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Characteristic Features of Biochemical Indicators of Mixed Saliva in Patients with Chronic Recurrent Aphthous Stomatitis

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Chronic recurrent aphthous stomatitis (CRAC) is a chronic disease of the oral mucosa, characterized by periodic remissions and exacerbations with the eruption of aft. According to WHO, it affects up to 20% of the population. Currently, most scientists are inclined to the leading role of the immune system in the pathogenesis of the disease. It has been established that with increasing severity of the disease T-suppression of immunity increases, which is characterized by a decrease in the number of T-lymphocytes and their functional activity. The increase in the number of T-suppressor cells accompanied by a decrease in the number of T-helper cells. The severity and duration of the disease correspond to the severity of the sensitization of the body with these antigens. The work was carried out based on scientific-educational practical dental center at the Bukhara State Medical Institute of Therapeutic Dentistry. A clinical examination of 67 patients aged 25–35 years with chronic recurrent aphthous stomatitis was conducted, 14 healthy individuals were included in the control group.

Keywords: Stomatitis; antigens; T cells.

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1. INTRODUCTION

Currently, there are quite a lot of diverse data on the problem of chronic recurrent aphthous stomatitis (CRAC) research, including the role of the infectious factor in its development [1]. There are neurogenic, immune, infectious and allergic theories of its origin [2]. Several authors note the importance of gastrointestinal pathology in the etiology of chronic recurrent aphthous stomatitis [3]. Other scientists favor endocrine theory or the leading role of immunological reactivity and body resistance [4]. However, the etiology and pathogenesis of this disease are still not fully understood, and patients continue to suffer from frequent and poorly treatable relapses. Also, according to the observations of domestic and foreign scientists, relapses of recurrent aphthous stomatitis are often associated with some provoking factors, including an infectious nature [5]. All these questions now require clarification using complex and fundamental methods. The etiology and pathogenesis of chronic recurrent aphthous stomatitis are not completely understood. It has been established that a significant role in the pathogenesis of chronic inflammatory processes belongs to the state of microbiocenosis of the oral mucosa [2,3,6,7,8,9]. Its participation in the processes of metabolism, synthesis of vitamins, the formation of the immune status and nonspecific resistance has been proven. Clinical and experimental data indicate the role of gastrointestinal pathology and liver disease in the chronic recurrent aphthous stomatitis pathogenesis [1,4,10,11,12]. The issue of the allergic genesis of the disease is widely discussed [5,13]. At the same time, the problem of free radical processes and antioxidant protection in saliva in this pathology remains poorly understood. It is known that violations of the immunological and free radical status can affect the course and prognosis of chronic diseases of the oral mucosa [14,9]. In this regard, the study of the pathogenetic mechanisms of chronic recurrent aphthous stomatitis is an important task of modern dentistry [15].

The purpose of the study: To determine to change features in biochemical parameters of blood and oral fluid in patients with chronic recurrent aphthous stomatitis.

