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EDITORIAL

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Why We Need a Close Cooperation between Russian and European Medicine

Currently, the well-established and close cooperation between Russia and Europe is endangered. Many feel that ties are worse than they have been for a long long time. This affects numerous aspects of our public life and our economy. This situation may suit certain forces in our countries. Historically, it is a catastrophe.

Russia and Europe are united in so many ways and over most of their history:

In geography, there is no natural divide between Europe and Russia. The heart of Russia is in Europe. The Ural divides Russia as much as Europe and Asia. It is some 1500 werst East of Moscow.

In history, large parts of Europe received population influx from nowadays Russia. For centuries Russia and Europe — side-by side — had to defend themselves from Turkish expansion. Russian aristocracy since the Romanov times received blood from European families, many of them from Germany.

In religion, the common thread was Islam, whereas Russia and Europe were and are united by Christianity through the Byzantine legacy.

In economy, highly industrialised Europe and Russia rich in all necessary natural resources are a perfect match. Without Europe's technological know how and without Russia's natural resources neither part will flourish.

And there is the all important sphere of culture. Greek science, Italian enlightenment, English rationalism, French systematism and German engineering and perfectionism meet the Russian soul. In its most successful eras Russia managed to amalgamate all this. Science — and medicine with it — is the finest product of culture. Here, Russia and Europe need to meet most urgently. It is up to us to realise the opportunities Russia and Europe have, when they collaborate and when they use them to the best of both of our interests.

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EDITORIAL

Dmitry Domenyuk

Executive Editor,
Archiv EuroMedica

Dear clinicians, researchers, colleagues and friends!

Environment and climate change, global warming, growth of population density, popula-tion mobility and migration activity facilitate the spread of new dangerous infections over the globe. Acceleration of the migration processes, urbanization due to growth of the population, which according to UN prognosis may reach 10 billion people by 2050 together with insufficient biological safety of the population, puts forward a number of drastic problems.

The outbreak of pneumonia of unknown etiology in Wuhan, China, which was officially mentioned for the first time on 31 December 2019 by WHO China Country Office, attracted attention not only of specialists but of the international community as a whole; whereas on 30 January 2020 the WHO recognized the outbreak of COVID-19 as a global emergency. On 11 March 2020 the WHO declares it a pandemic, for the first time since the 2009 H1N1 pandemic.

Luckily, COVID-19 mostly spares younger children. According to the WHO data, susceptibility to it among children younger than 10 years in Switzerland was 0,4%, among those aged 10 to 19 years — 2,6% from all COVID-19 patients. In Sweden the incidence among chil-dren younger than 10 years was within 0,5% and adolescents aged 10 — to 19 years — 1,3% from all reported cases of COVID-19. In Spain patients under the age of 18 years accounted for about 0,8% of all COVID-19 patients. In other parts of the globe the prevalence among children barely varies. In India the incidence among children under 10 years was 2,5%, and among those aged 10 to 19 — 5%, while in Island there were no reported COVID-19 cases among children under 10 years, and among older children — less than 0,8%.

Among precautionary measures related to perinatology and pediatrics, specialists suggest to monitor the following: risk of unfavorable impact of COVID-19 on fetal development, out-comes of the pregnancy and the newborn condition in the neonatal period; special attention to the newborns whose mothers had confirmed COVID-19; recommendations on breast feeding; clinical manifestations and laboratory abnormalities in children with confirmed COVID-19; elaborating criteria for pediatric patients with COVID-19 for identifying groups at the greatest risk of a severe course and unfavorable outcomes.

The currently available references explain the mild course and a low susceptibility of children to COVID-19 by such factors as age-specific immune response, more elastic respiratory system due to environmental hazards and a shorter impact of viruses on the airways. Besides, angiotensin-converting enzyme II acts as a functional receptor for the family Coronaviridae in children.

The recommendations of the Emergency Committee established by WHO, and International Medical Regulations on Pneumonia caused by SARS-CoV-2 state that the asymptomatic and mild course of COVID-19 in children may lead to underestimation of the role of children in spreading the novel infection. Therefore, in conditions of continuing pandemics it is necessary to adopt drastic measures on reduction of contacts between children and vulnerable populations. This will enable to prevent severe illnesses and unfavorable outcomes.

In section Pediatrics we present the paper featuring clinical and epidemiological characteris-tics of COVID-19 in children aged 0 to 16 years with

laboratory confirmed diagnosis in Volgograd Region, Russia. The authors identified clinical manifestations of COVID-19 that are specific to children. The analysis of the laboratory data (clinical, serological, molecular genetic testing) and results of instrumental studies with a separate SARS-CoV-2 RNA obtained by PCR method from upper respiratory tract samples. Further development of comprehensive algorithms for diagnosis and treatment of COVID-2019 will improve healthcare efficiency in combating the virus.

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EDITORIAL

COVID-MENTANDEMIC: COVID INDUCED MENTAL PANDEMIC

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INTRODUCTION

Whole world is silent, gazing at each other with ray of hope with empty looks, there is still darkness everywhere, all people are scared, unknown fear of uncertainty and death is prevailing everywhere, global health infrastructure has flooded with sick patients, world's economy has crashed, COVID19 pandemic is sweeping across world tolling billions of cases, millions of deaths and consequently destroying millions of families costing trillions USD extra burden of health and on global economic due to COVID-19 since its origin from Wuhan in November 2019.

This is to emphasize that 2020 is a year of survival and safety and 2021 would be year of immunity, as we all are hoping and wishing best the COVID vaccine would be ready by end of 2020 or early 2021.

It's most rampant pandemic of the century and even after 1 year it has worst global impact of this century. We don't know what's the exact pathogenesis, we don't have effective drugs against it, some killed virus and m-RNA based vaccines have recently became available with different degree of safety and immunity claims, but still too early to say anything about the safety and efficacy of these vaccines.

Apart from that mortality morbidity caused by COVID-19, as a consequence of COVID-19 simultaneously a similar pandemic is emerging called as ***COVID-19 Stress syndrome, I would preferably coin it as it as COVID-MENTANDEMIC***, because it is happening globally and nobody is untouched by it. It has negatively affected the physical, mental, social, psychological and financial wellbeing of all people across the world not leaving even an inch unaffected.

Everybody looks scared, wearing mask but then also scared and has no explanation and living in fear of acquiring infection and the deadly consequences of this fatal disease.

Whole world went in lockdown with significant economic loss, huge numbers of death and sufferings and worsening of the mental status of a common man due to loss of millions of job, salary cut down, morbidity and mortality encountered by themselves, their friends or family and in close social circle.

It had significant negative impact on the mental health of individuals reflecting as mood disorders, depression, anger, anxiety, psychosis, fear of unknown, OCD, feeling loneliness, socially isolated.

Special segment of population viz elderly, those with medical comorbidities and children suffered the most, although young and middle age also had significant stress but more obvious in the vulnerable and high risk groups.

PSYCHOLOGICAL ISSUES WITH CHILDREN

Children are experiencing luxurious prison where they have all facilities but with the persistent fear of COVID, including the types of fears that are very similar to those experienced by adults, such as a fear of dying, a fear of their relatives dying, or a fear of what it means to receive medical treatment. If schools have closed as part of necessary measures, then children may no longer have that sense of structure and stimulation that is provided by that environment, and now they have less opportunity to be with their friends and get that social support that is essential for good mental well-being. Online education, prolonged screen time and eyes, neurological, psychological and metabolic related issues viz obesity, vitamin D deficiency, physical deconditioning is increasing in the children due to sedentary lifestyle and no outdoor activities from last 1 yr. COVID-19 stress taking a toll on children's mental health, CDC finds The findings *highlight the importance of continued monitoring of children's mental health throughout the pandemic*. [1]

PSYCHOLOGICAL ISSUES WITH ELDERLY

Elderly and those with comorbid conditions are more scared and they are also home bound with risk of getting infection and dreadful disease. They are facing psychological and physical deconditioning and hence are more prone for mental health related issues. Social isolation, social distancing, social disconnectedness, and loneliness were found to be mediated with depression and anxiety in a similar study [2]. Its impacts can be particularly difficult for older people who may be experiencing cognitive decline or dementia. And some older people may already be socially isolated and experiencing loneliness which can worsen mental health. Social isolation and social disconnection — a documented bidirectional and complex relationship between mental health issues and social disconnectedness — itself poses a serious public health concern among older adults especially due to the psychosocial reasons and physiological health problems such as mental health problems, cardiovascular, autoimmune, neurocognitive, neurobiological, and other at-risk health problems. Government should take concrete instructions for elderly people socially isolated at home or quarantined at healthcare facilities (hospital, clinic, isolation unit, daycare, community centre, and place of worship) to have prescribed diet and medications and communicate about the meaning of social in-contact to mitigate their physical and mental health consequences [2, 3]. However, adherence to social isolation strategies could be weakened with time and such well-timed reinforced implementing preventive measures would efficiently prevent the aggravated morbidity of COVID-19 related to affective mental health problems in older adults. Elderly are most vulnerable for COVID-19 severity and mortality and most susceptible to mental health problems related to such pandemics hence special care needs to be taken for geriatric mental health during such crisis [4].

PSYCHOLOGICAL ISSUES WITH HEALTH CARE PROFESSIONALS (HCP)

HCP are the worst innocent victims of COVID-19 while fearlessly serving and saving lives of millions of patients, thousands of doctors, nurses and paramedical staff have succumbed to death or facing serious consequences of post COVID-19 infection worldwide, especially those who are COVID front liners. In a recent American Psychiatric Association poll, more than ***one-third of Americans said that the coronavirus was having a serious impact on their mental health***, and most (59%) said it was having a serious impact on their day to day lives.

A ***cross-sectional study of 1257 healthcare workers in 34 hospitals equipped with fever clinics or wards for patients with COVID-19 in China*** showed that a *considerable* proportion of HCP reported symptoms of depression, anxiety, insomnia, and distress. This was especially true of women, nurses, those in Wuhan, and frontline HCP directly engaged in diagnosing, treating, or providing nursing care to patients with suspected or confirmed COVID-19. ***Doctors and nurses revealed*** that they had harboured dark feelings owing to fears of spreading the disease to families, frustration about a lack of adequate protective gear, exhaustion, and profound grief for sick / dying patients.

The current review was done to conduct systematic appraisal of studies conducted on Mental health problems faced by healthcare workers due to the COVID-19 pandemic. Out of 23 articles selected by initial screening 6 original articles were included in the final review which showed that several socio-demographic variables like gender, profession, age, place of work, department of work and certain psychological variables like poor social support, self-efficacy were found to be associated with increased reporting of stress, anxiety, depressive symptoms, insomnia in HCP. There is increasing evidence which suggests that COVID-19 can be an independent risk factor for stress in HCP. Authors concluded that regular screening of medical personnel involved in treating, diagnosing patients with COVID-19 should be done for evaluating stress,

depression, and anxiety by using multidisciplinary psychiatry teams [5].

The current review suggests that HCW are encountering a considerably significant degree of stress, anxiety, depression, insomnia due to the COVID-19 pandemic.

Features specific to COVID-19 which are responsible for the mental health problems include speculations about its mode of transmission, rapidity of spread and lack of definitive treatment protocols or vaccine. Compared to the outbreak of SARS, widespread global connectivity extensive media coverage are leading to the catastrophic psychological reactions secondary to the outbreak [6].

Another Review by Ricci-Cabello: The prevalence of anxiety, depression, acute and post-traumatic stress disorder, and burnout, was high both during and after the outbreaks. These problems not only have a long-lasting effect on the mental health of HCWs, but also hinder the urgent response to the current COVID-19 pandemic, by jeopardising attention and decision-making. Governments and healthcare authorities should take urgent actions to protect the mental health of HCWs. In light of the limited evidence regarding the impact of interventions to tackle mental health problems in HCWs, the risk factors identified in this study, more so when they are modifiable, represent important targets for future interventions [7].

Critical care units are always demanding, both emotionally and physically challenging for doctors which can lead to easy and early burnout in them. Another survey in ICU doctors revealed that moderate to severe stress levels are prevalent in sizeable higher number (43.75% respondents) of critical care doctors working in Kashmir valley. As levels of stress increase with experience, timely interventions, workload, measures need to be taken before this blows out of proportion. Higher workload, prevalent in the government sector, is to taken care of.

