ORIGINAL ARTICLE

CONTENTS

The state of systemic immunity in congenital cleft lip and palate patients with diseases of oral cavity tissues

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ABSTRACT

Aim: To determine the state of dental health and the state of systemic immunity in patients in congenital cleft lip and palate patients.

Materials and Methods: The dental status and immunologic tests of 74 patients age 8-18 years old with congenital cleft lip and palate was analyzed: 43 children with unilateral and 31 children with bilateral complete combined cleft lip, alveolar process, hard and soft palate.

Results: Indicators of the prevalence and intensity of the caries process in patients with congenital congenital complete cleft lip, alveolar process, hard and soft palate were high, especially in children with bilateral cleft lip and palate - the decompensated course of caries was determined in 41.93% patients, with unilateral - 23.25%. Chronic catarrhal gingivitis was the most common in both groups of patients - the average severity of gingivitis prevailed - 51.16% with congenital unilateral cleft lip and palate and 51.61% - with bilateral. Atopic cheilitis, glossitis and chronic recurrent aphthous stomatitis were common. This patients have significant changes in the cellular chain of the immune system with a deficiency of the main phenotypes of lymphocytes - CD4+ CD8+ and inflammatory bacterial changes in blood serum.

Conclusions: Patients of unilateral and bilateral complete combined cleft lip, alveolar process, hard and soft palate have significant changes in the dental status and in the cellular chain of the immune system. The level of manifestation of these changes is directly proportional to the extent of localization of the pathology - unilateral or bilateral.

KEY WORDS: caries, congenital defects, cleft lip and palate, diseases of periodontal tissues, diseases of the mucous membrane of the oral cavity, immunological research

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INTRODUCTION

Orofacial clefts include a large group of congenital deformities with structural defects in the oral cavity and adjacent facial structures that occur in isolation, in combination, or as part of other malformations [1]. In Europe, the prevalence of cleft lip and palate is 1.55 cases per 1000 live births [2, 3]. A multifactorial model was proposed to explain the development of orofacial defects [4], about 20% of malformations are caused by genes, 10% by chromosomal mutations, and 70% by multifactorial origin [5, 6]. At the same time, several co-factors can contribute to the formation of congenital cleft lip and palate and aggravate the course of the disease; therefore, a comprehensive multidisciplinary care program is needed to ensure successful treatment outcomes for patients with congenital cleft lip and palate [7].

The leading method of treatment of congenital cleft lip and palate is surgical. But despite the improvement of the technique of surgical interventions, there is some uncertainty about the safety stages of surgical correction of congenital cleft lip and palate (including the suspension of planned operations). Because patients affected by congenital cleft lip and palate, suffer from a high degree of morbidity, in particular, infectious and inflammatory diseases of the oral cavity, respiratory tract and ENT organs (acute respiratory viral infections, acute bronchitis, acute pneumonia) and ENT organs (acute purulent adenoiditis). [8, 9, 10]. Thus, a retrospective analysis of the condition of children with congenital cleft lip and palate (n=339) showed that these children suffered annually more than 10 episodes of uncomplicated and complicated, as well as recurrent, acute respiratory viral infections with the duration of the acute period of the disease up to two weeks, which is a clinical indicator of immunocompromised status. In such cases, the leading diagnosis is secondary immune deficiency, which requires a review of the treatment approach. At the same time, children with bilateral congenital cleft lip and palate, even without cold symptoms, had a significantly higher incidence of perioperative respiratory complications (8.9%) than children with simple cleft lip (1.7%). The authors suggested that clinicians

should consider postponing primary plastic surgery for cleft lip and palate in infants with a suspected presence of a common cold [11].

