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Characteristic features of the biochemical indicators of mixed saliva in patients with chronic recurrent aphthosis stomatitis

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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

INTRODUCTION

At present, there is a lot of diverse data on the problem of studying chronic recurrent aphthous stomatitis (CRAS), including the role of the infectious factor in its development [1, 2]. There are neurogenic, immune, infectious and allergic theories of its origin [3]. A number of authors note the importance of gastrointestinal pathology in the etiology of CRAS [4]. Other scientists are inclined in favor of endocrine theory or the leading role of immunological reactivity and body resistance [5]. However, the etiology and pathogenesis of this disease are still not fully understood, and patients with CRAS continue to suffer from frequent and poorly treatable relapses. In addition, according to the observations of domestic and foreign scientists, recurrences of CRAS are often associated with some provoking factors, including infectious ones [2, 6]. All of these issues currently need clarification using complex and fundamental methods. The etiology and pathogenesis of chronic recurrent aphthous stomatitis are not fully understood. It has been established that a significant role in the pathogenesis of chronic inflammatory processes belongs to the state of the microbiocenosis of the oral mucosa [7, 8]. His participation in the processes of metabolism, vitamin synthesis, the formation of immune status and non-specific resistance has been proven. The role of gastrointestinal pathology and liver diseases in the pathogenesis of CRAS is evidenced by clinical and experimental data [9]. The allergic genesis of the disease is widely discussed [10, 11]. At the same time, the problem of free radical processes and antioxidant protection in saliva with 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 [12, 13]. In this regard, the study of the pathogenetic mechanisms of recurrence of CRAS is an urgent task of modern dentistry.

The purpose of this study is to determine the features of changes in the biochemical parameters of blood and oral fluid in patients with chronic recurrent aphthous stomatitis.

MATERIALS AND RESEARCH METHODS

The work was carried out on the basis ofscientific educational practical dental center at the Department of Therapeutic Dentistry, Bukhara State Medical Institute. A clinical examination of 67 patients aged 25-35 years with CRAS was conducted, 14 healthy individuals were included in the control group.

A general clinical blood test was analyzed, the immune status was assessed by the total number of leukocytes and leukocyte formula according to a unified method of counting in a counting chamber. Determination of serum IgA, IgM, IgG was carried out according to the method of Mancini G. et al., (1965) using monospecific serums against IgA, IgM, IgG. In addition, we performed a quantitative assessment of the phagocytic activity of leukocytes with latex in combination with the determination of the Hamburger phagocytic index, CEC (V. Gashkova method). ELISA was used to determine the levels of a-interferon and tumor necrosis factor a. To determine the biochemical parameters, an automatic biochemical analyzer Mindreywas used. The Rutberg method was used to determine the fibrinogen content. The unified method for the reaction with acetic anhydride (Ilk's method) was used to determine the total cholesterol content in blood serum (KFK-2MP was used). Alpha-cholesterol was measured on KFK-2MP. The level of triglycerides in the blood serum was determined by the enzymatic colorimetric method (the triglyceride reagent kits FS “DDS” of the company “Diacon-DS” were used). The Iendrashik method (colorimetric diazomethod) was used to determine the content of bilirubin and its fractions in blood serum. The activity of apaninaminotransferase (ALAT) - the unified colorimetric dinitrophenylhydrazine method of Reitman-Frenkel (used the reagent kits "Lahema"). The activity of aspartate aminotransferase (ASAT) - unified method according to the optimized optical test (used kits "Lahema"); serum alpha-amylase activity — by a unified aminoclastic method with a stable starch substrate (Karavei method) (a thermostat and a KFK-2MP photoelectrocolorimeter, Lahema reagent kits were used), and the content of sialic acids in blood plasma was determined by a unified resorcinol method. The Huergo and Popper method was used to conduct a thymol test. The content of beta-lipoproteins in serum was determined by the turbodimetric method of Burstein and Samaya; serum chlorine ions - by the Mercury method with diphenylcarbazone indicator. Urea content was determined by the diacetyl mono-oxime method (“Diasys” reagent kits were used); creatinine - by Popper et al. (Jaffe color reaction). Serum uric acid was determined by the Trivedi method, modified by Trinder, and total serum calcium by the photometric method (Lahema reagent kits were used); inorganic phosphorus - method S.N. Fiske at L. Subbarovv (used Olvex Diagnosticum reagent kits).

The study of biochemical and immunological parameters of the oral fluid. The determination of the level of sialic acids in the oral fluid was carried out by E.L. Hess et al.; alkaline phosphatase activity - by the method of Bessey, Lowry, Brock; the amount of total calcium - by color reaction with o-creosolphthaleincomplexon (o-KFK); the concentration of inorganic phosphorus - method S.N. Fiske at L. Subbarow. A study was made of the level of secretory immunoglobulin A (SIgA), as well as the balance factor of local protection factors (Keb.), Developed by V.G. Dorofeychuk and N.I. Tolkacheva et al. (1987). Determination of secretory sIgA and serum immunoglobulins (IgG, IgA) in the oral fluid was carried out by the method of radial immunodiffusion (RID) in a gel - G.Mancini, A.Carbonara (1965) using the guidelines of E.V. Chernokhvostova, S.I. Golderman (1975). Determination of lysozyme in the oral fluid was performed using the photonephalometric method (V.G. Dorofeychuk, 1968).

