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Analysis of the functional activity of salivary glands in children with influenza and other respiratory viral infections

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Acute respiratory viral infections (ARVI) occupy the first place in the structure of children's infections. Rashes on the mucous membranes in the oral cavity reflect the patterns of the infectious process as a whole.

Aim – to is aimed at evaluating the secretory function of salivary glands, physico-chemical, and morpho-structural features of oral fluid in different forms of severity of influenza stomatitis in children.

Materials and methods. The rate of salivation in 318 children with ARVI lesions of the oral cavity was performed on an empty stomach without stimulation in graduated tubes to further morphological examination. Qualitative analysis of secretion was determined visually. Determination of the viscosity was performed on a capillary viscometer Oswald; the buffer capacity was determined as described Krasse, the pH was determined, and crystalography of oral fluid was conducted. The research on the secretory function of salivary glands was conducted by sialometri method.

Results. The rate of salivation in patients with acute viral stomatitis caused by the influenza virus decreased with increasing severity of disease in severe ARVI 3.17 times compared to children in the control group. Counting the functioning of minor salivary glands showed their reduction to 11.46±0.14 with severe acute viral stomatitis. The qualitative analysis showed that salivary gland secretions increase their viscosity and the presence of visible inclusions. Determination of the pH of the oral fluid showed a shift to the acidic side. The buffer capacity is directly dependent on the rate of salivation and pH. The nature of changes in the crystals of the oral fluid is determined by the severity of lesions of the oral mucosa.

Conclusions. Changes in physico-chemical properties, acid-salt metabolism, morpho-texture pecularities, changes in the crystals of oral fluid occurring against the background of hiposalivation show a decrease in functional activity of salivary glands in ARVI in children with disease manifestations in the oral cavity.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Bioethics Commission of an institution. For each child, the informed consent of their mother to participate in the study was obtained.

The authors declare no conflict of interest.

Keywords: mucous membrane, pathological bites, occlusion, oral fluid, crystallogram, hyposalivation, acute respiratory viral infections (ARVI).

Аналіз функціональної активності слинних залоз у дітей, хворих на грип та інші респіраторно-вірусні інфекції

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У структурі дитячих інфекцій перше місце посідають гострі респіраторні вірусні інфекції (ГРВІ). Висипання на слизових оболонках ротової порожнини відображають закономірності інфекційного процесу в цілому.

Мета – оцінити секреторну функцію слинних залоз, фізико-хімічних, морфо-структурних особливостей ротової рідини при різних формах тяжкості грипозного стоматиту в дітей.

Матеріали і методи. Швидкість слиновиділення у 318 дітей, хворих на ГРВІ, з ураженням порожнини рота проведено натще без стимуляції у градуйованих пробірках для подальшого морфологічного дослідження. Якісний аналіз секрету визначено візуально. Встановлення в'язкості проведено на капілярному віскозиметрі Oswald, буферну ємність визначено методом Krasse, виміряно pH і проведено кристалографію ротової рідини. Дослідження секреторної функції слинних залоз здійснено сіалометричним методом.

Результати. Швидкість слиновиділення у хворих на гострий вірусний стоматит, спричинений вірусом грипу, зменшувалася при наростанні тяжкості захворювання: при тяжкому перебігу ГРВІ у 3,17 раза порівняно з дітьми контрольної групи. Підрахунок кількості функціонуючих малих слинних залоз показав їхнє зменшення до 11,46±0,14 при тяжкому перебігу гострого вірусного стоматиту. Якісний аналіз показав збільшення в'язкості секрету слинних залоз і наявність видимих включень. Визначення pH ротової рідини показало зсув у кислу сторону. Буферна ємність знаходиться у прямій залежності від швидкості слиновиділення і pH. Характер змін кристалів ротової рідини визначається важкістю уражень слизової оболонки порожнини рота.

Висновки. Зміни фізико-хімічних властивостей, кислотно-сольового обміну, морфо-структурних особливостей, зміни кристалів ротової рідини, що відбуваються на тлі гіпосалівації, свідчать про зниження функціональної активності слинних залоз при ГРВІ в дітей із проявами захворювання в ротовій порожнині.

Дослідження виконані відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалено Локальною біоетичною комісією установи. На проведення досліджень було отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова. слизова оболонка, патологічний прикус, оклюзія, ротова рідина, кристалограма, гіпосалівація, гострі респіраторні вірусні інфекції (ГРВІ).