Immunocompromised patients are prone to a variety of oral manifestations, including oral infections (eg, candidiasis, gingivostomatitis herpetic), aphthous ulcers, and severe periodontal disease, including aggressive periodontitis with premature tooth loss in children/adolescents, and this almost always indicates for the presence of an underlying systemic or local immunological disorder [12-15]. Thus, a clear association was found between severity of inflammation in the oral cavity and defects of local immune protection, which allowed the authors to predict the nature of the clinical course of chronic dental diseases in patients with congenital cleft lip and palate [16-18]. According to modern concepts, the functioning of the immune system and changes in the microbiome of the oral cavity are key

At the same time, despite numerous studies, the features of the functioning of the immune system in children with congenital cleft lip and palate are still being discussed, and in the scientific literature, only isolated data are given that reflect the state of systemic immunity in children with congenital cleft lip and palate. For example, it has been shown that in case of congenital cleft lip and palate, the physiological insufficiency of the immune system and its anatomical compromise lead to a sharp tension of the still immature homeostasis maintenance mechanism in these children [20].

In addition, babies with orofacial clefts are usually born underweight and with impaired immune function from growth retardation [21, 22], and the first stages of surgical treatment of congenital cleft lip and palate relate to physiological age-critical periods of the formation of the immune system [23, 24].

Clinical signs of immune deficiency in children with congenital cleft lip and palate give grounds to suspect defective functioning of the immune system. It is obvious that the solution to this problem and the determination of further therapeutic tactics require a complex pathogenetic approach, which includes an assessment of the features of the functioning of the immune system and, based on the obtained data, the development of new immunotherapeutic approaches aimed at correcting the detected disorders.

Undoubtedly, data on the state of innate and adaptive immune system have an important prognostic value for the successful rehabilitation of patients with congenital cleft lip and palate. Ambiguous, sometimes contradictory data from the scientific literature support the interest in evaluating the features of the functioning of the immune system in young patients with congenital cleft lip and palate.

AIM

To determine the state of dental health and the state of systemic immunity in patients in congenital cleft lip and palate patients.

MATERIALS AND METHODS

The dental status and immunologic tests of 74 children age 8-18 years old with congenital cleft lip and palate was analyzed: 43 children with unilateral complete combined cleft lip, alveolar process, hard and soft palate, and 31 children with bilateral complete combined cleft lip, alveolar process, hard and soft palate. All children were operated on in the Department of Reconstructive and Plastic Microsurgery at National Specialized Children's Hospital "OKHMATDYT" (Kyiv, Ukraine). The patients selected for this study underwent a clinical dental examination - determination of the prevalence and intensity of dental caries, the condition of periodontal tissues and the mucous membrane of the oral cavity. Informed consent in written form was obtained from all the parents for diagnostic studies and treatment methods. The study was conducted in accordance with the principles of bioethics set out in the World Medical Association Declaration of Helsinki - «Ethical Principles for Medical Research Involving Human Subjects» and «General Declaration on Bioethics and Human Rights» (UNESCO). The following subpopulations of T- and B-lymphocytes were determined as diagnosticum erythrocytic for the detection of human T-lymphocyte populations "Anti-CD 3", "Anti-CD 4", "Anti-CD 8", "Anti-CD 16", "Anti-CD 22", Ukraine, Kharkiv city, "Granum" - CD3 + lymphocytes (T cells); CD4 + lymphocytes (T-helpers); CD8 + lymphocytes (T-cytotoxic lymphocytes/suppressors); CD16 + lymphocytes (NK cells), CD22 + lymphocytes (B cells). The phagocytic activity of neutrophils was assessed by the method of determining the bactericidal activity of phagocytic cells (HST test). The study of the functional state of B-lymphocytes was carried out by determining the level of the main classes of serum immunoglobulins Ig G, Ig A, Ig M using immunoturbidimetric method and diagnostic reagent IgA 5+1, IgM 5+1, IgG 5+1 for vitro quantitative determination of IgA, IgM, IgG in blood serum by turbidimetric analysis (Dialab Produktion, Austria). The concentration of circulating immune complexes (CICs) in blood serum was determined by the immunoenzymatic colorimetric method of quantitative determination of CICs C1q in human serum or plasma (NovaTec Immunodiagnostics GmbH).