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

RESEARCH RESULTS AND DISCUSSION

Between 2015 and 2017, among 418 patients with dental pathology, 80 patients (46 women and 34 men) aged 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 the 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 HRAS was established on the basis of anamnesis and the characteristic clinical picture of the disease. Particular attention was paid to the condition of the oral cavity: the presence of decayed teeth, sharp edges of the teeth, amalgam fillings; prostheses made of dissimilar metals evaluated the quality of orthopedic structures and orthodontic appliances.

The level of caries activity was evaluated according to the method of P.A. Leus (1990). The state of oral hygiene was determined by the OHI-S index (DI-S) according to J.C. Green, J.R. Vermillion (1964).

Assessment of the prevalence and intensity of periodontal tissue lesions was carried out according to the periodontal index Russel A. (1956). In addition, a more pronounced and widespread lesion of periodontal tissues was found in patients with CHRAS (periodontal index 4.65±0.09 versus 2.25±0.06 points).

Along with traditional general clinical and dental methods, special laboratory studies of unstimulated mixed saliva were carried out to determine the pathogenetic mechanisms of the development of CPAS - determining the intensity of lipid peroxidation, antioxidant protection. The determination of the intensity of lipid peroxidation was carried out by the concentration of hydroperoxides according to the method of V.B. Gavrilova et al. (1983), malondialdehyde (MDA) and the total antioxidant activity of unstimulated mixed saliva according to the method of G.I. Klebanova. et al. (1985) [14, 15, 16]. To determine the content of MDA, we used the spectrofluorimetric method, with which we studied the colored complex formed by the reaction of MDA with tiabarbituric acid [17].

Clinical features of CRAS in the examined patients. In 80% of cases, CHRAS was diagnosed with discomfort, pain during eating and talking. The following clinical manifestations are more frequently observed in patients with CRAS ($p<0.001$): regional lymphadenitis (80%), Mikulichaphthosis (77%), simultaneous occurrence of aphthae in different parts of the oral mucosa (78%), and swelling of the oral mucosa (64%), 89% - for the presence of "ulcers" in the oral cavity, 5% - for dry mouth. 37% of patients noted similar complaints earlier, in 63% of patients complaints arose for the first time. The intensity of the pain syndrome depended mainly on the number of elements of the lesion and localization. When examining the oral cavity, aphthae were found, soft to the touch, painful on palpation, located against a hyperemic spot, covered with fibrinous coating. 54% of patients showed some swelling of the oral mucosa (MOP) the color was pale pink; in 46%, the surrounding SRS was not changed. 57% of patients noted increased salivation, 1% - dry mouth. In 47% of patients, 1-2 single aphthae of 3-10 mm in diameter were found, in 53% of patients, 2-3 were sharply painful when aphthas were touched with infiltration at the base, 5-11 mm in diameter. In 5% of cases, changes in the general condition of the body were noted.

The results of a clinical blood test revealed leukocytosis, lymphocytosis and monocytosis in patients with CRAS, which indicated signs of the presence of chronic inflammatory processes in the examined patients. Patients with CRAS and urogenital infection were the most widely scattered in the amount of IgA and IgM in the blood. On average, in patients with CRAS, the content of IgA and IgM exceeded the upper value of the norm 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 most patients with CRAS, we observed immunological signs of chronic inflammation. In addition, the prevalence and severity of allergic and autoimmune manifestations in individuals of these groups was also significantly higher ($p<0.001$) compared with the control. In many autoimmune diseases, it is known that IgA levels change. We found that there is a significant positive correlation between changes in IgA and an increase in the number of circulating immune complexes (CECs) above 90 units (i.e., above normal values). In patients with CRAS, an activated test with HCT (with nitro-blue tetrazolium) was determined, which makes it possible to determine the oxygen-dependent mechanism of bactericidal activity of phagocytes, or rather, its functional reserve. In patients with CRAS, a decrease in the values of the activated HCT test was detected compared with the norm ($p<0.05$).

Thus, indicators of the immune system were found in patients with CRAS, indicating a possible chronic inflammation, as well as the preservation of the autoimmune process, as indicated, in particular, by decreased phagocytic activity of neutrophils.

The state of natural defense factors, the state of cytokine profile indicators (TNF-a) were determined. A significant increase in the amount of TNF-a in serum was noted in comparison with the values in the control group. These changes are not surprising in connection with the presence of the virus and the activation of anti-inflammatory processes in the body of the examined patients. An increase in serum TNF-α in some cases is accompanied by a significant production of cytokines by the viruses, which in turn block host cytokine receptors. At the same time, there was a significant increase in the average values of TNF-α (50.8±5.7 pg/ml; $p<0.05$), compared with the values in healthy individuals (24.7+1.3 pg/ml). A statistically significant decrease in the concentration of lysozyme in serum was revealed in patients with CRAS.

In patients with CRAS, 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 were significantly reduced.