Introduction

In recent years, there has been a clear tendency to increase the weight of infections caused by respiratory viruses, especially among children, due to inadequate and reduced immune response to the invasion of an infectious agent. Acute respiratory viral infections (ARVI) occupy the first rank in the structure of pediatric infections [15]. Due to the general toxic, epitheliotropic, vasopathic effect of respiratory viruses have primary importance in the pathogenesis of ARVI, rashes on the mucous membranes in the oral cavity reflect the patterns of

the infectious process as a whole [10,15]. Over the past decade, the attention of researchers has increasingly been drawn to a connection between infectious agents, including viruses, with the formation of various inflammatory processes, including the salivary glands. It is known that the salivary glands are a special group of secretory organs that perform a large number of functions – excretory, endotory, immune, keeping buffer solutions by creating a pH value that prevents the colonization of the oral cavity by some potentially pathogenic microorganisms, etc. [1,18,29].

The results of a few reports show that the etiological factors that cause different forms of sialadenitis can be both bacterial and viral infections. Its background is the reduction of the non-specific defense of the organism. The last factor in the development of the inflammatory process of the salivary glands is the reduction or temporary stopping of salivary secretion by the gland, which creates a condition for the upward passage of ductal infection from the oral cavity [6,9,13,14,22,23]. The pathology of the salivary glands, caused by viral agents, constitutes a problem in clinical practice, leading to a long-term disruption of the normal functional activity of the oral organs [1,10,14,21,22,29]. Local pathological processes, in particular, malocclusion, can lead to disruption of saliva secretion and normal protein composition, physicochemical properties, as well as water-salt balance of oral fluid. The level of saliva secretion is negatively affected by changes in bite, malocclusion, and orthodontic treatment using oral appliances [25]. Children with malocclusion could have oral functional limitations and worse social lives; children with very severe malocclusion could further develop oral symptoms.

Until now, questions of infection of the organs of the oral cavity, in particular the salivary glands, with respiratory viruses, which can be considered as etiological and pathogenetic factors in the development of ARVI, remain unsolved.

The aim of the research is to evaluate the secretory function of salivary glands, physico-chemical, and morpho-structural features of oral fluid in different forms of severity of influenza stomatitis in children.

Materials and methods of the study

We conducted an examination with the use of complex laboratory tests in children with Severe Acute Respiratory Syndrome (SARS), who were treated in the infectious department of the Ternopil Regional Children's Clinical Hospital. Of the total number of examined patients, 318 children had lesions of oral tissues, of which a mild form of influenza stomatitis was diagnosed in 52 children, moderate – in 185 children, and severe – in 81 children. The control group consisted of children suffering from ARVI without damage to the oral cavity (66 people) from the relevant age groups. Regardless of the studied groups of children, in 161 (41.93%) children of cases out of the total number of examined children, pathological bites (prognathia, progeny, deepbite, openbite, crossbite) were detected due to impaired dental occlusion, which is considered a trigger factor for hyposalivation.

Due to observations of the oral cavity, special attention was paid to the condition of the sites of the salivary glands, the edema of surrounding tissues, gland infiltration, the viscosity of the secretion of the salivary glands, and their amount. Due to the observations of the small salivary glands, determined hyperemia of the mucous membrane over the gland, compactions in the buccal, labial, or palatine salivary glands, tuberosity on the palate, cheeks, and lips. Palpation of the glands revealed compaction and pain. Based on the severity of symptoms, acute viral sialadenitis caused by the influenza virus was divided into mild, moderate, and severe forms of the disease [28].

Oral fluid was collected on an empty stomach without stimulation in graduated tubes to determine the rate of salivation (ml/min) and for further morphological examination. Qualitative analysis of secretions was determined visually: color and transparency, as well as visible inclusions. The viscosity of the secretion was determined with an Oswald viscometer. A pH meter was used to determine the pH of mixed saliva, and the confidence interval of the pH of the oral fluid was also estimated [11]. Determination of the buffer capacity was carried out according to the Krasse method [11]. The functional activity of small salivary glands was determined by sialometry.