Better ergonomics would possibly help in decreasing stress. ICU doctors should have better remunerations as working in ICU is a health hazard to them and their families. Poor resources in our hospitals is an added stress factor. Critical care units have to be better equipped and at par with other national institutes.

Regular monitoring of stress levels at institutional level should be done to identify and intervene in those doctors who are at risk resources [8].

This study was published in 2017, before COVID Era so we can definitely extrapolate these findings during COVID pandemic which can give us fair idea about the stress level during COVID times in ICU HCP.

PSYCHOLOGICAL ISSUES WITH MIGRANT POPULATION

Migrants are less familiar in their new environment in which they temporarily live. They are prone to various social, psychological and emotional traumas in such situations, emanating from fear of neglect by the local community and concerns about wellbeing and safety of their families waiting in their native places. Migrants leave their native places in search of better opportunities and earnings. In many instances, the families in native places financially depend on the migrant earning members.

During COVID-19 outbreak, and the restrictions imposed on routine activities as part of social distancing norms to prevent the spread of the disease, scores of migrant workers tend to move back to their native places. During the prevailing COVID pandemic also, many migrant workers used all possible means to reach their home back but unfortunately many of them are however stuck at borders, (including state, district, national border). These are the most marginalized sections of the society who are dependent on daily wages for their living, possible means to reach their destinations and in times of such distress need sympathy and understanding of the society.

Immediate concerns faced by such migrant workers relate to food, shelter, healthcare, fear of getting infected or spreading the infection, loss of wages, concerns about the family, anxiety, and fear. Sometimes, they also face harassment and negative reactions of the local community. All this calls for strong social protection.

As an immediate response, measures to be taken should include, ensuring community shelters and community kitchens, making other relief material available, emphasising on the need for social distancing, identification of suspected cases of infection and adherence to protocols for management of such cases, putting up mechanisms to enable them reach to the family members through telephone, video calls etc. and ensuring their physical safety.

HOW TO AVOID COV-MENTANDEMIC

Recommendations of World Health Organisation (WHO) on mental health considerations in HCP:

Recognising that feeling stressed is an experience that many HCP are likely going through, the Department of Mental Health and Substance Use, WHO has developed a series of *mental health considerations* that can be used in communications to support mental and psychosocial wellbeing.

Role of team leaders or managers are as follows:

— Keeping all staff protected from chronic stress and poor mental health during this response

means that they will have a better functional capacity. Managers should focus on longer-term occupational capacity rather than repeated short-term crisis responses.
— Good quality communication and accurate information updates are provided to all staff. Rotate workers from higher-stress to lower-stress functions. Partner inexperienced workers with their more experienced colleagues. The buddy system helps to provide support, monitor stress and reinforce safety procedures.
— Initiate encourage and monitor work breaks. Implement flexible schedules for workers who are directly impacted or have a family member affected by a stressful event and to provide social support to each other.
— Access and facilitation to mental health and psychosocial support services should be smooth and informed to all HCP and these provisions and strategies are in place for both workers and manager. Managers can be role-models for self-care strategies to mitigate stress.
— Orient all responders, including HCP, paramedics, nursing, teachers and community leaders in quarantine sites, on how to provide basic emotional and practical support to affected people using psychological first aid.
— Manage urgent mental health and neurological complaints within. Appropriate trained and qualified staff should be deployed to these locations and the capacity of services to provide mental health and psychosocial support should be increased (see the mhGAP Humanitarian Intervention Guide).
— Ensure availability of essential medications and personnel to provide immediate care at all levels of health care.
— ***Helping Healers Heal***, which allows HCP to process psychological and emotional trauma. Helping Healers Heal, which allows HCP to process psychological and emotional trauma. To fortify the mental health support during the unprecedented COVID-19 crisis, many agency leaders combined 18 facility-based teams — totalling more than 1000 trained peer supporters — with behavioural health providers and staff.
— The combined group established an anonymous behavioural health hotline. At its peak, the support system also provided 31 wellness respite rooms that gave staff a quiet place to catch their breath, meditate, write, make artwork, or talk with *peer support champions* trained to provide emotional support. For busy clinical staffers who were less able to take mental health breaks, the team members made wellness rounds to look for and address signs of anxiety, burnout, compassion fatigue, and other symptoms [9].

COPING WITH KIDS STRESS DURING COV–MENTANDEMIC

Children may respond to stress in different ways such as being more clingy, anxious, withdrawing, angry or agitated, bedwetting etc. Respond to your child's reactions in a supportive way, listen to their concerns and give them extra love and attention. Try and keep children close to their parents and family and avoid separating children and their caregivers to the extent possible. If separation occurs (e.g. hospitalization) ensure regular contact (e.g. via phone) and re-assurance. Provide facts about what has happened, explain what is going on now and give them clear information about how to reduce their risk of being infected by the disease in words that they can understand depending on their age. This also includes providing information about what could happen in a re-assuring way (e.g. a family member and/or the child may start not feeling well and may have to go to the hospital for some time so doctors can help them feel better). Children need adults' love and attention during difficult times. Give them extra time and attention. Remember to listen to your children, speak kindly and reassure them. If possible, make opportunities for the child to play and relax. Keep to regular routines and schedules as much as possible, or help create new ones in a new environment, including school/learning as well as time for safely playing and relaxing. Helping children cope with stress during the 2019-nCoV outbreak [10].

Simple strategies that can address this can include giving young people the love and attention that they need to resolve their fears, and being honest with children, explaining what is happening in a way that they can understand, even if they are young. Children are very perceptive and will model how to respond from their carers. Parents also need to be supported in managing their own stressors so that they can be models for their children. Helping children to find ways to express themselves through creative activities, and providing structure in the day — if that is possible – through establishing routines, particularly if they are not going to school anymore, can be beneficial. Mental health and psychosocial support services should be in place, and child protection services need to adapt to ensure that the care is still available for the children of families who need it [1].

COPING WITH ELDERLY STRESS DURING COVID–MENTANDEMIC

Elderly population need infection and stress prevention with sympathetic approach with gradual

physical exercise and maintenance of the comorbid conditions under control with high degree of suspicion if any untoward symptom develops. On a positive note, there are many things that older people can initiate themselves or with the support of a carer, if needed, to protect their mental health at this time. These include many of the strategies that we are advocating across the entire population, such as undertaking physical activity, keeping to routines or creating new ones, and engaging in activities which give a sense of achievement. Maintaining social connections is also important. Some older people may be familiar with digital methods and others may need guidance in how to use them. Once again, the mental health and psychosocial support services and other services that are relevant to this population must remain available at this time.

CONCLUSION

COVID–MENTANDEMIC, COVID induced socio-psychological, physical and financial stress are being faced globally and with consequent pandemic of stress, depression, anxiety and many more psychological disorders would increase and continue in near future and all governments should take necessary steps for avoidance of this COVID-MENTANDEMIC by controlling coronavirus spread, developing effective vaccine and to keep themselves ready for facing COVID MENTANDEMIC support psychologically for better mental health being over coming few years.

Future Perspectives:

The mental health issues associated with the COVID-19 pandemic can be short-term or long-term. Existing literature addresses the immediate mental health concerns only. It is important to see the long-term mental health sequels of COVID-19 infection. Nothing is known about the after-effects of novel coronavirus infection; hence, there is a need for extensive research in terms of its impact on various groups of populations (pregnant, young children, adults, elderly and other vulnerable populations)

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ASSOCIATION BETWEEN COMORBIDITIES AND DISEASE SEVERITY IN COVID-19 PATIENTS OF AN INFECTIOUS DISEASES HOSPITAL IN RUSSIA

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ABSTRACT — The aim of the study was to investigate the association between the severity of COVID-19 and various comorbidities in hospitalized patients. For this reason, patient histories of 500 patients who were hospitalized in the infectious disease hospital (Moscow, Russia) during the coronavirus pandemic were analyzed. The results showed that cardiovascular and blood diseases, diabetes mellitus, diseases of the central nervous system + psychiatric disorders, and diseases of the urogenital system were all found to be associated with a more severe disease course (X^2 = 44.404; p <0.001; X^2= 55.395; p <0.001; X^2= 19.974; p <0.001; X^2= 11.723; p =0.003, respectively), while diseases of the digestive system and liver (including viral hepatitis), HIV infection, and diseases of the respiratory system + ENT organs where not found to be associated with severity of COVID-19 (X^2= 6.949; p =0.031; X^2=1.582; p =0.453; X^2= 0.528; p =0.768, respectively). There was also found no association between pregnancy and severity of COVID-19 (X^2= 0.705; p =0.703). The authors concluded that persons who are known to have comorbidities should take extra precautions to avoid getting infected with SARS-COV-2 since they may be at a higher risk of having a severe disease course if they get sick.

KEYWORDS — COVID-19, SARS-COV-2, concomitant diseases, severe disease course, diabetes, cardiovascular diseases.

INTRODUCTION

Since it was declared a pandemic on the 11 of March 2020, SARS-COV-2 infection rapidly spread throughout the world in 223 countries and territories, infecting more than 90 million persons worldwide and caused almost 2 million deaths. [3, 6] To date, no effective treatment has been registered and vaccines are only now rolling out, mainly in Europe and North America. Initially it was not clear who would be most affected by the infection but as time went by studies showed that persons of older age had higher risks of severe illness with coronavirus infection, with the greatest risk of severe illness being among those aged 85 years of age and older. [4, 2] Other studies showed that having various comorbidities also affected the severity of COVID-19 in patients. These included comorbidities such as diabetes mellitus, respiratory disease, hypertension, chronic kidney disease and chronic liver diseases, cerebrovascular disease, cardiovascular diseases, and malignancy. [1, 5] It is important to have a good understanding of who the most at-risk populations are since this will allow public health officials to develop effective policies aimed at those populations. This in turn can play an instrumental role in preventing the spread of coronavirus to the populations at higher risk of severe illness.

Purpose of the study is to evaluate whether there is any association between the severity of COVID-19 infection and various comorbidities.

MATERIALS AND METHODS

Patient histories of 500 patients who were hospitalized with COVID-19 or suspicion of COVID-19 from March to August 2020 in the Infectious Diseases Hospital No. 2 (Moscow) were randomly selected from the hospital's archive. The required data was extracted from the patient histories including diagnosis, age, sex, duration of hospitalization, comorbidities, complications, disease course (clinical manifestations: mild, moderate, severe), and outcome. The data was then statistically processed and analyzed which included descriptive statistics and chi-square tests for independence. Microsoft Excel and IBM SPSS Statistics version 22 was used for statistical analysis of the data. The association was considered statistically significant at p<0.01.

RESULTS AND DISCUSSION

Out of 500 patients who were randomly selected from the hospital's archive, 432 were diagnosed with COVID-19. Those 432 coronavirus patients were then further studied. 193 (44.7%) of them were found to be males while females accounted for 239 (55.3%)

of those patients. The average age of the patients was 39 years (st. dev. 21.279; S.E. 1.025), at the same time the minimum and maximum ages were 1 month and 96 years, respectively. The average duration of hospitalization was found to be 12 days (st. dev. 8.733; S.E. 0.420).

Of the 432 patients with SARS-COV-2 infection, 10 (2.3%) were classified as having a mild clinical manifestation, 364 (84.3%) were classified as having a moderate clinical manifestation, and 58 (13.4%) were classified as having a severe clinical manifestation. In terms of comorbidities the results were the following: cardiovascular and blood diseases — 122 (28.2%) patients, diseases of the central nervous system and psychiatric disorders — 42(9.7%) patients, diseases of the digestive system and liver (including viral hepatitis) — 94 (21.8%) patients, diabetes mellitus — 38 (8.8%) patients, HIV infection — 40 (9.3%) patients, diseases of the urogenital system — 44 (10.2%) patients, diseases of the respiratory system and ENT organs — 41 (9.5%) patients, skin diseases — 21 (4,9%) and diseases of the endocrine system (excluding diabetes) — 10 (2.3%) patients. Among the coronavirus patients there were also 51 (11.8%) pregnant women.