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Table 1: The results of a study of biochemical and immunological parameters of the oral fluid in patients with CRAS

Indicators of the oral fluid	Control N=14	CRAS
Alkalinephosphatase, mmol/hr	1,2 ±0,03	0,82 ±0,02*
Sialicacids, units	6,8 ±0,18	4,5±0,14*
Totalcalcium, mmol/l	4,97 ± 0,39	0,59±0,01*
Inorganicphosphorus, 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).

The results of the study of correlation relationships revealed reliably highly reliable relationships between the immunological and biochemical characteristics of the oral fluid during CRAS. All of the above indicates the presence of violations of biochemical and immunological processes in the oral fluid with CRAS.

With XPA, the 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 to the control. Increased levels of a2-globulins in women with CRAS may be associated with inflammation, autoimmune and rheumatic diseases. A significant increase in the activity of ALAT, ASAT, and acid phosphatase was also noted with XPA, while alkaline phosphatase activity and alpha-cholesterol levels were significantly lower than in individuals of the control group. An increase in the levels of total blood protein is typical for HRAS, which averaged 79.21±1.3 g/l, which is significantly (p<0.01) higher compared to the control (70.92±2.47 g/l), which is typical for inflammatory processes.

It was shown that, in contrast to the control group, patients with CHRAS are characterized by a high level of bilateral hereditary burden of somatic diseases (78.8% versus 42.5%), significant differences in the frequency of such a concomitant pathology as digestive diseases (87.5% versus 47, 5%), nervous system (73.8% versus 25%), endocrine system diseases (51.3% versus 22.5%), allergic diseases (40% versus 5%), blood and blood-forming organs diseases (75% against 2.5%). In patients with CRAS, various degrees of dysbiosis of the oral mucosa were observed in 77 (96.3%) cases.

The most common causes 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 CRAS, changes were found in individual indicators of free radical oxidation [18]. A significant increase (p <0.05), in comparison with the control group, in the content of primary lipid peroxidation products - hydroperoxides (2.16±0.03 versus 1.18±0.01 rel.units / ml) was characteristic for patients with CRAS and secondary malondialdehyde (1.27±0.13 versus 0.24±0.01 nmol/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 [19]. As for the concentration of hydroperoxides (GPs), we did not notice their intense rise. The average values exceeded the similar data in the comparison group (1.45±0.03 versus 1.35±0.03 relative units/ml), but these differences were not significant, p>0.05. Analysis of the average antioxidant activity of saliva for these clinical groups showed a decrease in p> 0.05.

Particular interest was the comparison of lipid peroxidation and antioxidant protection with the duration of the disease.

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

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

An increase in the concentration of GP with an increase in the duration of the disease was less intense [14]. With a disease duration of less than 1 year and from 1 year to 3 years, the mean GP values (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.unit/ml). In patients with a longer history of the disease, the concentration of GP in saliva was significantly higher than in the control group and than in the 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, which was 1.6 and 2.2 times, respectively, higher than the similar indices in the control group. It should be noted that a high direct correlation dependence of MDA and GP indices on the duration of the disease was obtained. The dynamics of the antioxidant activity of saliva in patients with CRAS with an increase in the duration of the disease was characterized by a downward trend. In patients with a disease duration of less than 3 years, AOA did not differ much 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 a further increase in the duration of the disease (over 3 years), a more significant decrease in AOA was noted: from 3 to 5 years - 27.2±0.06% and more than 5 children - 26.8±0.12%. These changes were unreliable, (p>0.05). However, in determining the correlation dependence of AOA parameters on the duration of the disease, an inverse relationship was established with a very high correlation coefficient of 0.909.

It should be noted on the dependence of the activity of free radical processes in patients with CPAS on the predominance of a particular type of microflora of the oral cavity. The most pronounced changes in lipid peroxidation were observed in the presence of Klebsiella and fungal flora.

Thus, in patients with CPAS, free radical processes in the oral cavity are observed, which are characterized by an increase in the intensity of LPO processes (level of malondialdehyde, hydroperoxides) and inhibition of the antioxidant system (decrease in antioxidant activity). The level of lipid peroxidation and antioxidant protection of saliva depends on the duration of the disease and the microflora on the oral mucosa.

CONCLUSIONS

1. In patients with CRAS, the following clinical manifestations are significantly more likely (p<0.001): regional lymphadenitis (80%), Mikulichaphthosis (77%), the simultaneous appearance of aphthae in different parts of the oral mucosa (78%), and swelling of the mucous membrane oral cavity (64%), a high level of tooth decay intensity (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 CRAS, significantly more often (p<0.01), hyperproteinemia, hypoalbuminemia, hyper-a2 globulinemia, ALAT, ASAT (p<0.05) are found. With CRAS 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 incidence of such concomitant diseases as diseases of the digestive system, nervous system, allergic diseases and blood diseases.
4. Chronic recurrent aphthous stomatitis is accompanied by violations of the antioxidant in the oral cavity, which is manifested by an increase in the content of lipid peroxidation products of primary - hydroperoxides and secondary products - malondialdehyde, a decrease in the antioxidant activity of saliva, which correlate with the duration of the disease.

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