Considering the significant sensitivity and informativeness of the crystallographic method of studying biological substrates in various diseases [12], we studied the pattern of oral fluid in children with ARVI. Oral fluid was collected in an empty test tube. 0.5–1.0 ml was dropped into a grease-free Petri dish, the drop diameter was 20–30 mm. The drop was dried for 24 hours at room temperature, and any air movement was excluded. The crystallographic

Fig. 1. Hyperplasia of small palatine salivary glands in catarrhal stomatitis caused by adenovirus

Fig. 2. Acute sialadenitis of the sublingual salivary gland in influenza caused by influenza virus type A (H_3N_2)

study of the preparations was carried out by transferring a drop of oral fluid into the solid phase and studying it on a Leica MZ light microscope at 60-fold magnification, phase-contrast, and polarized light. Photomicrographs of the areas selected for illustration were taken by displaying them on a computer monitor using a VISION Color CCD camera and Inter Video Win DVR software for photo documentation.

The obtained results of clinical and laboratory investigations were subjected to statistical processing using standard software for personal computers, «Microsoft Excel-2010» for Windows, and licensed Statistic Soft mathematical software. The results of investigations were processed statistically with the calculation of the average values (M), standard deviation (m).

All the research methods that were used meet the requirements for examination of patients and conducting scientific research meet the requirements of norms and principles of bioethics. When performing the work, the rules of patient's safety have been observed, the rights and principles of human dignity have been preserved, as well as moral and ethical norms in accordance with the fundamental tenets of the GPS (1996), the Council of Europe Convention on Human Rights and Biomedicine (from 04.04.1997), Declaration of Helsinki of the World Medical Association on Ethical Principles of Scientific Medical Research with Human Participation (1964–2000), Order of the Ministry of Health of Ukraine No 281 dated November 1, 2000. It was confirmed by the Ethics Committee minutes I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (protocol No 75 dated 01.11.2023). The informed consent of parents and children was obtained for conducting research.

Results of the study and discussion

Observation of the oral cavity of patients with SARS in children showed that acute viral sialoadenitis caused by the influenza virus is observed against the background of general symptoms of influenza and other SARS. Seals appear in the area of buccal, labial and/or palatal salivary glands (Fig. 1). Salivation rapidly decreases or stops, and xerostomia appears when several glands are affected. Acute symptoms disappear within one to two weeks, and recovery of gland function and resorption of the infiltrate do not occur during the observation period.

The mucous membrane over the gland is hyperemic, with a palpation a spherical shape of a painful movable compaction with a smooth surface, surrounded by edematous tissue (Fig. 2), is determined.

Determination of the rate of salivation in children with ARVI showed a decrease, the degree of which was most pronounced in the severe form of influenza stomatitis. Thus, if in the group of sick children without lesions of the oral cavity the indicator was 0.73±0.02 ml/min, then in patients with acute viral stomatitis caused by the influenza virus, it ranged from 0.54±0.03 ml/min with mild the course of the disease up to 0.23±0.01 ml/min in a severe form of ARVI, which is 3.17 times less than in children of the control group. In order to clarify the form of acute viral sialadenitis caused by the influenza virus, a study of oral fluid at different severities of ARVI disease was conducted. Counting the number of

functioning small salivary glands of the mucous membrane of the lower lip showed the following. With a mild course of SARS with manifestations of the disease, 15.43±0.51 small salivary glands function in the oral cavity (18.17±0.18 in the control group). As the severity of the disease increases, the number of functional salivary glands decreases, and in a severe course of acute viral stomatitis caused by the influenza virus, it is 11.46±0.14, which explains the presence of hyposalivation.

The research of the excretory function of the salivary glands, which consists of determining the viscosity (V) of the secretion of the salivary glands and its qualitative analysis – color, transparency, showed an increase in the viscosity of the secretion of the salivary glands and the visible inclusions, even with mild ARVI. The average viscosity of saliva in sick children without damage to the system of oral mucosa was 1.37±0.02 poise. In the study of the viscosity of the saliva of children with SARS in children, it was established that already in the mild form of the disease, it is slightly increased and amounts to 1.53±0.06 poise. With an increase in the severity of the disease, the value of V increases to 2.21±0.03 poise with moderate and up to 3.19±0.04 poise with severe acute viral stomatitis caused by the influenza virus.

Determination of the biophysical parameters of the oral fluid as one of the indicators of the functional reactions of the oral cavity consisted of assessing the level and stability of the pH of the oral fluid. Assessment of the confidence interval of pH fluctuations in children with ARVI showed that their magnitude varies depending on the severity of the disease. If, in the mild form of acute viral stomatitis caused by the influenza virus, there were no significant differences in the values of this indicator compared with the children of the control group (6.32±0.01 and 6.38±0.01, respectively), then during the course of the disease moderate and especially in severe forms, its value was 5.52±0.02 and 4.92±0.03.