2. MATERIALS AND METHODS

The work was carried out based on scientific-educational practical dental center at the Bukhara State Medical Institute of Therapeutic Dentistry. A clinical examination of 67 patients aged 25–35 years with chronic recurrent aphthous stomatitis was conducted, 14 healthy individuals were included in the control group. The total blood count was analyzed, the immune status was assessed by the total number of leukocytes and the leukocyte formula using a unified counting method in the counting chamber. Determination of serum IgA, IgM, IgG was performed according to the method of Mancini G. et al. (1965) using monospecific anti-IgA sera, IgM, IgG. Besides, they carried out leukocytes quantitative assessment of the phagocytic activity with latex in combination with the definition of the phagocytic index of the Hamburger, the CEC (V. Gashkov method). To determine the levels of α-interferon and tumor necrosis factor, ELISA was used. To determine the biochemical parameters used analyzer biochemical automatic Mindy. The Rutberg method was used to determine the content of fibrinogen. The unified method for the reaction with acetic anhydride (Ilka method) was used to determine the content of total cholesterol in serum (used KFK-2MP). Alpha-cholesterol was measured at KFK-2MP. The serum level of triglycerides was determined by an enzymatic colorimetric method (the triglycerides of the DDS, produced by Diacon-DS, were used in the reagent kits). The method of Iendrachik (colorimetric diazomethod) was used to determine the content of bilirubin and its fractions in blood serum. The activity of alanine aminotransferase (ALAT) - by the unified colorimetric dinitrophenylhydrazine method of the Reitman-Frenkel method (the “Lachem” reagent kits were used). Aspartate aminotransferase (ASAT) activity - by a unified method according to an optimized optical test (the “Lachem” kits were used); serum alpha-amylase activity - by a unified aminoclastic method with a resistant starch substrate (Karavey method) (a thermostat and a KFK-2MP photoelectric colorimeter, Lachem reagents were used), plasma sialic acid content was determined by the unified resorcinol method. The method of Huergo and Popper was used for the thymol test. The content of beta-lipoproteins in serum was determined by the turbidimetric method of Burstein and Samaya; serum chlorine ions - by the mercurimetric method with diphenylcarbazone indicator. The urea content was determined by the diacetyl monooxime method (the “Diasys” reagent kits were used); creatinine - by Popper et al. (Yaffe color reaction). The serum uric acid content was determined by the Trived method modified by Trinder, total serum calcium by the photometric

method (Lachem reagent kits were used); inorganic phosphorus - the method of S.N. Fiske at L. Subbarovv (used Olvex Diagnosticum reagent kits).

Study of the biochemical and immunological parameters of the oral fluid. The determination of the level of sialic acids in the oral fluid was performed by the method of E.L. Hess et al.; alkaline phosphatase activity - by the method of Bessey, Lowry, Brock; amounts of total calcium - by color reaction with o-creosolphthalein complexone (o-CPK); the concentration of inorganic phosphorus - method S.N. Fiske at L. Subbarow. Conducted a study of the level of secretory immunoglobulin A (SIgA), as well as the coefficient of balance factors of local protection (Keb.), Developed by VG Dorofaychuk and N. And. Tolkacheva et al. (1987). Determination of secretory sIgA and serum immunoglobulins (IgG, IgA) in the oral fluid was performed by radial immunodiffusion (RID) in a gel — G. Mancini, A. Carbonara (1965) using the methodological recommendations of E.V. Chernohvostovoy, S.I. Golderman (1975). The determination of lysozyme in the oral fluid was performed using the photo-neofelometric method (VG Dorofeychuk, 1968).

Statistical processing of the obtained results was carried out using the methods for assessing the reliability of differences in results, ways of variation statistics, autocorrelation method using standard methods and correlation analysis. Analyzing the obtained results was performed on a computer using Microsoft Office applications (Excel), a statistical software package.

3. RESULTS AND DISCUSSION

From 2015 to 2017, among 418 patients with dental pathology, 80 patients (46 women and 34 men) aged from 18 to 49 years who had chronic recurrent aphthous stomatitis (main group) were identified. The comparison group consisted of 20 conditionally healthy patients (11 women and 9 men) of the same age. The average age of manifestation of the disease as a whole was 33.0 ± 3.7 years, and the duration of the disease was 4.5 ± 3.7 years.

The diagnosis of chronic recurrent aphthous stomatitis was established based on anamnesis and a characteristic clinical picture of the disease. Particular attention was paid to the condition of the oral cavity: The presence of damaged teeth, sharp edges of the teeth, amalgam fillings; prostheses made of dissimilar metals, assessed the quality of orthopedic structures and orthodontic appliances.

The level of caries activity was estimated by the method of P. A. Leus (1990). The state of oral hygiene was determined by the OHI-S (DI-S) index according to J. C. Green, J. R. Vermillion (1964). The assessment of the prevalence and intensity of damage to periodontal tissues was carried out according to the periodontal index Russel A. (1956). Also, more pronounced and widespread damage to periodontal tissues was found in patients with chronic recurrent aphthous stomatitis (periodontal index 4.65 ± 0.09 versus 2.25 ± 0.06 points).