When the relationship between cardiovascular and blood diseases, and severity of disease course was analyzed, the association between them was found to be statistically significant: X^2 (2, N = 432) = 44.404; p <0.001. This means that having cardiovascular and blood diseases was associated with a more severe disease course. Surprisingly, diseases of the central nervous system and psychiatric disorders were also found to have a statistically significant relationship with the severity of COVID-19: X^2 (2, N = 432) = 19.974; p <0.001. This means that among the studied coronavirus patients, diseases of the central nervous system and psychiatric disorders were associated with more severe clinical manifestations. Analysis of diseases of the digestive system and liver (including viral hepatitis) showed that there was no statistically significant relationship between them and severity of SARS-COV-2 infection: X^2 (2, N = 432) = 6.949; p =0.031. On the other hand, diabetes (type 1 and 2) was proved to have a statistically significant relationship with severity of disease course: X^2 (2, N = 432) = 55.395; p <0.001. Therefore, diabetes was associated with more severe clinical manifestations of COVID-19. Even though HIV infection is known to weaken the immune system, analysis of its relationship with severity of disease course surprisingly showed that they had no statistically significant relationship: X^2 (2, N = 432) = 1.582; p =0.453. Hence, for the 432 patients with SARS-COV-2 infection studied, having HIV infection was not associated with having more severe clinical manifestations. Another interesting finding is the relationship between diseases of the urogenital system and severity of disease course which was found to be statistically significant: X^2 (2, N = 432) = 11.723; p =0.003. Thus, having a disease of the urogenital system was associated with more severe clinical manifestations.

When the relationship between diseases of the respiratory system + ENT organs and severity of disease course was analyzed, there was found to be no statistically significant relationship between them: X^2 (2, N = 432) = 0.528; p =0.768. This means that unexpectedly, in the studied coronavirus patients, having comorbidities of the respiratory system + ENT organs was not associated with a more severe course of disease. However, when the chi square test was done using data of diseases on the respiratory system only (excluding diseases of ENT organs) more the 20% of the cells had a value of less than 5 which means that the test was invalid. Thus, a cohort consisting of a wider range of patients with diseases of the respiratory system is required in order the study their true association with severity of COVID-19 in patients. The same results were obtained for chi square tests performed when relationships were analyzed for diseases of the skin and diseases of the endocrine system (except diabetes).

An analysis of the relationship between pregnancy and severity of SARS-COV-2 infection showed that there was no statistically significant relationship between the two: X^2 (2, N = 432) = 0.705; p =0.703. Thus, pregnancy was not associated with more severe clinical manifestations of COVID-19.

CONCLUSION

Persons who are known to have comorbidities should take additional precautions to prevent themselves from becoming infected with SARS-COV-2 since certain comorbidities are found to be associated with more severe cases of COVID-19.

It must be noted that association does not mean causation, therefore some of the diseases that were found to be associated with a more severe disease course may not have caused that themselves but they in fact may be linked to another disease that did, or they may just happen to have had affected the patients studied by chance. To accurately assess the association between various comorbidities and severity of SARS-COV-2 infection a more controlled study must be undertaken where the patients being studied have only one comorbidity or several but related comorbidities (affecting one organ or organ system).

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CLINICAL AND HISTOPATHOLOGICAL FEATURES OF LUNG INJURY IN COVID-19 INFECTION

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ABSTRACT — The aim of the study was to evaluate the histopathological changes in the lungs of patients who died of a new coronavirus infection (COVID-19) in relation to the length of hospital stay.
We evaluated lung autopsy material, autopsy reports, and death summaries of 39 patients who died of COVID-19. The length of hospital stay ranged from a few hours to 25 days. At all stages of the disease, lung alterations (desquamation of bronchial and alveolar epithelium), circulatory disorders (alveolar edema and hemorrhages, congestion in small blood vessels, thrombosis), compensatory response (fibrosis) were identified.
The patients who died during the first week of hospitalization demonstrated predominant signs of circulatory disorders (alveolar edema, hyaline membranes, alveolar hemorrhages, congestion in small blood vessels). Fibrosis, usually not typical for the first week of acute respiratory distress syndrome, was detected in 46% of the deceased during the first week of hospitalization, which may be due to late hospitalization or patterns of fibrosis development in COVID-19. For those who died in the 2nd and 3rd weeks of hospitalization, the compensatory response and progression of fibrosis were noted. By the 3rd week, pulmonary fibrosis was detected in 91% of patients. Thrombotic complications (thrombosis, pulmonary artery thromboembolism) were observed in almost half of fatalities occurring during weeks 2–3. Hemorrhagic infarction was found in 43% (6 patients) who died during week 2 of hospitalization, three of them were diagnosed with pulmonary embolism, indicating progression of pulmonary vascular damage.

KEYWORDS — COVID-19, acute respiratory distress syndrome, histopathology in COVID-19, lungs.

INTRODUCTION

The new coronavirus infection (COVID-19) is a serious public health problem worldwide. As of February 2021, more than 2 million deaths from a new coronavirus infection [17] caused by SARS-CoV-2, an RNA-containing virus of the Coronaviridae family, Betacoronavirus genus, have been reported by the World Health Organization since the pandemic began.

Angiotensin-converting enzyme type II (ACE2) is known to be the main receptor for SARS-CoV-2 cell entry. However, based on the results of studies showing predominantly low levels of ACE2 expression on alveolar cells compared to the epithelium of the proximal tubules of the kidney, intestine, and testicular cells, alternative ways of virus entry into cells, through additional receptors and co-receptors other than ACE2, are discussed [5].

Bhatnagar J. et al. (2021) used in situ hybridization to detect SARS-CoV-2 ribonucleic acid (RNA) in alveolar cells, hyaline membranes, lung macrophages, airway epithelial cells, and endothelial cells and vascular walls of the brain stem, pia mater, lungs, heart, liver, kidneys, and pancreas [1]. Electron microscopy showed SARS-CoV-2 in type I and II alveolar cells, airway epithelium, enterocytes, and renal tubule epithelial cells. No viral particles were found in other organs, including heart, spleen and liver [2]. In a study by Martines B. et al. (2020) SARS-CoV-2 was detected only in alveolar cells, alveolar macrophages, but not in other organs (heart, liver, kidney, spleen, intestine) using immunohistochemical methods and electron microscopy of the post-mortem tissues [7].

Internal organ lesions in COVID-19 revealed by numerous histopathological studies are not specific [13]. To date, there are no publications proving a direct cytopathic effect of SARS-CoV-2 viral particles. Consequently, the mechanism of internal organ damage in COVID-19, whether it is due to a direct cytopathic effects of the virus or mediated by respiratory failure, remains unclear.

In the vast majority of COVID-19 fatalities, death occurs through respiratory-mediated mechanisms. According to the analysis of 2000 autopsies of COVID-19 victims performed in Moscow between March 20 and May 22, the immediate cause of death in 90% of cases was acute respiratory failure (clinically

diagnosed as acute respiratory distress syndrome) [18].

Acute respiratory distress syndrome (ARDS) is a common complication of critical illness developing due to noncardiogenic pulmonary edema as a result of damage (dystrophy, necrosis, apoptosis) of endothelium, alveolar epithelium, their basal membranes (including the air-blood barrier) and increased permeability of microcirculation in response to various aggressive factors [9].

The histological classification of ARDS [9] includes three stages: exudative, fibroproliferative, and fibrotic.

Samsonova M. et al. (2020) observed that in contrast to viral pneumonia caused by influenza A/H1N1 virus, there is no definite relationship between the duration of the disease and histopathological changes in the new coronavirus infection. According to authors, this can be explained by the subtle onset of the disease and an asymptomatic period in some patients [15].

Polak S. et al. (2020) performed a systematic review of data from 192 autopsies of COVID-19 patients, which revealed alveolar epithelial damage and pulmonary circulatory disturbances at all stages of the disease, and fibrosis at third week of disease [12].

To date, a number of issues concerning the pathogenesis of the new coronavirus infection remain unresolved. Mechanisms of internal organ damage in COVID-19 can be clarified by thorough histopathological studies, since pathological examination is a powerful tool for learning the patterns of abnormalities in any disease.

The aim of the study was to analyze morphological changes in the lungs of patients who died from COVID-19 in relation to the length of hospital stay.

MATERIAL AND METHODS

We analyzed lung autopsy material from 39 patients with laboratory-confirmed new coronavirus infection while alive, autopsy reports and death summaries. The study included fatal cases in which the new coronavirus infection (COVID-19) was the main cause of death.

The mean age of the deceased was 62 years (ranging from 22 to 94 years). 15% (6 patients) were young (25–44 years), 23% (9 patients) were middle-aged (44–60 years), 44% (17 patients) were elderly (60–75 years), 8% (3 patients) were senile (75–90 years), 10% (4 patients) were long-livers (over 90 years). The length of hospital stay averaged 10 days (ranging from a few hours to 25 days). The following death rate was observed: during the first week of hospital stay — 33% (13 patients), during the second week — 36% (14 people), and during the third week — 31% (12 people). The direct causes of death were respiratory failure in 92% of cases (36 patients), pulmonary embolism (PE) in 5% (2 patients), and disseminated intravascular coagulation (DIC) in 3% (1 person).

The organ samples for histological examination were taken during autopsy in accordance with the current legislation to verify the pathological diagnosis and to clarify the cause of death. In compliance with the current Guidelines of the Ministry of Health of the Russian Federation, the organ samples were fixed for 72 hours in a neutral 10% formalin solution [6]. Later, the sections were processed using standard paraffin-embedding technique. Histological sections of 4 μm thickness were made. Histological sections of lungs were stained with hematoxylin and eosin. Special histological staining with phosphotungstic acid-hematoxylin (PTAH) was used to detect fibrin. Weigert-Van Gieson staining was used to detect elastic fibers, connective tissue, and collagen.

Histological preparations were examined using a NikonEclipseNi-U microscope (Japan). Qualitative parameters are presented as frequencies and percentages.

RESULTS

Histological examination of samples from patients who died during the first week of hospitalization (13 persons) revealed hyaline membranes (Fig. 1) in 10 patients (77% of those who died during the first week of hospitalization), alveolar edema (Fig. 2) was observed in 7 persons (54%), alveolar hemorrhages were noted in 6 persons (46%), fibroplastic response and fibrosis were detected in 3 (23%) and 6 (46%) persons, respectively. Small vessel congestion was found in 10 patients (77%), thromboembolism of pulmonary artery branches was seen in 2 patients (15%). Bronchial and alveolar epithelial desquamation was revealed in 6 (46%) and 5 (38%) patients, respectively. Metaplasia of alveolar epithelium was observed in 2 cases (15%). Purulent pneumonia was detected in 3 persons (23%).

In patients who died during the second week of hospitalization (14 persons), pulmonary fibrosis was detected in 12 cases (86%), hyaline membranes in 3 cases (21%), alveolar edema was observed in 8 cases (57%), alveolar hemorrhages were noted in 8 persons (57%). Small vessel congestion was observed in 11 persons (79%), thromboembolism of pulmonary artery branches was seen in 3 persons (21%), pulmonary vascular thrombosis (Fig. 3, 4) was found in 4 persons (29%). Bronchial and alveolar epithelium desquamation was detected in 3 (21%) and 2 (14%) cases, respectively. Hemorrhagic pulmonary infarction was detected in 6 patients (43%). Purulent pneumonia was found in 3 persons (21%).