Our research on the stability of the pH of the oral fluid in sick children without affected oral mucous membrane showed that the average index of the confidence interval of pH fluctuations (ΔpH) was 0.13±0.01, which corresponds to the normal level of functional reactions of the body. As for children suffering from influenza with signs of the disease in the oral cavity, the confidence interval of pH fluctuations in moderate and severe disease was 1.77 and 2.17 times smaller, respectively, compared to the control group. The results of changes in the biophysical properties of oral fluid indicate a decrease in the functional reserves of the oral cavity, which are responsible for a stable environment. It is obvious that violations of the quantitative and qualitative properties of oral fluid, which occur during respiratory viral infections, cause a violation of the homeostasis of the oral cavity.

Determination of the buffer capacity of saliva showed that it is directly dependent on the amount of saliva secreted per unit of time and the pH value. Thus, with a mild form of the disease, the buffer capacity of saliva does not reliably differ from the control group of children and is estimated as high, with moderate and severe forms of SARS – as normal and low, respectively. There is a connection between a decrease in salivation and a change in pH to the acidic side. Therefore, a decrease in salivation leads to an active reaction of oral fluid in the direction of increased acidity, which determines the features of the microbiocenosis of the oral cavity.

It is known that there is a highly dynamic relationship between biological fluids and the state of the body's organs and systems, the disturbances of which lead to changes in the chemical characteristics of the body's lipotropic fluids. Pathological processes occurring in the body are manifested by a change in liquid architectural structures in accordance with their characteristic textural features. During the analysis of samples of oral fluid of children without lesions of the mucous membrane of the oral cavity, the presence of clear crystalline structures of a certain morphology was revealed (Fig. 3). Constructions are characterized by a high degree of symmetry, edge, intermediate, and middle zones that have a clear border.

The morphological structure of the preparations of the middle part had a complete structured form with ordered centers of crystallization. The centers of the crystals, the number of which varies from 4 to 9 (on average 6.4±0.3), are arranged in an orderly manner. The crystallographic picture was characterized by the appearance on a light background of translucent needle-shaped rays collected in the form of bundles emanating from the centers of crystallization. Thick bundles of crystals in the center gradually branch out and thin out towards the periphery. The crystals have the correct geometric shape are densely arranged, so there were not many free areas of the crystallization field. Thus, crystallograms of the oral fluid of sick children

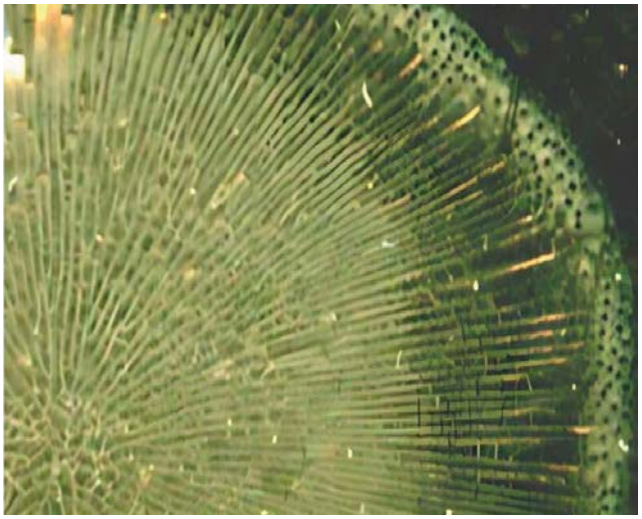

Fig. 3. Crystallographic method of studying the oral fluid of a patient with ARVI without affecting the oral cavity tissues. Magnification ×60

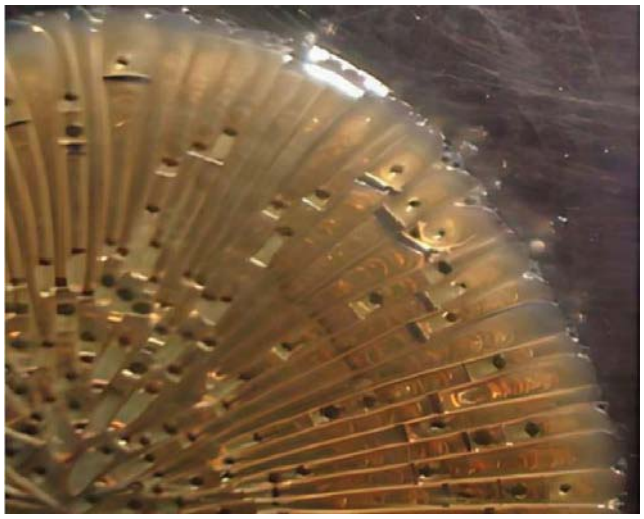

Fig. 4. Crystallographic method of studying the oral fluid of a patient with ARVI with lesions of the oral mucosa (moderate-severe form). Magnification ×60

without damage to the mucous membrane of the oral cavity are characterized by the presence of marginal, intermediate, middle zones, there is symmetry.