Data were analyzed with the statistical package IBM SPSS Statistics Base (version 22) and EZR. All results were considered statistically significant at a value of

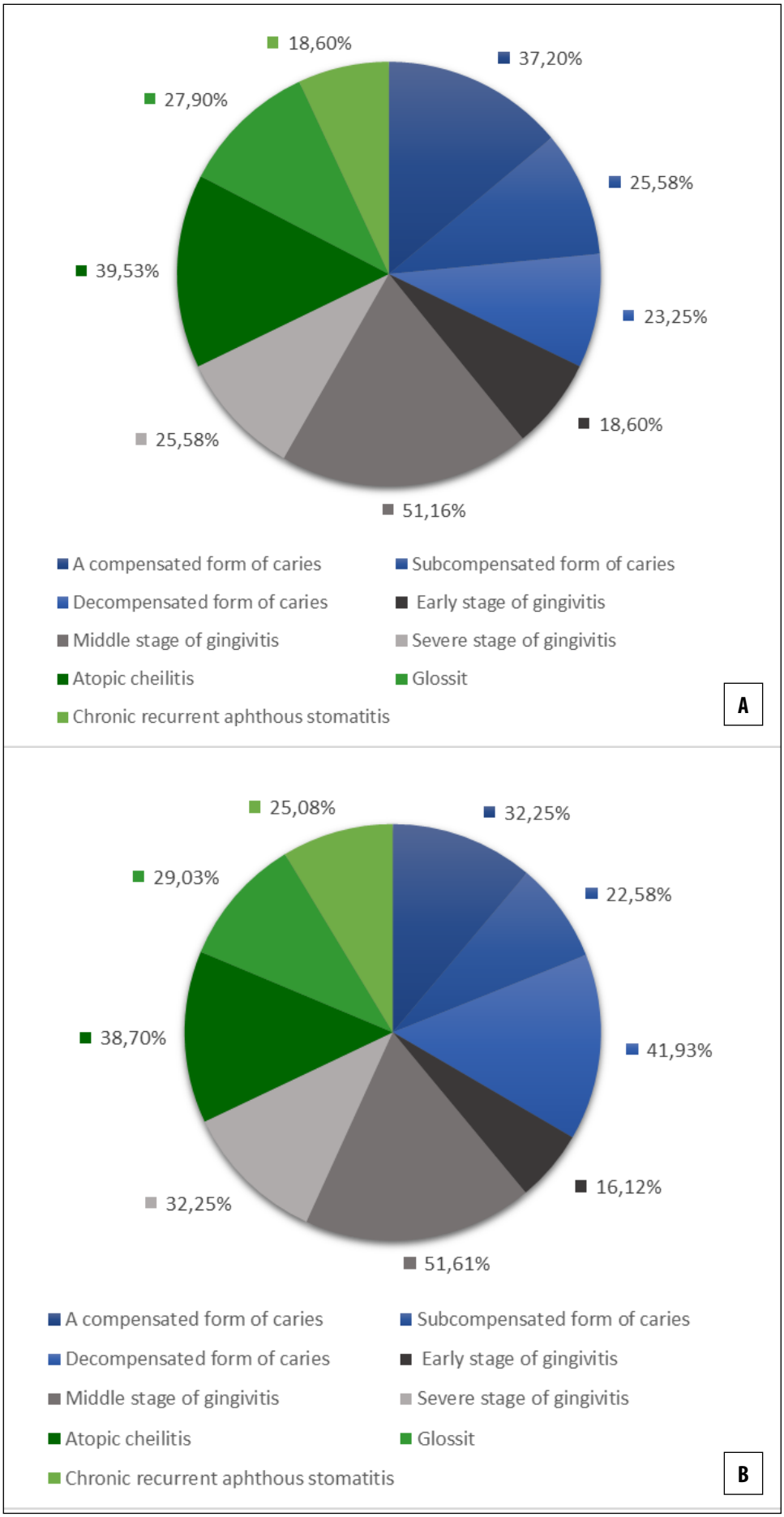

Fig. 1. The prevalence of the oral cavity diseases in children with congenital complete cleft lip, alveolar process, hard and soft palate: unilateral (a) and bilateral (b).