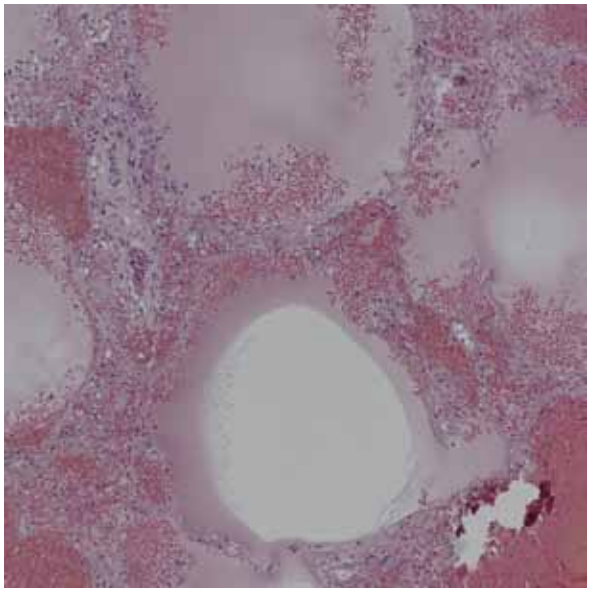

Fig. 1. *Hyaline membranes, alveolar edema. H&E staining,×10*

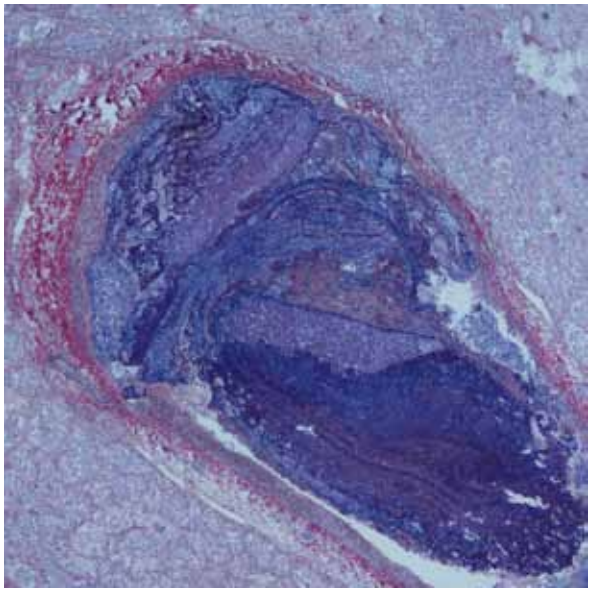

Fig.3. *Thrombus in the pulmonary artery. Phosphotungstic acid-hematoxylin (PTAH) staining, ×4*

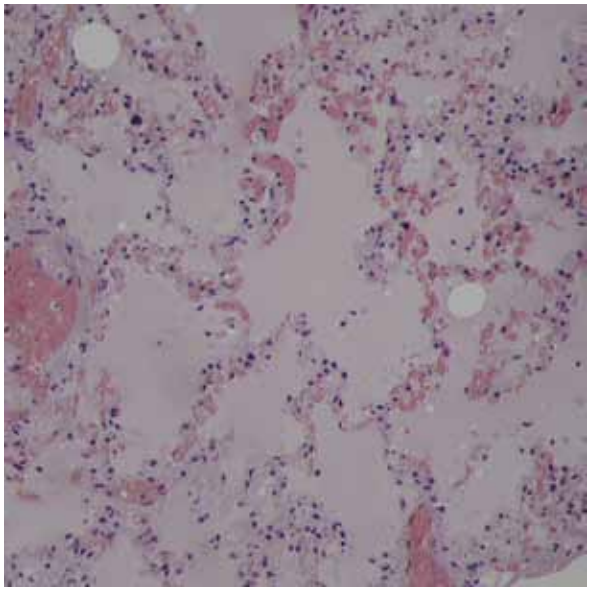

Figure 2. *Alveolar edema. H&E staining,×20*

In patients who died during the third week of hospitalization (12 persons), pulmonary fibrosis (Fig. 5) was detected in 11 cases (91%), hyaline membranes in 2 cases (16%), alveolar edema was observed in 1 case (8%), alveolar hemorrhages were noted in 8 patients (67%). Small vessel congestion was observed in 5 patients (42%), pulmonary vascular thrombosis - in 4 persons (33%), DIC syndrome was recorded in 1 person (8%). Desquamation of bronchial and alveolar epithelium was detected in 5 (42%) and 4 (33%) patients, respectively. Metaplasia of alveolar epithelium was observed in 3 patients (25%). Purulent pneumonia was seen in 4 cases (25%).

CONCLUSION

Thus, at all stages of the disease, lung alteration (desquamation of bronchial and alveolar epithelium), circulatory disorders (alveolar edema and hemorrhages, congestion in small blood vessels, thrombosis), compensatory response (fibrosis) were found.

In patients who died during the first week of hospitalization, circulatory disorders (alveolar edema, hyaline membranes, alveolar hemorrhages, microcirculatory system congestion) prevail. It is noteworthy that fibrosis, usually not typical for the first week of ARDS, was detected in 46% of the patients, which could be due to late hospitalization or specific pattern of fibrosis development in COVID-19.

Those who died in the 2nd and 3rd weeks of hospitalization showed predominant compensatory response and progression of fibrosis. By the 3rd week, pulmonary fibrosis was detected in 91% of patients.

Thrombotic complications (thrombosis, pulmonary thromboembolism) were noted in almost half of patients who died in weeks 2–3. Despite the large number of studies of hemostasis in COVID-19, the mechanisms of thrombosis are not fully understood.

Coagulation disorders have been noted in many viral diseases, including coronavirus infection, Ebola and Dengue fever [3, 11, 14]. Coronavirus infection is assumed to induce endothelial dysfunction caus-

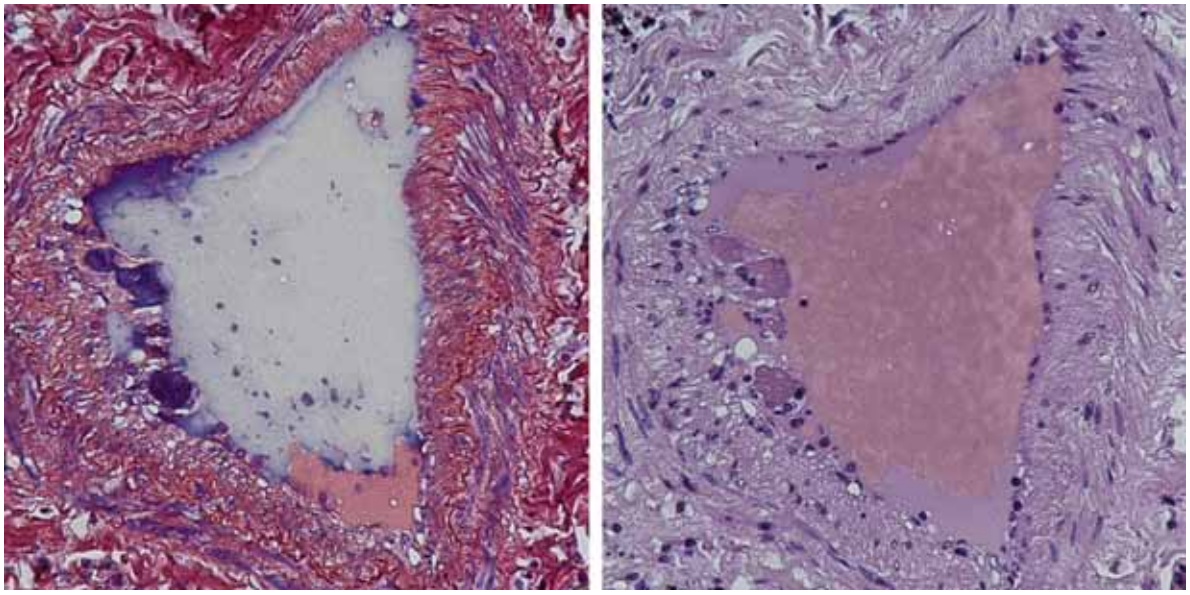

Fig. 4. *Mural thrombus in the pulmonary artery. PTAH staining, ×40 (on the left); H&E staining, ×40 (on the right)*

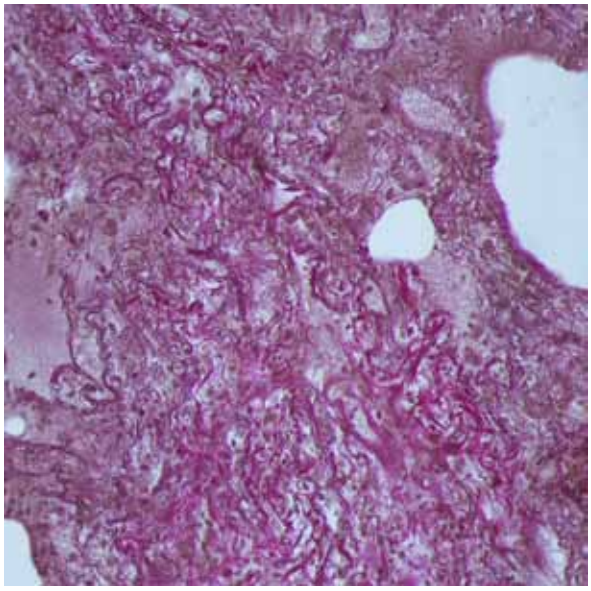

Fig. 5. *Lung fibrosis. Elastic fibers appear purple-red to brown in color. Collagen stained various shades of red. Weigert-Van Gieson staining, ×20*

ing abnormal coagulation. Thrombosis could also have underlying autoimmune mechanisms [8, 14, 19]. Varga Z. et al. (2020) suggest vasculitis and leukocytic infiltration of pulmonary vascular walls as a cause of endothelial damage [16].

Samsonova M. et al. (2020) having analyzed autopsy material of 123 patients who had died of COVID-19, revealed infiltration of pulmonary vascular wall by single lymphocytes only in 8.13% of patients, which is not typical for vasculitis [14]. In our study, no signs of vasculitis were found in any observation.

Notably, according to the results of our study, most deceased patients (86% of cases) with pulmonary thrombi were on mechanical ventilation. Consequently, the role of ventilator-associated complications in the pathogenesis of lung damage in COVID-19 cannot be excluded [10]. According to the experimental data, mechanical lung ventilation is accompanied by significant histological abnormalities in the lungs, including pulmonary vascular thrombosis [4].

Hemorrhagic lung infarction, detected in 43% (6 people) who died in the second week of hospitalization, of which three were diagnosed with PE, indicates the progression of pulmonary vascular system damage.

To date, many issues of pathogenesis of new coronavirus infection and its complications remain open. The ongoing pandemic and the requirements to improve the treatment strategy in severe COVID-19 necessitate further research in order to better understand the pathogenesis of this infection.

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CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF CHILDREN WITH PCR-CONFIRMED COVID-19 IN VOLGOGRAD REGION, RUSSIA

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ABSTRACT — The paper identifies for the first time for the Volgograd region (Russia) the clinical and epidemiological characteristics of children 0-16 years old with the laboratory confirmed diagnosis of COVID-19 hospitalized in a children's infectious clinic in April-August 2020. The Volgograd Region is one of the biggest territorial entities in Southern Russia; therefore our first published analytical data needs to be compared with relevant Russian/European data. The diagnosis was verified by the nucleic acid amplification: isolation of SARS-CoV-2 RNA by the polymerase chain reaction (PCR) from the upper respiratory tract mucosa. The study did not include outpatients. Rarity of such symptoms as headache and weakness (7.1%), as well as dysosmia (4.1%) in the complete absence of dysgeusia attracted our attention. In none of the patients we were able to identify an exanthem over the course of infection.

KEYWORDS — COVID-19 in children, SARS-CoV-2, clinical and epidemiological characteristics.

INTRODUCTION

Currently, the certain amount of knowledge has been accumulated on the etiology, epidemiology, clinic, diagnosis, treatment and prevention of a new type of coronavirus infection [1]. In the diagnostic aspect, along with molecular genetic research methods, there is the auxiliary possibility of making a diagnosis by the serological methods. In the treatment of COVID-19 in adults, there is a potential for using etiotropic therapy (favipiravir, remdesivir). Two Russian vaccines against this infection have been registered, another domestic development is planned to be registered, and their active introduction into the clinical practice has begun. At the same time, the children's contingent of patients is given slightly less attention than the age categories of the patients. This can be explained by the fact that according to available data, children get sick less often, with less pronounced clinical symptoms, less often require hospitalization, the disease is easier for them than for age-related patients, which, however, does not exclude cases of severe course. Available Russian data indicate that children account for 6-8% of reported COVID-19 cases [2].

Aim:

To analyze clinical and epidemiological indicators in hospitalized children with SARS-CoV-2 infection.

MATERIAL AND METHODS

The retrospective study was conducted on the basis of the specialized children's infectious diseases hospital providing specialized care to patients with COVID-19 in April-August 2020.

Based on the study of medical documentation, the results of clinical and epidemiological, laboratory (general clinical, serological, molecular genetic) and instrumental methods of research in children aged 0 to 16 years with isolated SARS-CoV-2 RNA by PCR from the upper respiratory tract mucosa were analyzed. The study did not include patients who were on outpatient treatment. The total of 169 medical records of children aged 0-16 years with PCR-confirmed infection caused by SARS-CoV-2 were retrospectively analyzed.

