed by activation of cytolytic T-lymphocytes that leads to a tumor necrosis factor expression. It leads to damage of endothelium of vessels that was registered in the previous researches by increase of level of endotheliocytes in blood. Cytokine attack to endotheliocytes cause “oxygen explosion” of a cell which is also associated with the increase pool middle
molecular weight (MMW) on average by 1.6 times in plasma of blood and by 1.8 times in erythrocytes in patients with RA without anemia. An increase of malondialdehyde in blood erythrocytes for 25% was noted. Local, disseminated damage of endotheliocytes under the influence of cytokine, lipid peroxidation (LP) products is followed by alteration of vascular endothelium, the increased permeability of a vascular wall and involvement of new organs and systems in this process, in particular a liver. The hepatocellular answer is shown by production and release of proteins of a sharp phase, i.e. the increase of C-reactive protein by 1.7 times and fibrinogen by 1.4 times [PL 0.05] in RA patients without anemia.

The anemia observed in RA patients (the II group of patients) accompanied with disorder of microcirculation and a hemic hypoxia, disorder of processes of aerobic oxidation leads to accumulation of toxic substances, which are related to endotoxins. Thus, the increase observed by us in serum of blood of a tumor necrosis factor, reactive protein and molecules of average weight in plasma and erythrocytes points to a condition of an endotoxemia in RA patients with anemia.

### Table 1: Laboratory indicators of an inflammation and endogenous intoxication in patients with RA complicated by anemia and H. Pylori infection.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Healthy people n=14</th>
<th>I group of RA patients without anemia n=16</th>
<th>II group of RA patients with anemia, without H. Pylori n=20</th>
<th>III group of RA patients with anemia, with H. Pylori n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/ml)</td>
<td>18,9±0,81</td>
<td>20,4±1,33</td>
<td>38,6±1,23</td>
<td>54,6±4,83</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>3,01±0,44</td>
<td>5,08±0,47</td>
<td>6,86±1,01</td>
<td>8,81±1,04</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2,61±0,11</td>
<td>3,55±0,24</td>
<td>3,91±0,24</td>
<td>4,93±0,45</td>
</tr>
<tr>
<td>Malondialdehyde erythrocyte membranes (nmol per 1 mg of protein)</td>
<td>1,71±0,11</td>
<td>2,12±0,17</td>
<td>2,81±0,14</td>
<td>4,56±0,38</td>
</tr>
<tr>
<td>Pool middle molecular weight (plasma) unit of act.pl.</td>
<td>2,51±0,14</td>
<td>4,01±0,18</td>
<td>4,18±0,21</td>
<td>6,78±0,44</td>
</tr>
<tr>
<td>Pool middle molecular weight (erythrocyte) unit of act.pl.</td>
<td>4,61±0,33</td>
<td>8,12±0,51</td>
<td>9,51±0,73</td>
<td>12,14±0,81</td>
</tr>
</tbody>
</table>

Note: * - reliability of differences [PL 0.05].

Among a wide range of the metabolites possessing the ability to have endotoxic effect, big attention deserve proteins, which are formed by microorganisms, namely H. Pylori. Quite large number of the scientifically based data has been collected by now, the data testifying that a Helicobacter pylori infection, as well as any other, has got not only local, but also systematic effects (inflammatory and autoimmune), causing the corresponding reactions from some organs and systems. The estimated mechanism, which is the cornerstone of the extra gastric pathology connected with H. Pylori, includes direct influence of a bacterium; inflammatory process along with a cytokine release is activated.

It is apparent from the presented results of research (table 1), that the tumor necrosis factor level in patients of the III group exceeded the initial level of healthy people by 2.9 times [PL 0.05]. The cascade of anti-inflammatory cytokine at this group of patients starts the main mechanism of development of disease where IL-6 stimulates development of proteins of inflammation's sharp phase in liver, in particular C-reactive protein and fibrinogen whose contents exceeded reference values respectively by 2.9 times and by 1.9 times [PL 0.05].

During the analysis of the indicators characterized by activity of free radical oxidation in sick RA patients with an anemia and H. Pylori infection, an increase of level of a malondialdehyde erythrocyte membranes by 2.7 times is revealed when comparing with healthy people.

The complex of biochemical and immunological damages is followed by changes of level of a middle molecular pool in plasma and erythrocytes. The increase of concentration of pool middle molecules of the average size in plasma and erythrocytes on average by 2.7 times and by 2.6 times, respectively [PL 0.05], it was revealed, which allowed to state a development of a syndrome of endogenous intoxication in patients of the III group.

**CONCLUSION**

We concluded that several endogenous pathological factors, such as TNF-α, C-reactive protein, fibrinogen, malondialdehyde were determined as the reason of system inflammatory reaction in patients with rheumatoid arthritis. Analyzing all set of the changes given above, it is possible to make a pre-conclusion that 3 groups of changes described by us are characterized, according to literature, by the system inflammatory reaction and whose initiation begins with a syndrome of
endogenous intoxication of inflammatory and autoimmune character.

REFERENCES