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COMPLICATIONS IN THE MAXILLOFACIAL REGION IN PATIENTS WHO HAVE SUFFERED FROM COVID-19

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Abstract. This article is a review of clinical cases describing complications in the maxillofacial area in patients who have recovered from COVID-19. The study includes analysis of a variety of manifestations of infection beyond respiratory symptoms and focuses on the impact of the virus on the condition of the facial anatomy and maxillofacial system. Various aspects are considered, such as the influence of cytokines, receptors and inflammatory processes on the tissues of the facial area. The result is a comprehensive overview of the variation in complications, including effects on the salivary glands, neurotropic effects, and those associated with the use of medical therapies. The summary of these cases highlights the importance of paying attention to the maxillofacial region in COVID-19 survivors and calls for additional research to better understand the effects of the virus on this anatomical region.

Key words: COVID-19, complications, maxillofacial area, cytokines, receptors, inflammation, salivary glands, neurotropic effects, medical therapy.

ОСЛОЖНЕНИЯ ЧЕЛЮСТНО- ЛИЦЕВОЙ ОБЛАСТИ У ПАЦИЕНТОВ ПЕРЕНЁСШИХ КОВИД 19

Аннотация. Данная статья представляет собой обзор клинических случаев, описывающих осложнения в челюстно-лицевой области у пациентов, переболевших COVID-19. Исследование включает анализ разнообразных проявлений инфекции, выходящих за пределы респираторных симптомов, и фокусируется на влиянии вируса на состояние лицевой анатомии и челюстно-лицевой системы. Рассмотрены различные аспекты, такие как влияние цитокинов, рецепторов и воспалительных процессов на ткани области лица. В результате предоставляется комплексный обзор вариаций осложнений, включая воздействие на слюнные железы, нейротропные эффекты, и связанные с применением средств медицинской терапии. Обобщение этих

случаев подчеркивает важность внимания к состоянию челюстно-лицевой области у пациентов, переживших COVID-19, и призывает к дополнительным исследованиям для более глубокого понимания последствий воздействия вируса на данную анатомическую область.

Ключевые слова: COVID-19, осложнения, челюстно-лицевая область, цитокины, рецепторы, воспаление, слюнные железы, нейротропные эффекты, медицинская терапия.

KOVID-19 BILAN KASAL BO’LGAN BEMORLARDA YUZ-JAG’ SOHASINING ASORATLARI

Annotatsiya. Ushbu maqolada COVID-19 dan kasallangan bemorlarda yuz-jag’ sohadagi asoratlarni tavsiflovchi klinik holatlar ko‘rib chiqiladi. Tadqiqot nafas olish belgilaridan tashqari infeksiyaning turli ko'rinishlarini tahlil qilishni o'z ichiga oladi va virusning yuz anatomiyasi va yuz-jag’ sohasi holatiga ta'siriga qaratilgan. Sitokinlar, retseptorlar va yallig'lanish jarayonlarining yuz-jag’ sohasidagi to'qimalarga ta'siri kabi turli jihatlar ko'rib chiqiladi. Natijada, asoratlarning o'zgarishi, shu jumladan so’lak bezlari ta'siri, neyrotrop ta'sirlar va tibbiy muolajalarni qo'llash bilan bog'liq bo'lganlarning keng qamrovli ko'rinishi. Ushbu holatlarning qisqacha mazmuni COVID-19dan omon qolganlarda yuz-jag’ sohasiga e'tibor berish muhimligini ta'kidlaydi va virusning ushbu yuz-jag’ sohasiga ta'sirini yaxshiroq tushunish uchun qo'shimcha tadqiqotlar o'tkazishni talab qiladi.

Kalit so'zlar: COVID-19, asoratlar, yuz-jag’ sohasiga, sitokinlar, retseptorlar, yallig'lanish, so'lak bezlari, neyrotrop effektlar, tibbiy terapiya.

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, poses a global threat to human health, causing numerous health and social challenges. Beyond its primary impact on the respiratory system, there is an accumulating body of evidence pointing to the multifaceted effects of the virus on various organs and systems of the body. One aspect that has attracted the attention of researchers is the potential impact of COVID-19 on the maxillofacial region, which can manifest itself in a variety of complications [8,14].