The microscopic picture of crystallograms of oral fluid in children with influenza stomatitis was characterized by an increase in the number of crystallization centers, especially expressed in moderate and severe forms of the disease, which averaged 9.8±0.2. An increase in the number of rays in the crystal beam was observed – 6.2±0.1. The centers and sizes of crystals in the oral fluid of this group of subjects are smaller than those of children in the control group. The correct geometric shape of the crystals is often getting lost, resulting in the appearance of secondary and tertiary beams. In most crystallograms there is a marked loss of the intermediate zone, resulting in a structure characterized by a bi-zonal structure in violation of the construction of the central zone (Fig. 4).

Beams of crystals were located sufficiently randomly, crossed, interrupted, and moved with the loss of symmetry shapes formed additional branching. Unstable order branching was led by the disintegration of the crystals and itself damages. Bundles of crystals were arranged rather chaotically, intersected, interrupted, moved with a loss of symmetry of forms, forming additional branches. The irregular order of branches was accompanied by the disintegration of crystals and their severe damage.

All of the above disorders, which are manifested by the loss of the intermediate zone, the displacement of the geometric center of the structure, the change in the order of branching, are the initial systemic disorders of the crystallograms of the oral fluid in children and usually accompany a mild form of the disease. Along with the formation of systemic violations, we also noted the presence of subsystem violations. They were manifested in the formation of pathological wrinkled structures, which probably reflected the increased content of protein substances in the environment. These changes in crystallograms were observed during the course of ARVI in moderate and especially severe forms (Fig. 5).

At the same time, the crystallographic picture of the oral fluid of children was characterized by the loss of the intermediate zone, violation of the symmetry of placement, the formation of violations of the systemic and subsystem types, which appear in the formation of pathological structures. Such changes in the group of patients with ARVI in children were statistically significant compared with the control group.

The appearance in the oral fluid of an excessive amount of products of an incomplete metabolism, elements of tissue degradation, immune complexes, and other pathological formations leads to a change in the viscosity of the medium and creates conditions for the development of abnormal crystals. According to P.A. Millones-Gómez et al. [20], this is caused by an increase in the content of high-molecular compounds and the presence of other substances characteristic of the inflammatory process. All of the above prevent the formation of structures characteristic of biological fluid – mixed saliva. As a result of the study, we established a relationship between the severity of the lesions of the oral muco-

sa in children with SARS and the nature of changes in the crystals of the oral fluid, which makes it possible to be an additional criterion for diagnosis. It should be noted that changes in the oral cavity, which include hyposalivation and xerostomia, may be associated with both malocclusion and orthodontic treatment using oral appliances.

Nowadays, the issue of infection by the respiratory viruses of the organs of the oral cavity, in particular salivary glands, remains unresolved; they can be considered as etiological and pathogenic factors in the progress of the upper respiratory tract infections (URTI). Adequate salivation is critical to both oral and general health, as it provides a complex environment to support the oral microbial population, and salivary gland dysfunctions, accordingly, disrupt homeostasis and lead to numerous diseases. Confirmed by a number of publications [1,2,5,8,14, 17,19,25,26,29,30] that the lesions that come up with URTI can lead to prolonged disturbance of normal functional activity of the organs of the oral cavity, including protective, immune, digestive, excretory, endocrine functions, and osmoregulation [4]. The main pathogenetic link in the clinical manifestations of ARVI is infectious inflammation of the mucous membranes, which contributes to their swelling and increased secretion viscosity, which, in turn, leads to the adhesion of pathogens of respiratory infections on the mucous membranes of the oral cavity and respiratory tract. The disturbance of microbiocenosis structure in the oral cavity and acid-salt exchange of oral fluid in children suffering from influenza-associated hepatitis decreases the level of functional reserves of the oral cavity. The decrease in stability factors of oral fluid is the factor of non-specific resistance of oral mucosa, which determines the course of ARVI with oral mucosa lesions [10]. All of the above create favorable conditions for the development of bacterial superinfection, which aggravates the course of SARS.