RESULTS

The results obtained generally coincide with similar Russian and foreign studies [3, 4].

Of the 169 patients studied, the majority were male: 89 (52.7%) boys versus 80 (47.3%) girls. The average age of hospitalized children was 8.5±4.2 years; the largest number of patients was in the age cohort of 10–16 years (72 children).

According to the patient geography, it was expected that the largest number of children lived in the regional center — 66 (39.1%), in the second big city– 17 (10.1%), even less — in the districts of the region.

The distribution by severity of hospitalized children was as follows: 57% of patients had a mild infection, 24% — asymptomatic, 17% — moderate and 2% — severe.

Almost all patients from the group of moderate severity (27; 15.9%) had the disease in pneumonia,

which was verified by X-ray methods and did not require any respiratory support. When trying to differentiate between viral pneumonia and complicated bacterial forms of pneumonia, we found that bacterial changes in CBC (leukocytosis >15×10^9/l and/or rod neutrophils >10%) were detected in only three patients (11.1%). Since the specific marker of bacterial inflammation — procalcitonin — was not determined, as well as the bacteriological examination of sputum was not performed, we are inclined to conclude that the absolute majority of patients (88.9%) did not show signs of bacterial genesis of pneumonia.

Regarding the duration of the hospital treatment of COVID-19 in children, it was found that the lowest stay time was in the cohort of children aged 1 month – 1 year (10.3±6.4 days) with a moderate course, and the highest (18±3.7 days) children 6–9 years old also have a moderate course. Thus, we were not able to identify the relationship between the age of the child, the severity of the disease and the duration of the hospitalization.

The distribution of the patients according to the presence of complaints at admission to hospital was interesting to us. About a quarter (24.3%) of patients had no complaints, as well as clinical manifestations of the infectious process. Most often, patients, or rather their representatives, complained of an increase in body temperature (53.3%), less often of catarrhal manifestations — cough and sore throat (25.4%), as well as runny nose and nasal congestion (20.7%). Attention is drawn to the rarity of such symptoms as headache and weakness (7.1%), as well as dysosmia (4.1%) in the complete absence of dysgeusia. Gastrointestinal symptoms (3.6%) and manifestations of respiratory disorders (2.4%) were also rare. In none of the patients we were able to identify an exanthem over the course of infection.

The analysis of the objective indicators at admission to the hospital generally corresponds to the mild and the asymptomatic forms of the infectious process. The body temperature in almost all age groups was within the normal range of the figures. The highest rates (38.1±0.4 °C) were found in the group of children 1 month – 1 year with the moderate course. In the laboratory data, we did not notice any significant deviations from the age norms. So in the group of children up to 1 month in CBC with the normal leukocyte levels, the relative lymphocytosis was observed. The parameters of the red blood and the platelets were also intact in the most cases. Only in 2.9% of the cases, the undetected cytolysis was detected with an increase in AlT/AsT in the range of 38.33–95.83 u/l, the violation of the bilirubin metabolism occurred at the level of a statistical error (1.2%). No patients were found to have elevated levels of CRP.

According to the analysis of the conducted pharmacotherapy of sick children, it can be established that in the most cases one or another drug was prescribed, even with an asymptomatic course of the disease. Thus, in 61.5% of the cases, drugs of recombinant interferon-alpha in the intranasal form of release were prescribed, less often (43.8%) — umifenovir in tablet form, 26.6% of children received tablet imidazolylethanamide of pentanediic acid. This group of drugs can be attributed to *conditional* etiotropic therapy, since they can only indirectly participate in the elimination of SARS-CoV-2. Drugs with a proven etiotropic effect (favipiravir, remdesivir) are not used in pediatric practice at the time of publication of the article. Other groups of drugs were used much less frequently. Thus, systemic GCS (dexamethasone, prednisone) were used in 2.9% of cases, infusion therapy for detoxification — 3.6%, anticoagulants — 0.6%. Drugs from the NSAID group were prescribed to 15.4% of patients, mucolytic (ambroxol) — 23.5%.

Attention is drawn to the fact that in the fairly large number of the cases (41.4%), the antibacterial therapy was prescribed. Taking into account that only 27 (15.9%) had radiologically confirmed pneumonia, and of these, in turn, the signs of bacterial genesis of pneumonia were determined only in three (11.1%) and none of them showed a picture in the form of pronounced areas of *consolidation*, it can be assumed that in certain cases the appointment of the antibacterial therapy was premature and required the more differentiated approach. The most frequently prescribed antibacterial drugs from the group of the cephalosporins of the 3rd generation (68.6% of all prescriptions), much less often macrolides-azithromycin (17.1%), in isolated cases — aminoglycosides (amikacin). One in five received a combination of two or more of these antibiotics.

CONCLUSION

Analyzing the data obtained, we can conclude the following.

1. About 82% of children infected with SARS-CoV-2 have the mild to asymptomatic disease.

2. In 15.9% of the patients, the disease occurred in a moderate form in the form of uncomplicated pneumonia, which does not require any respiratory support.

3. According to the objective clinical and laboratory indicators, there were no specific deviations.

4. In the treatment of COVID-19 in children, drugs related to conditionally antiviral drugs were most often prescribed: in 61.5% of cases, recombinant interferon-alpha drugs were prescribed, less often (43.8%) — umifenovir, 26.6% of children received imidazolylethanamide pentanedioic acid.

5. Attention is drawn to the fact that in the fairly large number of the cases (41.4%), the antibacterial therapy was prescribed, the approach to the appointment of which should be more differentiated.

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COMMUNICATION EFFORT SCORE (CES) IN PATIENTS HOSPITALIZED IN INTERNAL MEDICINE WARD

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ABSTRACT — Aims: There are more than thirty prognostic scoring systems defined in the literature for emergency patients up to now. The purpose of this study is to develop communication effort score (CES) to be used in internal medicine ward by considering it from a different angle, and also to examine the relation of this index with prognosis.
Methods: The study had a prospective-observational study design, and was conducted on patients followed-up in the ward due to acute diseases. The patients were graded under 4 categories according to communication effort within the first 8 hours after referring to emergency department, between exhibiting active communication effort and being closed to communication.The prognostic performance of CES was tested comparatively with other scoring systems by using AUROC analysis.
Results: Data were collected on 308 consecutive acute medical admissions, 55.2% of whom were men, with the mean age of 65.4 ± 15.6 years The mortality rate of the patients in hospital was 2% in CES-1, 4.8% in CES-2, 27.2% in CES-3; and 51.6% in CES-4.The CES model showed a good discrimination power for in-hospital mortality as 0.813 AUC(95% CI, 0.77–0.85). These results were better than the prognostic scoring systems (RAPS, MEWS, REMS, WPS, GAP, and NEWS) and the other specific and general descriptive scoring systems (ECOG, GCS, qSOFA, CCL). The sensitivity and specificity of CES for the optimal cut-off point (2.5) in predicting in-hospital mortality were 0.957 and 0.632, respectively.
Conclusions: The present study showed that CES, which is a new definitive score, is a strong predictor of both in-hospital mortality and short-term mortality.

KEYWORDS — Communication Effort Score, CES, acute medical admission, internal medicine ward, early warning scoring systems, prognosis.

HIGHLIGHTS

— The CES model showed a good discrimination in in-hospital mortality (AUROC:0.813).
— The CES model also showed good discrimination in 1-month mortality (AUROC:0.827).
— The optimal cut-off level was 2.5 with 95% sens, 63% spec for in-hospital mortality.
— CES is a strong predictor of in-hospital and 1-month mortality (HR:3.2 and 3.4 respec).

INTRODUCTION

Several scoring systems have been developed — either disease-specific or general-varying according to the place used and the purpose of use for first evaluation of patients, to identify the seriousness of their diseases, and to determine the risk of mortality and morbidity. For example, specific scoring systems such as the New York Heart Association (NYHA-1974) system used for functional classification of patients admitted with heart failure [1], Killip (1967) heart failure classification used for patients admitted with acute coronary syndrome [2], Eastern Cooperative Oncology Group (ECOG-1960) [3] performance score used for cancer patients, Child-Pugh Score [4] used in patients with cirrhosis, CURB-65 (2003) Score [5] used for patients with pneumonia, quick Sepsis-related Organ Failure Assessment (qSOFA-2016) [6]used in patients with sepsis, and general scoring systems such as Charlson Comorbidity Index (CCI-1987) [7], which shows the chronic disease burden.

Scoring systems that evaluate the seriousness of the disease in detail including clinical and laboratory parameters are used in guiding the treatment in Intensive Care Units (ICUs), while scoring systems that are simpler and faster are preferred in emergency services. The Glasgow Coma Scale (GCS-1961) [8], which is widely used in evaluating conscious and coma in emergency services, and several other prognostic scoring systems were developed, such as Rapid Acute Physiology Score (RAPS-1987[9]), used in critical patient identification, Modified Early Warning Scores (MEWS-2001) [10], Rapid Emergency Medicine Score (REMS-2004) [11], Goodacre score (2006 [12]), Worthing Physiological Scoring System (WPS-2007) [13], Groarke (2008) [14], VitalPac Early Warning Score (ViEWS-2010) [15], National Early Warning Score (NEWS-2012) [16], and Glasgow Coma Scale-Age-Systolic Blood Pressure (GAP-2011) [17], which is used in trauma patients. In this respect, according to a compilation that included 48 studies that received high references, 28 different early warning scoring systems regarding patients admitted to emergency services were developed [18]. In another study, that number is reported as 34 [19]. Although there are many scoring systems used in specific disease groups or featured clinics, there is no scoring system

used in general identification or performance evaluation of patients in internal medicine wards.

With this study, the purpose was to develop a scoring system from a different perspective, based solely on observation and communication, reflecting the performance status of patients followed-up with acute internal diseases in wards, to examine the relation of this scoring system with mortality, and to compare it with various scoring systems defined in the literature so far.

METHODS

Study design

The study was a prospective and observational study conducted on patients who were hospitalized due to acute internal diseases in the internal medicine ward of Dr. Lutfi Kırdar Kartal Training and Research Hospital in Istanbul between May 2019 — November 2019. The study was in line with the Helsinki Declaration, and was conducted after the necessary ethical board permission was obtained.

Patient population

Patients who were over the age of 18 admitted to the Emergency Service due to acute internal diseases (acute kidney damage, acute GIS bleeding, acute pancreatitis, acute liver damage, and electrolyte disorder) and referred to the internal medicine ward were included in the study consecutively. Patients who required acute surgical intervention, who were evaluated with acute or subacute traumas, whose first intervention was carried out in another healthcare center, or who were admitted to ICU, were not included in the study.

Communication Effort Score (CES)

All patients admitted to the Emergency Service, and who were then admitted to the internal medicine service with acute internal diseases were evaluated by the internal medicine specialist in the visits within the first 8 hours. The attitudes of the patients during the visits, and their efforts to communicate were carefully evaluated by the entire team, grouped in 4 stages, and were then recorded in the Case Report Forms. These four groups were as follows;

1. Agile (alert) physical communication effort
2. Slow physical communication effort
3. Verbal communication effort
4. No communication effort

To define these groups in more detail:

1. Patients who were very open to communication, who participated actively in physical terms straightened up dynamically in their beds, or waited upright in bed during visits.
2. Patients who were open to communication, physically participated in a resigned way, followed the instructions exhaustedly, tried to straighten up slowly during the visits, or waited in a position sitting with a 45-degree angle.
3. Patients who could only communicate verbally, who could not participate physically, who could follow the instructions only with help, who did not try to straighten up physically during the visits, and who waited in a semi-lying position.
4. Patients who did not have any communication efforts, who shut themselves out physically and psychologically, did not follow instructions, did not straighten up during visits, and those who did not change the full-lying position.

Clinical follow-up

The demographic data, comorbidities, hospitalization indications, clinical findings (anamnesis, arterial blood pressure, heart peak beat, respiratory count per minute, O2 saturation, body temperature, and consciousness status) were recorded in the Case Report Forms specific to the study and to the database.

The hospital admission dates, hospital stay times, release from the ward dates, discharge status (as are, with cure, refusal of treatment, transfer to ICU, and exitus), and the dates of transfer to ICU of all the patients were recorded in the same way. The hospital stay (ward ± ICU) times as of the date of admission to the Emergency Service were recorded, and the 30, 90 and 180-day follow-ups were performed. The in-hospital mortality status of the patients was checked from the hospital data systems; and the 30-day, 90-day and 180-day mortality status was checked from the national death notification system. The findings were recorded in the Case Report Forms.