The relevance of this study is due not only to the prevalence of COVID-19, but also to the possibility of developing long-term consequences after infection. Despite extensive research on the effect of the virus on the respiratory system, the

mechanisms and consequences of its impact on the structures of the maxillofacial region still remain insufficiently studied.

The purpose of this review is to systematically examine common complications associated with the maxillofacial region after COVID-19. Since the onset of the COVID-19 pandemic, drawing attention to the impact of the virus on the maxillofacial region has become an integral part of research efforts. There is increasing evidence indicating a variety of infection manifestations in this area that are not limited to respiratory symptoms [30].

Experimental and clinical data confirm that SARS-CoV-2 can infect the epithelium of the oral and nasopharyngeal mucosa, which creates the preconditions for affecting the tissues of the maxillofacial region. The mechanisms of action can vary from direct effects of the virus on cells to activation of inflammatory cascades and immune responses [19].

Manifestations in the maxillofacial region include, but are not limited to, symptoms such as dysgeusia and anosmia, which may reflect the effect of the virus on receptors in the olfactory and gustatory areas of the face. In addition, complications may include inflammatory processes in the salivary glands, which provides an additional aspect for studying the consequences of infection [13].

Despite extensive observations, it is important to elucidate the more precise mechanisms by which the virus affects the maxillofacial region and determine which factors may increase the risk of complications in this part of the body. The impact of the SARS-CoV-2 virus on the tissues of the maxillofacial area occurs through the activation of complex inflammatory mechanisms, which largely determine the nature of complications. Beginning with the invasion of epithelial cells by the virus, cytokine activation occurs, leading to direct inflammation and activation of the immune system [7].

In response to the virus, the body initiates complex biological mechanisms, including the release of various cytokines. Among them, key molecules include interleukin-6 (IL-6), tumor necrosis factor (TNF-α) and interferon-γ (IFN-γ). These biologically active substances play the role of signals, activating inflammatory processes in the body [3,15].

Interferon-γ (IFN-γ) is an important immune cytokine that plays a key role in regulating the immune system and fighting infections. Produced primarily by

activated T lymphocytes and natural killers in response to viral infections, bacterial pathogens, and other stimuli [16].

IFN-γ has many functions, including:

1. Macrophage activation: IFN-γ stimulates macrophages to more effectively phagocytose (engulf) and kill microbes.

2. Enhance immunity: This cytokine enhances immunity by enhancing the differentiation and activation of T cells.

3. Regulation of antigen presentation: IFN-γ improves the process of antigen presentation, which promotes more efficient recognition and attack by the immune system [32].

IFN-γ is also important in the context of viral infections, including COVID-19. Its use may be associated with maintaining a balance between antiviral and proinflammatory responses, which is essential for effective control of infection.

Tumor necrosis factor (TNF-α) is a cytokine actively involved in the immune response and regulation of inflammatory processes. Produced by a variety of cells, including macrophages, T lymphocytes, and neutrophils, TNF-α is a key component of the immune system and has several important functions [40].

1.Anti-inflammatory function: In the early stages of inflammation, TNF-α ensures the recruitment and activation of other cells of the immune system to the site of infection or injury, which helps fight pathogens.

2. Induction of Apoptosis: TNF-α can activate the apoptosis (programmed cell death) pathway, playing a role in the removal of damaged or infected cells, which is especially important in the context of fighting viruses and cancer cells.

3. Regulation of immune responses: This cytokine influences the functions of other immune cells such as T and B lymphocytes, enhancing the immune response.

4. Role in pathological processes: In some cases, excessive release of TNF-α is associated with pathological conditions such as chronic inflammatory diseases and autoimmune disorders [29,34].

Particular attention is paid to the effects on the maxillofacial area, since these processes may be associated with possible complications after suffering from COVID-19. Elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and interferon-γ (IFN-γ) may play a critical role in causing dysregulated inflammatory responses in facial tissues. Hyperactivation of

macrophages and leukocytes stimulated by these cytokines can lead to chronic inflammation and tissue damage [11].

Tissue damage, in turn, can involve various structures in the maxillofacial region, including mucosal cells, blood vessels, and induction of fibrosis. This process can be worsened by overactivation of the immune system, which has important implications for understanding the effects of a virus such as COVID-19 on facial tissue [4].

Moreover, the effect of the virus on receptors in facial tissues, such as angiotensin-converting enzyme (ACE), provides an additional mechanism for the inflammatory response. This can cause an imbalance in the blood pressure regulation system and further aggravate tissue changes [5].