In saliva, one-piece patterns of patients suffering from oral flat lichen and non-specific inflammatory lesions of oral mucosa M.F. M.S. Carvalho et al. [7] estimated the levels of cytokine protein and the structure of oral microbiota. The authors observed the significant differences in the structure of oral microbiota among saliva patterns in non-specific inflammatory lesions and lichen planus, which corresponds to the character of chronic inflammation of the oral mucosa and can be used as a diagnostic instrument. G. Scelza et al. [24] studied extrahepatic signs of Hepatitis C infection, oral lichen planus, and hyposalivation according to the clinical evaluation of the oral dryness (CODS), found out the presence of hyposalivation with an average point of CODS 4.71±1.72 point. In 1, 3 and 6 months after the period of antiviral treatment using direct-acting antiviral medicines, physical examination of the oral cavity demonstrated a decrease in hyposalivation level. K.R. Larsen et al. [16] discovered that xerostomia was significantly more widespread and severe in patients (46.9%) suffering from the oral lichen planus, lichenous lesions, and generalized stomatitis than in healthy patients of the control group. However, the authors do not associate hyposalivation with the hypofunction of salivary glands, the amount of systemic diseases or medicines, age, or sex.

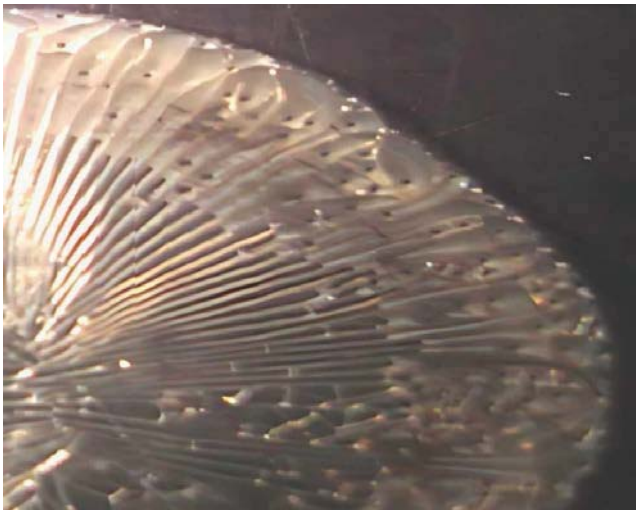

Fig. 5. Crystallographic method of studying the oral fluid of a patient with ARVI with lesions of the oral mucosa (severe form). Magnification ×60

The works of a number of authors are devoted to the study of biological fluids of the body [7,24], who studied drops of colloidal dispersions for the content of nanoparticles, polymers, surface-active substances, proteins, other soluble substances, bacteria and viruses. The method of examination of biological fluids of the human body allows obtaining general information concerning the change of biochemical composition in different pathological conditions. Crystallography is a simple, available screening objective method of diagnostics of many pathological conditions. The main aspect of this diagnostic test is the property of biological fluids to form crystals. The mechanisms of salivary gland secretion and immunopathogenesis in relation to oral health and infectious diseases remain the focus of modern research

[4]. Most recently, investigators have studied the lifetime and evaporation of virus-loaded drops generated by humans and animals in the context of understanding the spread of COVID-19 [3]. In prospective studies, it is necessary to take into account the activity and localization of the pathological process of URTI on the organs and tissues of the oral cavity, as well as the influence of various types of pathogens of respiratory viral infections on clinical symptoms and manifestations. diseases in the oral cavity.

Conclusions

Infectious inflammation of the mucous membranes in SARS is accompanied by their swelling, pronounced hyposalivation, as a result of which the viscosity of the oral fluid increases, which creates favorable conditions for the development of bacterial superinfection. Against the background of hyposalivation, there are changes in the physico-chemical properties, acid-alkaline metabolism of the oral cavity, crystal formation disorders, which probably lead to immunobiological disorders of the oral cavity. The detected violations can be considered as interdependent processes, since hyposalivation causes insufficient mediator activity of protective mechanisms and dryness of the mucous membrane; on the other hand, hyposalivation in viral sialoadenitis in SARS affects the exocrine function of the salivary glands, which leads to a decrease in their functional activity. The obtained results can be used to develop an algorithm for dental examination and treatment of patients with post-COVID syndrome.

Prospects for future research. In the future, it is planned to investigate the secretory function of the salivary glands in children with oral manifestations of post-COVID syndrome.

The authors declare no conflict of interest.

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