Statistical Analyses

The data were analyzed by using IBM Statistical Package for Social Sciences (SPSS version 22 for Windows), and were considered significant at $\alpha<0.05$. After confirming the approximate normality of the data by using skewness and kurtosis, descriptive statistics for clinical parameters and all scoring systems were presented by arithmetic mean (standard deviation; SD) or median [min-max], or percentages (% and number). For testing hypothesis about difference of means between the 2 groups, continuous variables were compared using either the t-test (normal distribution) or the Mann-Whitney test (non-normal distribution). To test the hypothesis about the difference in frequency, the Chi-Square test was used.

The prognostic performance of the new scoring system (CES) was tested comparatively with others

(RAPS, MEWS, REMS, WPS, GAP, NEWS, ECOG, GCS, qSOFA and CCI). Discrimination power (i.e., the ability to distinguish between survivors and non-survivors) was assessed using the Receiver Operator Characteristic (ROC) Curves and the Area under ROC curves (AUROC).GCS and GAP were defined as 1-GCS and 1-GAP in order to compare AUROCs, because the high scores of them show poor prognosis, unlike others. A value of 0.5 indicated no discrimination, 0.7–0.8 indicated reasonable discrimination, exceeding 0.8 indicated excellent discrimination, and 1 indicated perfect discrimination. In addition, the sensitivity and specificity of CES were calculated based on the optimal cutting value. Univariate cox-regression analyses were carried out to assess the association for in-hospital, and 1-month mortality in all scoring systems. The Hazard Ratio (HR) with 95% confidence interval (CI) was calculated in the regression models.

RESULTS

Data were collected from 308 consecutive emergency medical admissions. A total of 170 (55.2%) were male, and the mean age was 65.4+15.6 years [min–max: 18–94]. A total of 68.2% of the patients were discharged with recovery, 5.5%in their current conditions, 5.8%by rejecting the treatment upon their will, 3.9% died, 16.9% were transferred to ICU; and 98.1% of those who were transferred to ICU died in hospital. In this respect, the in-hospital mortality rate was determined to be 20.5% (63/308).

The hospital stay duration of the survivors was 7 days [1–47], and that of those who died was 13 days [2–58]. A total of 31.7% of in-hospital deaths (20/63) occurred in 1 week, 52.3% (33/63) in 2 weeks, 87.3% (55/63) in 1month. The comparative analysis of clinical findings and various scoring systems according to the in-hospital mortality status of the patients is summarized in Table 1.

Communication Effort Score (CES)

The patients were classified according to communication efforts during the first examination in the hospital admission. A total of 15.9% of all patients were categorized as CES-1 (n:49), 34.1% as CES-2 (n:105), 29.9% as CES-3 (n:92), and 20.1% as CES-4 (n:62). According to CES scores of the patients, hospital stay times and in-hospital mortality rates are presented in Table 2.

According to the communication effort scores, the in-hospital, 1-month, 3-month and 6-month mortality rates of the patients are presented in Fig 1. As seen, the in-hospital mortality rates were 2% in patients with CES-1; 4.8% in patients with CES-2; 27.2% in patients with CES-3; and 51.6% in patients with CES-4; and it was determined that the 1-3-6-month mortality rates had a similarly increasing trend.

Comparison of CES with other scoring systems

As seen in Table 3, the scores that predicted in-hospital mortality showed a discrimination power between 0.568 and 0.813, and the discrimination power of the same scores were determined between 0.570 and 0.827 for 1-month mortality.

The CES Model showed good discrimination with 0.813 AUC (95% CI, 0.77–0.85) for in-hospital mortality, and 0.827 AUC (95% CI, 0.79–0.86) for 1-month mortality. In this respect, the in-hospital mortality and 1-month mortality power of CES were significantly better than the prognostic scoring systems (RAPS, MEWS, REMS, WPS, GAP, and NEWS), and other specific and general descriptive scoring systems (ECOG, GCS, qSOFA, and CCI) (Fig. 2).

The cut-off point that gave the maximum combined sensitivity and specificity for CES was 2.5. The sensitivity and specificity of CES for this cut-off point was 0.957 and 0.632, respectively.

Univariate Cox Regression Analysis was made to compare the power of all scoring systems in predicting the in-hospital mortality and 1-month mortality. It was determined that all scoring systems predicted in-hospital mortality and 1-month mortality, and CES, the new score, had the highest predictive power (for in-hospital mortality: HR:3.26, 95% CI:2.45–4.24; for 1-month mortality: HR:3.46 95% CI:2.77–4.31) (Table 4).

DISCUSSION

The present study of ours showed that CES, which is a new descriptive scoring system, is a strong predictor of both in-hospital mortality and 1-month short-term mortality. This scoring system, which is scored between active communication and being closed to communication, is important for high-score patients to show the requirement of being monitored more closely. In addition, it was found that the rate of in-hospital mortality of patients with CES 1 was 2%, and those with CES 4 was increased to 51.6%.

ECOG, which shows the performance status in cancer patients, evaluates the physical activity and bed-dependency status of patients only, and is similar to ours because it does not depend on any clinical or laboratory values [3]. It has been demonstrated with this study that CES is a scoring system that can be used as a prognosis indicator, even in internal medicine ward, where not only cancer patients but also all chronic diseases are included, and after our recent scor-

Table 1. *Analysis of scoring systems according to their prognosis in our patient population*

	survivors (n: 245)			non-survivors (n: 63)			p sig
	Mean	SD	Min-Max	Mean	SD	Min-Max	
Age, years	63,9	(16,3)	[18-94]	71,5	(10,6)	[40-91]	<0,001
LHS, days	9,48	(9,3)	[1-47]	16,65	(12,6)	[2-58]	<0,001
Clinical findings							
HR, bpm	88,1	(16,7)	[48-140]	94,7	(19,1)	[58-150]	<0,001
RR, c/min	15,0	(3,9)	[8-35]	19,2	(6,3)	[10-34]	<0,001
SBP, mm Hg	119,3	(24,4)	[50-200]	114,0	(28,5)	[60-220]	0,065
MAP, mm Hg	87,6	(15,6)	[37-140]	83,6	(17,4)	[40-140]	0,016
BT, °C	36,8	(,6)	[35,6-39,5]	36,7	(,7)	[34,8-39]	0,396
SaO_2, %	95,1	(3,3)	[80-100]	94,0	(3,4)	[83-99]	0,015
Scoring systems							
CES	2,32	(,9)	[1-4]	3,43	(,7)	[1-4]	<0,001
RAPS	0,88	(1,3)	[0-5]	1,27	(1,7)	[0-6]	0,013
MeWS	1,11	(1,4)	[0-7]	2,31	(2,2)	[0-10]	<0,001
REMS	4,95	(2,8)	[0-12]	6,26	(2,3)	[1-14]	<0,001
WPS	1,22	(1,7)	[0-8]	3,02	(2,6)	[0-11]	<0,001
GAP	20,79	(2,1)	[10-24]	19,75	(1,7)	[14-24]	<0,001
NEWS	2,52	(2,1)	[0-12]	5,02	(3,5)	[0-17]	<0,001
qSOFA	0,42	(,6)	[0-3]	0,95	(,8)	[0-3]	<0,001
CCI	4,41	(2,7)	[0-11]	5,98	(2,9)	[0-14]	<0,001
GKS	14,82	(,9)	[6-15]	14,61	(,9)	[10-15]	0,023
ECOG	1,68	(1,3)	[0-4]	3,17	(1,1)	[0-4]	<0,001

LHS: *Length of hospital stay, HR: Heart rate,RR: Respiratory rate, SBP: Systolic blood pressure, MAP: Mean arterial pressure, BT: Body temperature, SaO_2: Oxygen saturation, CES: Communication effort score, ECOG: Eastern Cooperative Oncology Group performance score, GCS: Glasgow Coma Scale, RAPS: Rapid Acute Physiology Score, MEWS: Modified Early Warning Scores, REMS: Rapid Emergency Medicine Score, WPS: Worthing Physiological Scoring System, GAP: Glasgow Coma Scale-Age-Systolic Blood Pressure, NEWS: National Early Warning Score, CCI: Charlson Co-morbidity Index, qSOFA: quick Sepsis-related Organ Failure Assessment*

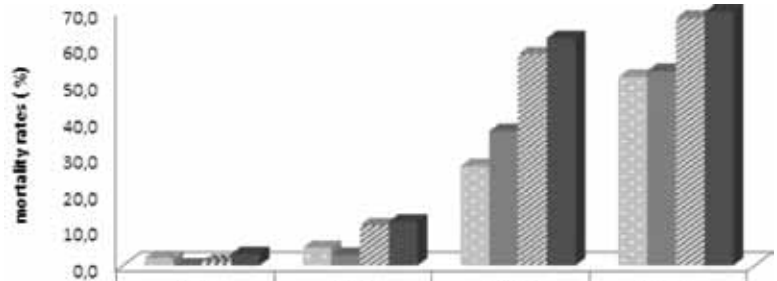
Table 2. *Length of hospital stay and in-hospital mortality rates according to communication effort scores*

		survivors					non-survivors				
score on admission	no of patients	number of patients (%)		length of hospital stay mean(sd) [min-max]			number of patients (%)		length of hospital stay mean(sd) [min-max]		
CES 1	49	48	(98,0%)	3,4	(2,1)	[1-9]	1	(2,0%)	58,0	(.)	[58]
CES 2	105	100	(95,2%)	11,1	(9,8)	[1-47]	5	(4,8%)	33,8	(16,0)	[12-58]
CES 3	92	67	(72,8%)	11,2	(10,5)	[1-44]	25	(27,2%)	16,6	(10,5)	[3-37]
CES 4	62	30	(48,4%)	10,1	(8,2)	[2-35]	32	(51,6%)	13,6	(10,6)	[2-37]

ing system, it is the strongest predictor [for in-hospital and 1-month mortality: HR:2.3(1.78–2.95) and 2.34 (1.97–2.77)] and again, it has the best discrimination power after CES for mortality (AUROC 0.780 and 0.810,respectively).

Similarly, GCS, which is widely used in the evaluation of consciousness and coma, is a scoring system that evaluates both verbal, motor, eye and clinical response, and is similar to ours in that it is independent from the laboratory[8]. Although it meets the needs in emergency services and Intensive Care Units, it does not seem to be appropriate to use in identifying patients who are generally conscious in the internal medicine ward. In fact, the low short-term mortality prediction in our study population supports this situation.