Along with traditional clinical and dental methods, to establish chronic recurrent aphthous stomatitis's pathogenetic mechanisms of the development, special laboratory studies of unstimulated mixed saliva were carried out - determination lipid peroxidation intensity, antioxidant protection. The determination of lipid peroxidation intensity was carried out according to the concentration of hydroperoxides by the method of V. B. Gavrilova et al. (1983), malonic dialdehyde (MDA) and the general antioxidant activity of unstimulated mixed saliva by the method of G.I. Klebanov et al. (1985). To determine the content of MDA, a spectrofluorimetric method was used, with the help of which a colored complex formed by the reaction of MDA with thiobarbituric acid was investigated (Gavrilov VB, Gavrilova AR, Mazhyav LN, 1987).

Clinical features of chronic recurrent aphthous stomatitis in the examined patients. In 80% of cases, chronic recurrent aphthous stomatitis was diagnosed with discomfort, pain when eating and talking. In patients with chronic recurrent aphthous stomatitis, the following clinical manifestations are more often observed ($p < 0.001$): Regional lymphadenitis (80%), Mikulich's aphtosis (77%), simultaneous appearance of aft in different areas of the oral mucosa (78%), swelling of the oral mucosa (64%), 89% - for the presence of "ulcers" in the oral cavity, 5% - for dryness in the oral cavity. 37% of patients noted the presence of similar complaints previously, 63% of patients had complaints about the first time. The intensity of the pain syndrome depended mainly on the number of lesion elements and localization. On examination, oral aphthae, soft to the touch, painful on palpation, located on the background of a hyperemic spot, covered with fibrinous bloom were found. Some edema of the oral

mucosa was found in 54% of patients, at the same time, the color was pale pink, in 46% of the surrounding oral mucous membrane was not changed. 57% of patients noted increased salivation, 1% - dryness in the oral cavity. 47% of patients had 1-2 single aphthae 3-10 mm in diameter, 53% of patients - 2-3 sharply painful aphthae when touched with infiltration at the base, 5-11 mm in diameter. In 5% of cases, changes in the general state of the organism were noted.

The results of a clinical blood test revealed leukocytosis, lymphocytosis, and monocytosis in patients with chronic recurrent aphthous stomatitis, which indicated signs of chronic inflammatory processes presence. Patients with chronic recurrent aphthous stomatitis and urogenital infection differed most strongly in the amount of IgA and IgM in the blood. On average, in patients with chronic recurrent aphthous stomatitis, the content of IgA and IgM exceeded the upper value of the normal value in 34% of women. The average IgM values are 335.7 ± 6.9 g / l ($p < 0.005$) and 246.7 ± 14.8 g / l, ($p < 0.004$). In the majority of patients with chronic recurrent aphthous stomatitis, we observed immunological signs of chronic inflammation. In addition, the prevalence and severity of allergic and autoimmune manifestations in individuals of these groups were also significantly higher ($p < 0.001$) compared with the control. It is known that with many autoimmune diseases there is a change in IgA levels. We found that there is a significant positive correlation between the change in IgA and an increase in the number of circulating immune complexes (CIC) above 90 units (i.e. above normal values). In patients with chronic recurrent aphthous stomatitis, an activated test with NST (with nitro-blue tetrazolium) was determined, which makes it possible to determine the oxygen-dependent bactericidal mechanism of phagocytes, or rather, its functional reserve. In patients with chronic recurrent aphthous stomatitis, there was a decrease in the indices of activated NBT test compared to the norm ($p<0.05$).

Thus, indices values are on the part of the immune system, indicating possible chronicity of inflammation, as well as the preservation of the autoimmune process, as indicated by the reduced phagocytic activity of neutrophils, were found in patients with chronic recurrent aphthous stomatitis.

Conducted determination of natural factors protection state, the status of cytokine profile indicators (TNF) There was a significant increase in the number of TNF in the serum compared with the values in the control group. These changes are not surprising due to the presence of the virus and the activation of anti-inflammatory processes in the body of the examined patients. The increase in TNF in the serum in some cases is accompanied by a significant production of cytokines by viruses, in turn, blocking the host cytokine receptors. At the same time, there was a significant increase in the mean values of TNF-α (50.8 ± 5.7 pg/ml; $p < 0.05$), compared with values in healthy individuals (24.7 + 1.3 pg/ml). A statistically significant decrease in serum lysozyme concentration was found in patients with chronic recurrent aphthous stomatitis.