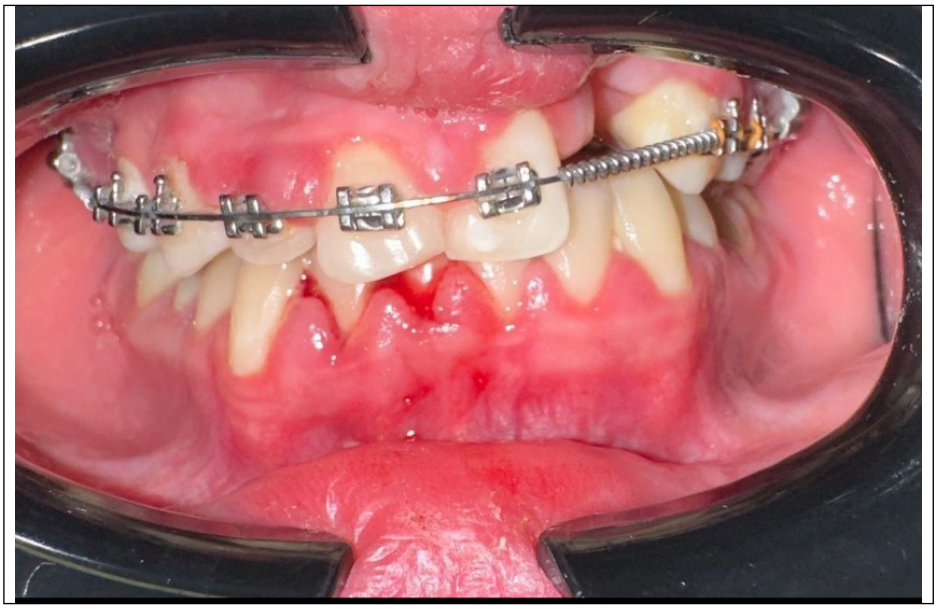

Fig. 2. Patient with congenital unilateral complete cleft lip, alveolar process, hard and soft palate.

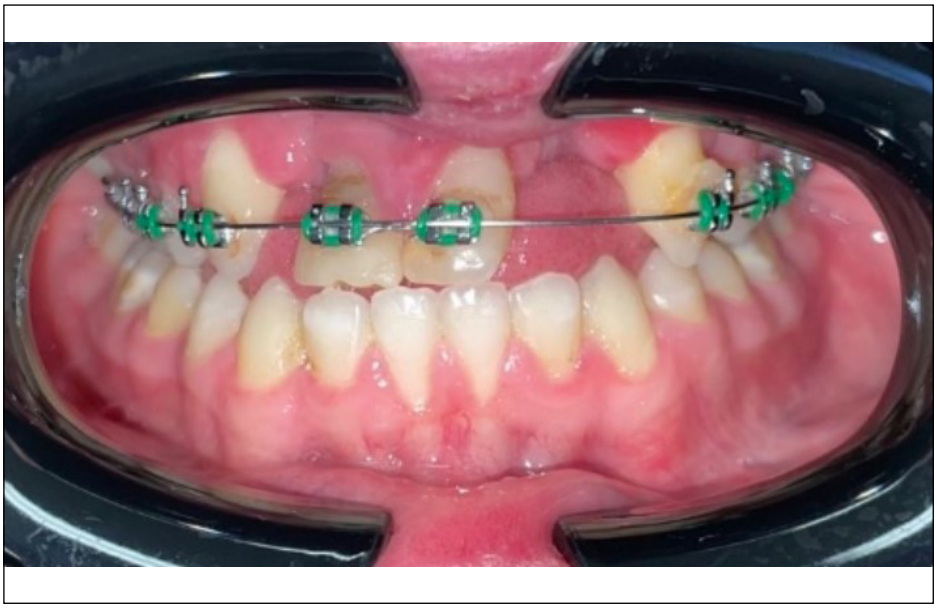

Fig. 3. Patient with congenital bilateral complete cleft lip, alveolar process, hard and soft palate.

$p<0.05$. Quantitative data are presented as mean (M) ± standard deviation (SD), unless otherwise stated. The normality of the data distribution was checked using the Shapiro-Wilk test.