CCI, which shows the burden of chronic disease in 17 areas, from myocardial infarction to meta-



	CES 1	CES 2	CES 3	CES 4
in-hospital	2,0	4,8	27,2	51,6
1-month	0,0	2,9	36,8	53,2
3-month	1,0	11,0	57,8	67,7
6-month	3,1	12,0	62,2	69,4

Fig. 1. *Mortality rates according to communication effort score*

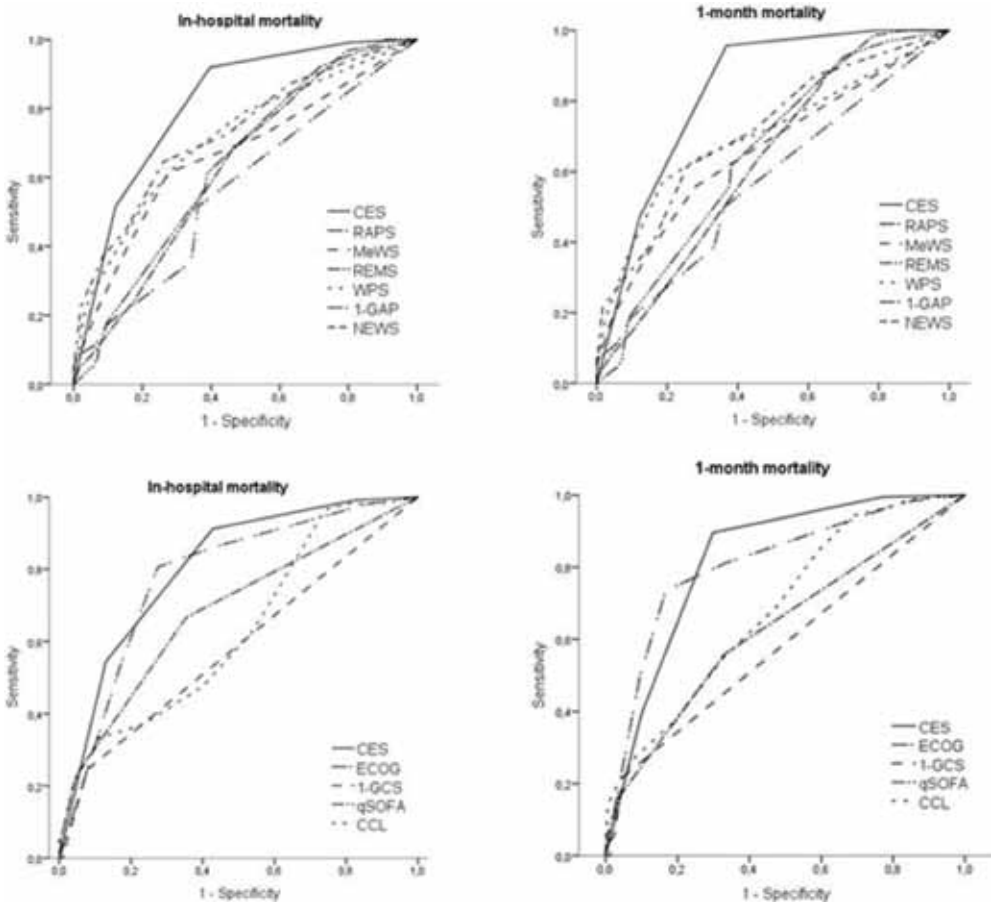


Fig. 2. *Receiver operating curves for predicting hospital admission according to the new scoring system (CES) and RAPS, MEWS, REMS, WPS, GAP, NEWS and ECOG, GCS, qSOFA, CCI*

static tumors, also has a usage in patients in internal medicine wards dealing with comorbidities[7]. It was demonstrated with this study that this index, which is originally used in 10-year mortality prediction, has the strength of predictive power in in-hospital mortality and short-term mortality albeit this power is weak.

The qSOFA, which is defined in adult patients suspected of infection in out-of-hospital, Emergency Service or general hospital conditions, is used to identify the sepsis-related prognosis[6]. This score, which is created based on simple clinical indicators like blood pressure and respiratory count, and mental state, was proven with our study that it can be used as a short-term mortality indicator in patients in the general internal medicine ward, except for sepsis. It was shown that the in-hospital and 1-month mortality predic-

Table 3. *Discriminatory power for predicting in-hospital mortality and 1-month mortality for all scores*

	In-hospital mortality		1-month mortality	
	AUROC (95% CI)	p sig.	AUROC (95% CI)	p sig.
CES	0,813 (0,77-0,85)	<0,001	0,827 (0,79-0,86)	<0,001
RAPS	0,568 (0,51-0,62)	0,020	0,570 (0,51-0,62)	0,012
MeWS	0,667 (0,61-0,72)	<0,001	0,658 (0,60-0,71)	<0,001
REMS	0,632 (0,58-0,68)	<0,001	0,631 (0,58-0,68)	<0,001
WPS	0,715 (0,66-0,77)	<0,001	0,703 (0,65-0,76)	<0,001
1-GAP	0,641 (0,59-0,69)	<0,001	0,649 (0,60-0,70)	<0,001
NEWS	0,730 (0,68-0,78)	<0,001	0,715 (0,67-0,76)	<0,001
ECOG	0,780 (0,73-0,83)	<0,001	0,810 (0,77-0,85)	<0,001
1-GCS	0,583 (0,52-0,65)	0,007	0,584 (0,53-0,63)	0,001
qSOFA	0,682 (0,62-0,74)	<0,001	0,631 (0,58-0,68)	<0,001
CCI	0,630 (0,57-0,69)	<0,001	0,687 (0,64-0,73)	<0,001

GCS and GAP were defined as 1-GCS and 1-GAP in order to compare AUROCs, because the high scores of them show poor prognosis, unlike others

Table 4. *Univariate cox regression analysis for predicting in-hospital mortality and 1-month mortality*

	In-hospital mortality		1-month mortality	
	Sig.	HR (95% CI)	Sig.	HR (95% CI)
CES	<0,001	3,26(2,45-4,24)	<0,001	3,46(2,77-4,31)
RAPS	0,038	1,22(1,01-1,47)	0,041	1,19(1,01-1,40)
MeWS	<0,001	1,33(1,18-1,49)	0,002	1,45(1,31-1,62)
REMS	<0,001	1,21(1,08-1,35)	0,006	1,24(1,04-1,36)
WPS	<0,001	1,48(1,34-1,63)	<0,001	1,50(1,36-1,65)
GAP	<0,001	0,78(0,70-0,87)	<0,001	0,76(0,69-0,85)
NEWS	<0,001	1,41(1,30-1,54)	<0,001	1,38(1,27-1,49)
ECOG	<0,001	2,30(1,78-2,95)	<0,001	2,34(1,97-2,77)
GCS	0,012	0,81(0,62-1,06)	0,004	0,72(0,58-0,90)
qSOFA	<0,001	1,95(1,58-2,36)	<0,001	2,15(1,74-2,54)
CCI	<0,001	1,23(1,11-1,37)	0,003	1,14(1,04-1,24)

CES: *Communication effort score, ECOG: Eastern Cooperative Oncology Group performance score, GCS: Glasgow Coma Scale, RAPS: Rapid Acute Physiology Score, MEWS: Modified Early Warning Scores, REMS: Rapid Emergency Medicine Score, WPS: Worthing Physiological Scoring System, GAP: Glasgow Coma Scale-Age-Systolic Blood Pressure, NEWS: National Early Warning Score, CCI: Charlson Co-morbidity Index, qSOFA: quick Sepsis-related Organ Failure Assessment*

tion scores are quite good when compared with other scoring systems [HR and 95%CI: 1.95(1.58–2.36) and 2.15 (1.74–2.54), respectively].

In this study, 6 of the early warning systems, which were also valuable as prognosis indicators in the emergency services, were applied to our patient population. In general, these systems are scored through clinical parameters like respiratory count, heart rate, blood pressure, conscious status, fever, and SaO_2. It was shown with regression analyses that WPS was a stronger predictor in both in-hospital mortality and 1-month mortality in patients in the internal medicine ward (HR:1.48, 95% CI:1.34–1.63). It was also determined that NEWS ranked the first with the highest number of discriminatory power among these, and WPS ranked the second (AUROC 0.730 and 0.715, respectively). Although a recent study conducted by Wei et al. has shown that REMS is stronger in predicting hospital stay time and in-hospital mortality compared to RAPS and NEWS[20], another study conducted on a fairly high patient population showed that NEWS is superior in distinguishing patients with cardiac arrest, unexpected ICU admission, or mortality risk[19].In another study comparing six scoring systems, it was reported that WPS had a good discriminatory power in identifying patients in terms of 24-hour and overall hospital mortality. The results of these two studies conducted on similar patient population of a similar nature support the result of the present study of ours [21].

The one-way scoring design of the WPS, just like GAP, is important in terms of ease of use. The other four scoring systems are more difficult to use, because they gradually make a bilateral scoring for both low and high values. When the other small differences among them were evaluated, the age factor was added to REMS and GAP; the body temperature was added to WPS and MEWS; O_2 saturation was added to WPS, REMS and NEWS; REMS and RAPS were based on average blood pressure, while others took only SKB as the basis; and REMS, RAPS and GAP used GCS in the evaluation of consciousness, and others used AVPU. Another point not be overlooked is that increasing scores in GCS and GAP show a clinical wellbeing, while in other scoring systems, including ECOG, CCI and qSOFA, increasing scores show deterioration.

The present study of ours naturally had limits. Firstly, only the acute medical patients with comorbidities were included in the study. For this reason, the results of it cannot be generalized for surgical or trauma patients or patients with ICU requirements. However, many statistically significant findings were found in the present study, which require further and wider investigation of patients hospitalized in internal medicine wards. We care about our study in terms of being a reference for future studies.

As a result, as the evidence accumulates, the beneficial clinical outcomes of scoring systems become clear. It is envisaged by us that CES, as one of these systems, can be used as an early prognostic indicator for patients who are at risk of worsening at the time of

admission to hospital. For this reason, CES can help both at the level of nursing care, in terms of the frequency of the physician visits, and with the decisions to be taken in patient management from the initial application to the resuscitation.

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Conflict of Interest

The authors state that they have no conflict of interest.

Data Availability

The dataset used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

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THE ROLE OF ENVIRONMENTAL FACTORS IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES PART 1. AIR POLLUTION

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ABSTRACT — Background. Many factors and mechanisms are involved in the pathogenesis of cardiovascular diseases (CVD). Among them, as recent studies show, environmental factors play a vital role. At the same time a number of modern achievements in health care, including the improvement of early diagnosis and treatment methods for CVD has not significantly affected the rates of morbidity, mortality and disability in the population worldwide. This circumstance emphasizes the need to study the influence of additional factors, including environmental factors, in the fundamental processes of CVD pathogenesis and the subsequent translation of this knowledge into clinical practice.
Goal. To study the effect of air pollution on the development and progression of cardiovascular diseases and discuss underlying causes.
Methods. Analysis of modern international literary sources indexed in the PubMed / Medline and Embase databases.
Results. Current clinical and experimental data support the relationship between air pollution with the risk of development and mortality caused by cardiovascular diseases. However, the pathophysiological mechanisms underlying this relationship are still underreported. It is believed that a vital role in the pathogenesis is played by endothelial dysfunction, increased thrombus formation, inflammatory processes and oxidative stress, which underlies the formation and progression of atherosclerosis, as well as an imbalance of the autonomic nervous system, which contributes to the development of arterial hypertension.
Conclusion. According to the study, atmospheric air pollution has a significant impact on the pathogenesis of cardiovascular diseases. There is an urgent need for a further study of the specific pathogenetic mechanisms underlying the influence of these environmental factors on the development and progression of CVD to develop further treatment and prevention strategies to minimize the negative impact.

KEYWORDS — Environmental factors; cardiovascular diseases; atherosclerosis, atmospheric air, pollution.

INTRODUCTION

Modern achievements in the diagnostics and treatment of cardiovascular diseases (CVD), such as early diagnosis and new therapeutic strategies, have not yet significantly affected the high rates of morbidity and mortality from CVD [9–11, 15, 20]. The prevalence of CVD increases steadily in countries with middle and low living standards, as well as in the developed countries. An example of this is the dynamics of static CVD mortality (coronary heart disease, heart attack, and stroke) in the United States from 1960 to 1990. CVD mortality rates gradually declined, after which there was a significant slowdown in the rate of decline. Still, shortly after, on the contrary, there was a steady rise in mortality and morbidity rates. Considering this trend by 2030, approximately 40% of the population will suffer from some form of CVD, according to experts' estimates [30, 37]. The widespread increase in morbidity and mortality from CVD and the inability to influence it significantly indicate a lack of understanding of the fundamental pathogenetic processes of CVD and insufficient attention of researchers to effects of environmental factors.

According to several researchers, human health is closely related to environmental factors [1, 2, 4]. Many diseases, including CVD, are caused by some chronic pathological processes resulting from a complex interaction between genetic predisposition and environmental / lifestyle factors, which leads to structural and functional disorders of tissues and cells of the cardiovascular system (CVS). Although the specific contribution of these factors is underresearched, there is every reason to believe that environmental and lifestyle factors play a more significant role in CVD development compared to genetic predisposition [4]. This opinion is supported by several studies, which have shown that changes in environmental factors and lifestyle can significantly affect the risk of CVD and further prognosis [1, 2, 4]. Hence, the data indicate that in most cases, it is possible to both prevent the development of CVD and improve the course and prognosis of an existing CVD by changing environmental factors and lifestyle of patients.

The purpose of this article, which is the first part of our review, is a comprehensive analysis of the negative impact of such an environmental factor as air pollution on the development and progression of CVD.