One of the important aspects that require attention when considering complications of the maxillofacial area after COVID-19 is respiratory pathologies. Viral exposure to facial tissue can lead to a variety of conditions affecting the upper and lower respiratory tract [18].

Existing data indicate the possible development of obstructive upper respiratory tract diseases after COVID-19. This may include tracheal stenosis, soft tissue obstruction in the laryngeal area, and upper airway hyperresponsiveness. Such changes can cause characteristic symptoms such as shortness of breath, wheezing and voice problems [12,17].

Information about possible complications from COVID-19 and mechanical ventilation (MV) includes various breathing problems such as bronchitis and other complications. Complications of mechanical ventilation may include ventilator-associated pneumonia, tracheostomy obstruction, tracheal stenosis, and other problems.

The use of mechanical ventilation (ALV) in the treatment of COVID-19 can lead to cerebral hypoxia in most patients. The duration of mechanical ventilation for this disease usually exceeds the duration of respiratory support for other pneumonia and acute respiratory disorders [20].

Patients after mechanical ventilation may develop pathologies of cognitive functions and other mental disorders, including the so-called "intensive care syndrome" (ICU syndrome) [6]. This syndrome may include sleep disturbances and cognitive impairment. Interestingly, mechanically ventilated COVID-19 patients may experience frequent complications such as strokes, brain injuries, and

ventilator-associated pneumonia. Sedation required for mechanical ventilation may adversely affect cognitive function. Prolonged stay on mechanical ventilation, especially with extrapulmonary etiology of disturbances of consciousness, increases the risk of complications and can lead to brain hypoxia [41].

An important aspect of considering complications of the maxillofacial area after suffering from COVID-19 are inflammatory processes that affect various structures in this area. A viral infection can provoke not only a systemic inflammatory response, but also local processes specific to the orofacial area. Studies have shown that the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) significantly affects the oral microbiome, accelerating the development of systemic diseases by introducing harmful oral pathogens to nearby and distant organs [33].

Periodontitis is a chronic inflammatory disease of the supporting structures of the teeth, affecting approximately half of adults aged 30 years and older [25]. Existing research suggests a possible link between COVID-19 and the development of inflammatory periodontal diseases. The virus can affect the epithelial cells of the gums, activating inflammatory cascades and contributing to the development of periodontitis and periodontitis. Moreover, a growing body of research has identified an association between periodontitis and COVID-19, highlighting the need for a comprehensive understanding of their relationship.

Research highlights potential cross-talk, raising concerns about the systemic implications of this association. Notably, both periodontal disease and COVID-19 demonstrate associations with a variety of cardiometabolic complications, including cardiovascular problems, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, insulin resistance, obesity, non-alcoholic fatty liver disease, and neurological and neuropsychiatric manifestations. [24,36]. The COVID-19 virus interacts with ACE2 receptors in the body, using these receptors to enable its entry into human cells.

ACE2 является функциональным рецептором на поверхности клеток, через который SARS-CoV-2 проникает в клетки-хозяева и высоко экспрессируется в сердце, почках и легких, а также обширно присутствует в полости рта, особенно в языке и тканях пародонта. В тканях пародонта ACE2 играет ключевую роль в поддержании баланса между здоровьем и заболеванием. Ось ACE2/Ang-(1-7)/MasR играет решающую роль в модификации процессов,

связанных с острым и хроническим воспалением, включая приток лейкоцитов, фиброгенез и пролиферацию определенных типов клеток.

Thus, the ACE2/Ang-(1-7)/MasR axis is involved in various physiological and pathophysiological processes, including inflammation and fibrosis. Its activation has potential therapeutic implications for COVID-19 as it may help control the inflammatory response mediated by the virus [35,37,39]. However, ACE2 activity levels are altered in the presence of concomitant diabetes, leading to increased expression due to uncontrolled levels glucose in chronic diabetes mellitus (DM2).

Thus, uncontrolled hyperglycemia likely increases the risk of periodontitis and induces ACE2 overexpression in periodontal tissues of patients with T2DM. These events may play an important role in susceptibility to SARS-CoV-2 infection and the development of mild and severe forms of COVID-19 [27].