RESULTS

Indicators of the prevalence and intensity of the caries process in patients with congenital congenital complete cleft lip, alveolar process, hard and soft palate were high, especially in children with bilateral cleft lip and palate - the decompensated course of caries was determined in 41.93% patients, with unilateral - 23.25%. Among the inflammatory processes in the periodontal tissues, chronic catarrhal gingivitis was the most common in both groups of patients. The clinical dental examination of the patients determined that the average severity of gingivitis prevailed in the examined patients - 51.16% with congenital unilateral cleft lip and palate and 51.61% - with bilateral. Among the diseases of the mucous membrane of the oral cavity atopic cheilitis, glossitis and chronic recurrent aphthous stomatitis were more common than others (Fig. 1-3).

Patients of both groups underwent an immunological examination, the purpose of which was to identify disorders in the cellular and humoral links of the immune system, as well as possible primary defects of immunity. It is known that primary immunodeficiency diseases can be accompanied by other malformations, including cleft of the hard palate and lip [25]. Among the patients examined by us, there were no patients with signs of primary cellular or humoral immunodeficiency; however, we observed significant changes in the number of the main cellular subpopulations.

The analysis of indicators of the immune system in patients with bilateral combined lesions showed that the total number of leukocytes corresponded to normative indicators. However, it was observed relative lymphocytosis (Table 1).

Indicators of cellular immunity were probably reduced compared to patients with unilateral combined lesions. Thus, the relative number of CD4+ lymphocytes was lower by 21.8% ($p<0.05$), and CD8+ lymphocytes by 29.7% ($p<0.05$). At the same time, a high level of CD22+ lymphocytes was found - by 27% compared to patients in group 2 ($p<0.05$).

A study of the indicators of the immune system in patients with unilateral complete combined lesions showed that in this group of patients the total number of leukocytes was preserved, the relative number of lymphocytes improbably exceeded the indicator of the first group of patients by 12.3%. It should be noted that the content of CD4+lymphocytes, CD8+lymphocytes was probably higher than the similar indicators of the first group, but decreased in comparison with the normative values. Compared to the patients of the first group was found lower relative content of B-cells, which may be caused by relatively smaller inflammatory manifestations in the periodontium and mucous membranes compared to the bilateral combined lesion.

In our opinion, these changes are caused by a long-term inflammatory process in the mucous membrane with long-term persistence of highly pathogenic pathogens. These pathogenic microorganisms destroy periodontal tissues, affect the cellular link of the immune system and also secrete enzymes that cause in the progression of the inflammatory process.

A pronounced deficiency of both CD3+ lymphocytes and the main immunoregulatory subpopulations, namely T-helpers (CD4+ lymphocytes) and T-cytotoxic lymphocytes/suppressors (CD8+ lymphocytes) against the background of a normal total number of leukocytes is a sign of a long-term inflammatory process with decompensation immune response.

It is known that the immune system, like all regulatory systems of the body, necessarily reacts to all pathological processes. In those cases when the activation lasts for a long time or in the conditions of genetic and acquired defects in individual parts of the immune system, the infectious process develops regardless of the antigenic properties of the microorganism, acquires a chronic character, and has a tendency to steady progression [26].

Taking into account the pronounced changes on the part of mucous membranes of an inflammatory nature, the high percentage of detection of isolates of highly virulent pathogens during bacteriological examination was evaluated the concentration of C-reactive protein and procalcitonin in blood serum (Table 2).

In both groups investigating patients found a high level of these indicators that relative to normative values, which indicates an active inflammatory process of bacterial etiology and requires a long-term appointment of antibacterial drugs, taking into account the isolates of pathogens and their sensitivity.

In patients with bilateral combined cleft, the level of both indicators was significantly higher than in patients with unilateral lesions. In addition, also this group of patients has the highest percentage of decompensated forms of caries (41,93%), atopic cheilitis (38,7%) and moderately severe catarrhal gingivitis (51,61%). Combination of mucosal damage with decompensated caries against the background of a large area of damage that creates the conditions for the persistence of highly virulent pathogens, which cause a constant antigenic load on the immune system, and as a result, its "exhaustion" and a relative deficiency of the cellular immune response.

A significantly lower level of C-reactive protein and procalcitonin in the blood serum of patients in 2 group may be due to a smaller percentage of patients with a decompensated form of caries (23,25%) in this group and a relatively high percentage of detection of atopic cheilitis (39,53%) and glossitis (27,9%) in this group of patients. It is the presence of a chronic highly virulent polyresistant bacterial infection that causes a long-term increase in serum C-reactive protein and procalcitonin.