In patients with chronic recurrent aphthous stomatitis, the quantitative content of IgA and IgM in the oral fluid was increased when compared with the control group of patients; on the contrary, the level of total calcium ion, sialic acids, inorganic phosphorus, sIgA, lysozyme, and alkaline phosphatase activity was significantly reduced.

Correlation study results revealed a reliably highly reliable relationship between the immunological and biochemical characteristics of the oral fluid during. All of the above indicates the presence of violations of biochemical and immunological processes in the oral fluid during chronic recurrent aphthous stomatitis.

With chronic recurrent aphthous stomatitis, levels of total protein, the percentage of alpha-2 globulins and gamma-globulins are significantly higher, and the fractions of albumin, alpha-1-globulins, and beta-globulins are significantly reduced compared with the control. Elevated levels of a2 globulin in women with chronic recurrent aphthous stomatitis may be associated with inflammation, autoimmune and rheumatic diseases. A significant increase in the activity of ALAT, ASAT, acid phosphatase was also noted at, while alkaline phosphatase activity and alpha-cholesterol levels were significantly lower than in the control group. For chronic recurrent aphthous stomatitis, an increase in total blood protein levels is typical, which averaged 79.21 ± 1.3 g / l, which is significantly ($p < 0.01$) higher than the control (70.92 ± 2.47 g / l), which is typical of inflammatory processes. It was shown that, in contrast to the control group, patients with HRAC are characterized by a high level of bilateral hereditary burden of somatic diseases (78.8% versus 42.5%), significant differences in the

incidence of such concomitant pathology as diseases of the digestive organs (87.5% versus 47, 5%), the nervous system (73.8% versus 25%), diseases of the endocrine system (51.3% versus 22.5%), allergic diseases (40% versus 5%), diseases of the blood and blood-forming organs (75% against 2.5%). In patients with XRAS, various degrees of oral dysbacteriosis were observed in 77 (96.3%) cases.

The most common cause of exacerbation of the disease were allergic reactions (41.3%), acute infectious diseases (37.5%), relapses of chronic diseases (35%) and various stressful situations (40%).

As a result of a biochemical study of mixed saliva in patients with CRAC, changes in individual indicators of free radical oxidation were found. A significant increase ($p < 0.05$) was observed in patients with XRAS compared with the control group, the content of primary lipid peroxidation products - hydroperoxides (2.16 ± 0.03 versus 1.18 ± 0.01 rel. Units/ml) and secondary - malondialdehyde (1.27 ± 0.13 versus 0.24 ± 0.01 moll/ml. pl.). The antioxidant activity of saliva was reduced - 59.2 ± 0.04% in the main group and 15.4 ± 0.05% in the comparison group. Concerning the concentration of hydroperoxides (HP), we did not observe an intensive increase in them. Mean values exceeded similar data in the comparison group (1.45 ± 0.03 versus 1.35 ± 0.03 rel. Units/ml), but these differences were not significant, $p > 0.05$. Analysis of the mean values of the antioxidant activity of saliva according to these clinical groups showed a decrease in $p > 0.05$.

An intensive increase in the level of MDA in the saliva was established as the duration of the disease increased. So, if with the duration of XRAS less than one year, the average values of MDA (0.39 ± 0.01 nmol/ml. Pl.) Slightly differ from those in the control group (0.27 ± 0.01 nmol/ml. Pl.) then already with the duration of the disease from 1 year to 3 years they (0.68 ± 0.02 nmol/ml. pl.) exceed the values of the control group by 2 times and are significantly higher.

The average level of MDA in the saliva of patients with PACER with a disease duration of 3 to 5 years (1.31 ± 0.11 nmol/ml.) Exceeded control values by 4 times, and with a duration of more than 5 years (1.38 ± 0, 11 nmol/ml .pl.) - 6.8 times.