The interaction of the COVID-19 virus with ACE2 receptors is a critical aspect of the pathogenesis of the disease and has attracted the attention of numerous researchers. Understanding this interaction is important for developing potential therapeutic interventions and gaining insight into the molecular origin and pathophysiology of the cellular response in correlation with the role of ACE2 receptors in COVID-19.

There is also a possible effect of the virus on the salivary glands, which may contribute to the development of inflammatory processes. Dry mouth, hyposecretion of saliva and other changes associated with viral infection can create the preconditions for diseases of the salivary glands, such as sialadenitis. Scientists say that the salivary glands represent potential reservoirs of the COVID-19 virus, capable of causing both acute and chronic sialadenitis. The ACE-2 receptor is considered key for the virus, and studies conducted on SARS-CoV confirm that salivary gland epithelial cells with high levels of ACE-2 are susceptible to COVID-19 infection [28].

ACE-2 expression in the minor salivary glands was even higher than in the lungs, indicating the salivary glands as a potential target of the virus. Before symptoms appear in the lungs, SARS-CoV RNA can be detected in saliva, which may explain asymptomatic infections. For SARS-CoV, saliva is a significant reservoir and patients with COVID-19 test positive for the virus in saliva. These data

confirm the possibility of asymptomatic spread of the virus through saliva. In addition, it is important to note the role of saliva in the diagnosis of COVID-19 [10]. In addition to respiratory and inflammatory complications, neurological aspects after COVID-19 represent an important area of study, especially in the context of the maxillofacial region. Neurological complications can have a significant impact on facial function and pose challenges that require an integrated approach to diagnosis and treatment. Neurological manifestations, including headache, stroke, seizures, Guillain-Barré syndrome and acute disseminated encephalomyelitis, have been documented as clinical manifestations of COVID-19. However, in rare cases, COVID-19 can also affect cranial nerves, leading to varied and atypical manifestations [26,38].

There is evidence of possible effects of COVID-19 on nerve structures, including the trigeminal nerve. The development of trigeminal neuralgia, characterized by intense pain in the face, may be associated with inflammation of the nerve fibers after infection. This poses a challenge to understanding the mechanisms of neurological complications and requires the development of effective treatments. Varicella zoster virus (VZV), a neurotropic virus, enters latency in ganglion neurons after chickenpox. COVID-19, which causes severe acute respiratory syndrome, can trigger a cytokine storm.

Even in cases of oligosymptomatic COVID-19, there is evidence of possible retrograde reactivation of VZV from the nasal cavity, which can lead to the rare presentation of herpes zoster (HZ) [22,31].

Neuromuscular complications, such as paresis and paralysis of facial muscles, may be a consequence of the effects of COVID-19 on nerve structures. This can manifest itself as temporary or long-term disorders of facial muscles, requiring a differentiated approach to rehabilitation and treatment. Acute cerebrovascular accident due to COVID-19 is characterized by a severe course and a high risk of death.

The prevalence of Guillain–Barré syndrome in COVID-19 is less than in uninfected individuals, but it is noticeably higher by 3.3 times. Patients with combined Guillain–Barré syndrome and SARS-CoV-2 often present with impaired sense of smell and damage to cranial nerves, mainly facial and vestibular [1,21].

Complications in the maxillofacial area in patients who have recovered from COVID-19 highlight the importance of effective diagnosis. For this purpose, modern

imaging methods (CT, MRI, 3D DT), laboratory tests and clinical examination are used. Case analysis highlights the need for a comprehensive diagnostic approach to develop individualized treatment and rehabilitation plans [9,23].

It has been studied that manifestations of oral candidiasis after a new coronavirus infection include hyperemia, swelling of the oral mucosa and the abundant presence of a milky-white cheesy coating. Laboratory studies confirmed the predominant presence of Candida albicans and the presence of Candida tropicalis [2].

In conclusion, it can be noted that complications in the maxillofacial area after suffering from COVID-19 represent a serious problem that requires careful diagnosis and comprehensive treatment.

Analysis of the reviewed cases emphasizes the heterogeneity of manifestations and the possibility of various pathologies in this area. The importance of using various diagnostic methods confirms the importance of early detection and effective management of complications. Prevention and timely intervention can significantly improve treatment outcomes and quality of life for patients who have suffered from COVID-19. Additional research and extensive clinical observations are needed to better understand this issue and optimize diagnostic and treatment strategies in this area.

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