DISCUSSION

Scheuerle et al. in 24 patients with orofacial defects, including: congenital cleft lip and palate studied the existence of an immunological deficiency. Fresh blood samples were analyzed for age-matched immunoglobulin counts, T cells, B cells, and natural killer cells, as well as lymphocyte stimulation and response function.

All patients had certain disorders of the immune system. Seven had specific T-cell abnormalities, and three patients had abnormalities of all test categories. The obtained results indicate that patients with any orofacial defect have abnormalities in the immune system [27]. In 40% of 20 children with severe congenital facial defects had reduced B-cell counts, and 60% had reduced T-cell counts. Chemotaxis was reduced in polymorphonuclear leukocytes in 56% and mononuclear leukocytes in 75% of patients. According to the authors' conclusions, the association of immune abnormalities and congenital facial defects may be more common than previously thought [28].

It is known that after the contact of the immune system with a viral infection, an adequate response from T-lymphocytes is an increase in the number and activity of CD3+ and CD8+ T-cells, which provide specific antiviral immune protection. Inadequate response of CD3+ and

Table 1. The main indicators of the cellular link of immunity in patients with cleft palate (M±m)

Index	1 group	2 group	p
Leukocytes, x109/l	6,51±1,4	6,23±2,31	p>0,05
Lymphocytes, %	41,1±2,06	46,8±1,95	p>0,05
CD3+lymphocytes, %	41,3±1,75	45,7±2,31	p>0,05
CD4+lymphocytes,%	22,6±1,13	28,9±1,02	p<0,05
CD8+lymphocytes,%	20,3±1,16	28,9±1,14	p<0,05
CD4/CD8	1,12±0,11	1,34±0,12	p>0,05
CD22+lymphocytes,%	38,6±1,23	28,9±0,96	p<0,05
CD16+lymphocytes,%	10,9±0,86	13,1±0,83	p>0,05

Notes: p - the probability indicator difference between groups

Table 2. Serum concentration of pro-inflammatory markers in patients with cleft palate (M±m)

Index	1 group	2 group	p
C-reactive protein mg/l	40,1±2,28	20,5±1,68	p<0,05
Procalcitonin, ng/mL	1,05±0,09	0,82±0,06	p<0,05

CD8+ T-cytotoxic lymphocytes to viral antigens indicates defects in the functioning of antiviral immunity, which should be provided by the predominance of adaptive cytotoxic killer cells. The obtained results indicate that natural killer cells play an important role in the control of primary infection by eliminating infected B cells and enhancing the antigen-specific T-cell response by releasing immunomodulatory cytokines [29, 30]. It has been confirmed that in congenital orofacial defects there is a significant decrease in the number of natural killer cells in younger children and their activation in older children. Against the background of immunoregulatory imbalance, there is a decrease in the level of T-lymphocytes at the expense of T-helpers and an increase in the concentration of cytotoxic T-lymphocytes, as well as activation of the B-cell link of immunity. Which indicates the importance of studying the effect of cytokines and their corresponding immunoregulatory cells on the stimulation of the adaptive immune response, which is the most effective protective mechanism for eliminating infectious agents and inflammatory processes [3, 31, 32]. While studying the cytokine status was found that in patients with congenital cleft lip and palate has increased level of pro-inflammatory cytokines, which depends on the clinical form of the cleft. The greatest deviations observed in babies with congenital bilateral congenital cleft lip and palate. The marked changes in cytokine status led to the identification of secondary immunodeficiency in children, which requires immunomodulatory measures [33].

CONCLUSIONS

1. The clinical dental examination of the patients determined that the cariogenic situation is significantly worse in children with congenital complete cleft lip, alveolar process, hard and soft palate - the decompensated course of caries was determined in 41.93% patients. Chronic catarrhal gingivitis was the most common in both groups of patients and the average severity of gingivitis prevailed in congenital bilateral cleft lip and palate - 51.61%. Atopic cheilitis, glossitis and chronic recurrent aphthous stomatitis were more common than others among the diseases of the mucous membrane of the oral cavity.
2. Therefore, patients of unilateral and bilateral complete combined cleft lip, alveolar process, hard and soft palate have significant changes in the cellular chain of the immune system with a deficiency of the main phenotypes of lymphocytes - CD4+ CD8+ and inflammatory bacterial changes in blood serum. The level of manifestation of these changes is directly proportional to the extent of localization of the pathology - unilateral or bilateral.