Increasing the concentration of HP with an increase in the duration of the disease was less intense. With a disease duration of less than 1 year and from 1 year to 3 years, the mean values of SE (1.47 ± 0.04 and 1.41 ± 0.03 rel. Units/ml) practically did not differ from those in the control group (1, 35 ± 0.03 rel. Units/ml). In patients with a longer history of the disease, the concentration of HP in saliva was significantly higher than in the control group and in previous groups. So, in the group of patients with a disease duration of 3 to 5 years, it was 2.31 ± 0.09 relative units/ml, and with a duration of more than 5 years - 3.05 ± 0.1 relative units / ml, that in 1.6 and 2.2 times, respectively, exceeded the similar indicators in the control group. It should be noted that a high direct correlation dependence of the MDA and GP indicators on the duration of the disease was obtained. The dynamics of the antioxidant activity of saliva in patients with HRAC with an increase in the duration of the disease was characterized by a tendency to decrease. In patients with a disease duration of fewer than 3 years, the AOA differed little from those in the control group (29.4 ± 0.05%): less than 1 year - 27.7 ± 0.3% and from 1 year to 3 years - 35.8 ± 0.07%. With further increase in the duration of the disease(over 3 years), there was a more significant decrease in AOA: from 3 to 5 years - 27.2 ± 0.06% and more than 5 years - 26.8 ± 0.12%. These changes were unreliable, ($p > 0.05$). However, when

Table 1. The results of the study of biochemical and immunological parameters of the oral fluid in patients with chronic recurrent aphthous stomatitis

Indicators of oral fluid	Control N=14	Chronic recurrent aphthous stomatitis
Alkaline phosphatase, mmol / hl	1,2 ±0,03	0,82 ±0,02*
Sialic acid, units	6,8 ±0,18	4,5±0,14*
Total calcium, mmol / l	4,97 ± 0,39	0,59±0,01*
Inorganic phosphorus, mol / l	8,23 ±0,42	2,7±0,39*
IgA, g / l	0,07 ±0,001	0,16±0,001*
IgM g / l	0.09 ±0,001	0,17±0.002*
Lysozyme,%	45.1 ±2,4	12.42±0,21*
sIgA, g / l	0,31 ±0,08	0.08±0.004*

** - statistically significant differences relative to control ($p < 0.05$)*

determining the correlation dependence of the AOA indicators on the duration of the disease, an inverse relationship was established with a very high correlation coefficient - 0.909.

It should be noted on the dependence of the activity of free radical processes in patients with CRAC on the predominance of one or another type of oral microflora. The most pronounced lipid peroxidation shifts were observed in the presence of Klebsiella and fungal flora.

Thus, in patients with CRAC, there are violations of free radical processes in the oral cavity, which are characterized by an increase in the intensity of the POL processes (malonic dialdehyde level, hydroperoxides) and inhibition of the antioxidant system (decrease in antioxidant activity). At the same time, the level of lipid peroxidation and antioxidant protection of saliva depends on the duration of the disease and the microflora on the oral mucosa.

4. CONCLUSION

1. In patients with recurrent aphthous stomatitis, the following clinical manifestations are more likely to occur ($p < 0.001$): regional lymphadenitis (80%), aftoz Mikulich (77%), simultaneous appearance of aft in different parts of the oral mucosa (78%), swelling of the mucous membrane oral cavity (64%), a high level of intensity of dental caries (PEC -0.37 + 0.06). The complex periodontal index was 1.96 ± 0.031, the OHI-S index was 2.14 ± 0.06.
2. With recurrent aphthous stomatitis, hyperproteinemia, hypoalbuminemia, hyper-a2globulinemia, ALAT, ASAT ($p < 0.05$) are significantly more often ($p < 0.01$). With RAC in the oral fluid, there is a decrease in the activity of alkaline phosphatase, the level of total calcium and lysozyme and sIgA.
3. It has been established that patients with chronic recurrent aphthous stomatitis are characterized by a significant level of bilateral hereditary burden of somatic diseases, a high frequency of such comorbidities as diseases of the digestive system, nervous system, allergic diseases, and blood diseases.
4. Chronic recurrent aphthous stomatitis is accompanied by impaired antioxidant in the oral cavity, which is manifested by an increase in the content of LPO primary products - hydroperoxides and secondary products - malondialdehyde, a decrease in the antioxidant activity of saliva, which correlates with the duration of the disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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