REFERENCES

1. Impellizzeri A, Giannantoni I, Polimeni A, Barbato E, Galluccio G. Epidemiological characteristic of Orofacial clefts and its associated congenital anomalies: retrospective study. BMC Oral Health. 2019;19(1):290. doi: 10.1186/s12903-019-0980-5. DOI
2. Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Global Birth Prevalence of Orofacial Clefts: A Systematic Review. J Med Assoc Thai. 2015;98(7):S11- S21.
3. Reiser SC, Tellermann J, Akota I, Pilmane M. Profiling and characterization of localized cytokine response in congenital cleft affected lip tissue. Life (Basel). 2021;11(6):556. doi: 10.3390/life11060556. DOI

4. Schutte BC, Murray JC. The many faces and factors of orofacial clefts. Hum Mol Genet. 1999;8(10):1853-9. doi: 10.1093/hmg/8.10.1853. DOI
5. Beaty TH, Marazita ML, Leslie EJ. Genetic factors influencing risk to orofacial clefts: today's challenges and tomorrow's opportunities. F1000Res. 2016;5:2800. doi: 10.12688/f1000research.9503.1. DOI
6. Reynolds K, Zhang S, Sun B et al. Genetics and signaling mechanisms of orofacial clefts. Birth Defects Res. 2020;112(19):1588-1634. doi: 10.1002/bdr2.1754. DOI
7. Cheshmi B, Jafari Z, Naseri MA, Davari HA. Assessment of the correlation between various risk factors and orofacial cleft disorder spectrum: a retrospective case-control study. Maxillofac Plast Reconstr Surg. 2020;42(1):26. doi: 10.1186/s40902-020-00270-7. DOI
8. Sahni V, Grover V, Sood S, Jain A. The periodontal status of orofacial cleft patients: A systematic review and meta-analysis. Cleft Palate Craniofac J. 2024;61(2):302-318. doi: 10.1177/10556656221127549. DOI
9. Rossell-Perry P, Gavino-Gutierrez A. Cleft lip and palate surgery during COVID-19 pandemic. Plast Reconstr Surg Glob Open. 2021;9(6):e3692. doi: 10.1097/GOX.0000000000003692. DOI
10. Xu K, Lin Y, Gao Y, Wang Y. Analysis of clinical pathway for patients with cleft lip and palate. J Craniofac Surg. 2021;32(2):461-465. doi: 10.1097/SCS.0000000000006870. DOI
11. Takemura H, Yasumoto K, Toi T, Hosoyamada A. Correlation of cleft type with incidence of perioperative respiratory complications in infants with cleft lip and palate. Paediatr Anaesth. 2002;12(7):585-588. doi: 10.1046/j.1460-9592.2002.00906.x. DOI
12. Jung S, Gies V, Korganow AS, Guffroy A. Primary immunodeficiencies with defects in innate immunity: Focus on orofacial manifestations. Front Immunol. 2020;11:1065. doi: 10.3389/fimmu.2020.01065. DOI
13. Metgud R, Kumar A, Bhat K. Isolated cleft lip with generalized aggressive periodontitis: A rare entity. J Indian Soc Periodontol. 2015;19(1):88-92. doi: 10.4103/0972-124X.145825. DOI
14. Wu Q, Li Z, Zhang Y et al. Dental caries and periodontitis risk factors in cleft lip and palate patients. Front Pediatr. 2023;10:1092809. doi: 10.3389/fped.2022.1092809. DOI
15. Marzouk T, Youssef M, Tsigarida A et al. Association between oral clefts and periodontal clinical measures: A meta-analysis. Int J Paediatr Dent. 2022;32(4):558-575. doi: 10.1111/ipd.12934. DOI
16. Pilmane M, Sidhoma E, Akota I, Kazoka D. Characterization of cytokines and proliferation marker Ki67 in cleft affected lip tissue. Medicina (Kaunas). 2019;55(9):518. doi: 10.3390/medicina55090518. DOI
17. Ozola L, Pilmane M. Local defense factors in cleft-affected palate in children before and during milk dentition age: A Pilot Study. J Pers Med. 2023;14(1):27. doi: 10.3390/jpm14010027. DOI
18. Howe BJ, Cooper ME, Wehby GL et al. Dental Decay Phenotype in Nonsyndromic Orofacial Clefting. J Dent Res. 2017;96(10):1106-1114. doi: 10.1177/0022034517709961. DOI
19. Yu JC, Khodadadi H, Baban B. Innate immunity and oral microbiome: a personalized, predictive, and preventive approach to the management of oral diseases. EPMA J. 2019;10(1):43-50. doi: 10.1007/s13167-019-00163-4. DOI
20. Ji Y, Garland MA, Sun B et al. Cellular and developmental basis of orofacial clefts. Birth Defects Res. 2020;112(19):1558-1587. doi: 10.1002/bdr2.1768. DOI
21. Becker M, Svensson H, Källén B. Birth weight, body length, and cranial circumference in newborns with cleft lip or palate. Cleft Palate Craniofac J. 1998;35(3):255-261. doi: 10.1597/1545-1569_1998_035_0255_bwblac_2.3.co_2. DOI
22. Wyszynski DF, Sarkozi A, Vargha P, Czeizel AE. Birth weight and gestational age of newborns with cleft lip with or without cleft palate and with isolated cleft palate. J Clin Pediatr Dent. 2003;27(2):185-190. doi: 10.17796/jcpd.27.2.475367q2601u3x4w. DOI
23. Bordon Y. Baby steps for the immune system. Nat Rev Immunol. 2018 Oct;18(10):600-601. doi: 10.1038/s41577-018-0062-y. DOI
24. Gourbal B, Pinaud S, Beckers GJM et al. Innate immune memory: An evolutionary perspective. Immunol Rev. 2018;283(1):21-40. doi: 10.1111/imr.12647. DOI
25. Sokolova I, Herman S, Tomilina T et al. Imunolohiya v suchasniy stomatolohiyi: metod. posib. dlya stud. stomatol. f-tu, likariv-interniv-stomatolohiv ta likariv stomatol. profilyu. [Immunology in modern dentistry: method. manual for students stomatol. Faculty of Medicine, intern dentists and stomatologists. profile]. Kharkiv; 2018, p.116. (Ukrainian)
26. Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's Essential Immunology. 13th ed. John Wiley & Sons, Ltd. 2017, p.579.
27. Scheuerle AE, Good RA, Habal MB. Involvement of the thymus and cellular immune system in craniofacial malformation syndromes. J Craniofac Surg. 1990;1(2):88-90. doi: 10.1097/00001665-199001020-00003. DOI
28. Miller GC, Say B. Immunodeficiency in children with severe craniofacial anomalies. South Med J. 1982;75(1):14-19. doi: 10.1097/00007611-198201000-00005. DOI
29. Hotoura E, Giapros V, Kostoula A et al. Tracking changes of lymphocyte subsets and pre-inflammatory mediators in full-term neonates with suspected or documented infection. Scand J Immunol. 2011;73(3):250-255. doi: 10.1111/j.1365-3083.2010.02499.x. DOI
30. Williams H, McAulay K, Macsween KF et al. The immune response to primary EBV infection: a role for natural killer cells. Br J Haematol. 2005;129(2):266-274. doi: 10.1111/j.1365-2141.2005.05452.x. DOI

31. Akdis M, Aab A, Altunbulakli C et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016;138(4):984-1010. doi: 10.1016/j.jaci.2016.06.033. DOI
32. Akdis M, Burgler S, Crameri R et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2011;127(3):701-721 doi: 10.1016/j.jaci.2010.11.050. DOI
33. Inoyatov A, Abdurakhmanov M, Sharopov S, Azimov M. The condition of immune system of infants with congenital cleft lip and palate. Med Health Sci J. 2012;10L23-30. doi:10.15208/mhsj.2012.5. DOI

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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