AIR POLLUTION

Our modernized environment is flooded with various synthetic chemicals and pollutants that may damage organs and tissues in the human body. According to some estimates, more than 30,000 synthetic substances are currently circulated, of which at least 5,500 are produced in significant volumes, amounting to about 100 tons per year [29]. Almost all major rivers and lakes are significantly polluted by synthetic compounds, pesticides, and heavy metal ions. However, many pesticides, including lindane, chlordane, and dichlorodiphenyltrichloromethylmethane (dust, DTT), have been found in the Canadian Rockies, human-made mercury has been found in uninhabited Arctic regions [46]. These data indicate that as a result of pollution of human habitats and the ubiquitous spread of pollutants, there are no unpolluted ("clean") places on the planet. High levels of pollutants are mainly released into the air, thus can be transported over long distances. According to research results, air pollution in many developing countries significantly exceeds the WHO standards [29, 46].

The largest contributors to air pollution are mixtures of complex aerosols containing both particles and gases. Among the contaminating particles, particulate matter (PM) is distinguished, which are divided into two peaks corresponding to large particles (10-2.5 μm) and small particles (0.1-2.5 μm), when analyzed by weight. The fine particle fraction also contains a small proportion of ultrafine particles, which, while making a modest contribution to the total PM volume, contains the most considerable amount of pollutants by quantity.

Aerosols released directly into the environment mainly consist of minerals, soot, particles of salts, pollen, and spores, while secondary aerosols are formed from sulfates, nitrates, and organic compounds. In addition to particulate matter, indoor and outdoor air contains various gaseous pollutants, including volatile organic compounds (VOCs), nitrates, nitrogen and sulfur oxides, and ozone. The WHO estimates that worldwide air pollution may be associated with 7 million premature deaths per year. Of these, 1.6 million deaths are in China and 1.3 million in India. However, in the USA, premature mortality from air pollution ranges from 55,000 to 100,000 [8, 34]. According to some data, when speaking about the mortality rates, air pollution competes with the consequences of hypertension, smoking, and lack of physical activity [12, 24]. It is unfortunate that in some developing countries of our planet, more than 95% of the urban population lives in cities that significantly exceed standards of pollution established by WHO [24]. According to a study by J. Lelieveld et al. [34], the primary sources of pollution in different geographic regions are as follows (Table). Notably, in developing countries (China and India) a significant proportion of deaths (about 10 million cases) due to air pollution were associated with domestic and commercial energy use [34]. Also, an estimated 3.54 million deaths are attributable to air pollution from biomass burning used to heat the homes.

In some other countries, particularly the United States and Western Europe, agriculture, power generation and road transport are major air pollutants. Agricultural pollution, which contributes to particulate matter of approximately 2.5 μm (PM 2.5), accounts for almost 20% of total ambient air pollution. According to the study, the mortality rate due to agricultural air pollution worldwide is approximately 6.6 million deaths [34].

Exposure to PM 2.5 is associated with approximately 70-80% of premature deaths from CVD [5]. The reasons for such a high vulnerability of organs and tissues of the cardiovascular system (CVS) to such particles remain unclear. There is evidence that even short-term exposure to polluted air is associated with myocardial infarction, stroke, arrhythmia, atrial fibrillation, and hospitalization due to exacerbated heart failure [6, 7, 24]. There is a very close relationship between chronic exposure to pollutants and the progression of atherosclerosis, impaired blood pressure regulation, increased peripheral thrombosis, as well as impaired endothelial function, and increased insulin resistance [6, 7, 14, 24, 26].

It is worth bearing in mind that air pollution has a variable effect on cardiovascular health depending on individual susceptibility and several additional factors. For example, people with pre-existing CVD, atherosclerosis or diabetes mellitus, or heavy smokers are more vulnerable to the adverse effects of air pollutants. Age, gender, ethnicity, and nutritional and socioeconomic status are important factors that influence human susceptibility to pollutants [26].

In contrast, people with good health are less prone to be affected by air pollutants. For example, an extensive study of 17,545 male workers found no correlation between CVD and long-term exposure to particulate matter. The absence of a negative impact on CVS health in these subjects was associated with a higher socioeconomic status and a healthy lifestyle [40]. However, another study reports that even young and healthy people show signs of endothelial damage and dysfunction in response to pollutants. Nonetheless, as the researchers suppose, such damage to CVS components in healthy people with a low risk of CVD can be compensated for a long time and not manifest clinically [39].

Table 1. *Premature mortality of the population of different countries, caused by various sources of air pollution. According to J. Lelieveld et al. [34]*

Source of pollution	% Worldwide mortality	% Mortality in the USA	Countries	The main constituents of polluted air
Residential (household) energy	31	6	China, India, Indonesia, Vietnam	Carbon dioxide, carbon monoxide, VOCs, nitrates, nitrogen oxides, sulfur oxide IV, mercury, PM 2.5
Agriculture	20	29	Europe, Russia, Japan, USA	Inorganic PM 2.5, ammonia, sulfates, nitrogen oxides
Power generation	14	31	USA, Russia, Korea, Turkey	Sulfates, nitrates, PM 2.5, mercury
Industrial pollution	7	6	Japan, Germany, China	Sulfates, PM 2.5, VOCs, hydrocarbons
Biomass burning	5	5	Canada, Africa, and South America, Australia, Southeast Asia	PM 2.5, nitrates, carbon monoxide, sulfur oxide IV, lead, mercury
Vehicles (transport)	5	21	USA, Germany, Russia, Japan	Ultrafine PM, PM 2.5, nitrates, nitrogen oxides, VOCs, ozone
Natural sources	18	2	Countries in Africa and the Middle East	PM 10 air dust

In addition to individual susceptibility factors, vulnerability to outdoor air pollution can be influenced by additional environmental influences such as noise, temperature, proximity to main roads or green areas of the city, and the combined effects of other pollutants and toxins. Thus, in people living near large roads, where the level of noise and pollution from vehicles is high, the tunica intima and tunica media of the carotid arteries are thicker than those living in areas further away from highways [3, 25, 31]. According to consistent results from some studies, the proximity of the roadway to residential areas was associated with an increased risk of acute myocardial infarction [33, 35, 44], sudden cardiac death [47], death from coronary heart disease [47], mortality after stroke [28], and mortality risk after hospitalization with acute heart failure [36]. It is believed that the risk of developing cardiovascular diseases and increased mortality from CVD in people living near major roads are due to vehicle emissions containing ultrafine PM [28, 36].

In addition to ultrafine particulate matter, emissions from road traffic also contain VOCs such as acrolein, benzene, and butadiene, which have been shown to exhibit significant cardiovascular toxicity by themselves [6]. Acute exposure to VOCs, in particular acrolein, can cause dyslipidemia [21], vascular damage [22], endothelial dysfunction [23] and platelet activation [42], whereas chronic exposure accelerates atherogenesis [43], destabilizes atherosclerotic lesions [38], may impair cardioprotective signaling and may cause dilated cardiomyopathy [32, 35]. Hence, VOCs and other gaseous pollutants such as nitric oxide, carbon monoxide, ozone, and sulfates, which account for more than 98% of the mixture we breathe in urban areas, can significantly alter the effects of PM and contribute to CVD in some way, especially in urban areas [7, 14].

Air pollution by particulate matter is also considered as one of the risk factors for comorbid (combined) diseases of the cardiovascular and respiratory systems [12, 18].

The connection between exposure to air pollution and cardiovascular diseases is also supported by data from studies in experimental (preclinical) animal models. Under controlled conditions, increased exposure to ambient PM has been shown to enhance atherogenesis, insulin resistance, and peripheral thrombosis in experimental animals [5, 6]. Experimental and clinical evidence suggests a strong relationship between CVD and air pollution; the underlying mechanisms are still unknown. It is crucial to define physiological and molecular mechanisms to recognize critical factors that control human susceptibility to the toxic action of particulate matter. Understanding will help us learn the effect of the pollutant on CVS health and develop therapeutic and prophylactic measures against this context to reduce CVD risk.

Concerning the mechanisms of the undesirable effects of air pollution on the cardiovascular system health, there are suggestions that PM enhances systemic inflammation and causes imbalances in the autonomic nervous system. According to many researchers, these processes are one of the leading investigation directions in this area. It is believed that particulate matter inhalation can lead to increased inflammation by *spreading* pro-inflammatory or oxidative mediators and cytokines from the respiratory system into the systemic circulation [13, 16, 19]. Inflammation and nervous system disbalances, in turn, potentially contribute to endothelial damage and the development of endothelial dysfunction, increasing the risk of atherosclerosis and thrombosis. Endothelial damage leads to a decrease in the ability to produce

anticoagulant substances and the loss of a protective barrier covering the subendothelial layer. As a result, thrombogenesis occurs, and microthrombi are formed in the affected areas [16, 17]. Also, hypoxia develops due to prolonged exposure to particulate matter on the respiratory system, which enhances inflammatory reactions and oxidative stress, linking exposure to PN to the pathogenesis of CVD [9]. Thus, chronic exposure to PM increases the risk of arterial hypertension, atherosclerosis, and the subsequent formation and complications of CVD.

This opinion is supported by several studies [27, 41]. It has been shown that oxidants formed in the lungs under the influence of PM can accelerate the formation of atherosclerotic lesions [41]. Furthermore, inactivation of the free radical (superoxide) due to the action of the antioxidant enzyme superoxide dismutase in the lungs can prevent endothelial dysfunction and the formation of PM-induced insulin resistance [27]. Remarkably, activation of the receptors in the respiratory system and nerve endings by inhaled particulate matter can lead to heart rate changes, heart rate variability, arrhythmias, and other electrocardiographic changes. Such changes increase the sympathetic tone, which subsequently predisposes to the development of arterial hypertension. These developing hemodynamic and electrophysiological changes may, to some extent, explain the PM-induced increase in the risk of acute cardiovascular events (myocardial infarction, stroke, acute heart failure, etc.) [28, 26, 44, 47] described above.

CONCLUSION

Numerous clinical and experimental evidence presented in this article indicates a close relationship between air pollution and CVD. There is a direct relationship between the degree of air pollution and the risk of CVD development, the risk of complications and deaths from CVD. Concurrently, the specific pathophysiological mechanisms underlying the negative impact of atmospheric air pollution on the pathogenesis of CVD remain poorly understood, which creates the need for further investigation and clarification. Understanding these mechanisms is of fundamental value and significant practical importance, which lies in the possibility of using such information for the development of therapeutic and prophylactic measures to minimize the negative impact of pollutants.

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INFLUENCE OF GEOMAGNETIC DISTURBANCE ON THE PSYCHOLOGICAL STATE OF THE INHABITANTS OF THE NORTH

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ABSTRACT — The aim of the work was to determine the influence of geomagnetic disturbance on the psychoemotional status of residents of polar and Subpolar latitudes. Materials and methods. 44 male and female volunteers with an average age of 49.2 (41.7; 55.4) years, living in auroral and sub – auroral latitudes were examined using tests of Ch. Spielberger-Yu. Hanin, E. Khaimah and psychosomatic techniques. The daily CR index (Computed Radiography) was used as an integral indicator of geomagnetic disturbance. Results. The volunteers were divided into two groups: psychologically sensitive to changes in space weather (I) and-not having such sensitivity (II) (based on the presence or absence of certain coincidences of the peak values of reactive anxiety and the CR index). The groups had an equal number of persons. It was found that the most problematic area of stress-overcoming behavior in both groups was behavioral, the most effective for group I — cognitive, for group II — emotional sphere. Individuals with psychological sensitivity to geomagnetic disturbances were significantly more anxious than those who did not have this sensitivity. Conclusion. Thus, despite the fact that all the inhabitants of the Northern latitudes observed by us were not sufficiently effective in constructing the actual stress-overcoming behavior, the risk of developing psychosomatic diseases was higher in the owners of psychological sensitivity to geomagnetic disturbance, taking into account their tendency to suppress emotions and significantly higher anxiety.

KEYWORDS — polar and subpolar latitudes, anxiety, psychological sensitivity, geomagnetic disturbance, multi-latitude monitoring, stress-overcoming behavior.

INTRODUCTION

Changes in space weather, which characterizes the state of near-earth space, are associated with processes occurring in the biosphere [10, 13]. Geomagnetic disturbance (GMD) as an external stress factor causes an increase in the processes of hemostasis, lipid peroxidation, a decrease in the production of nitric oxide, the level of immune protection, disorders of carbohydrate and lipid metabolism, the circadian rhythm of melatonin release, which, in turn, leads to an increase in blood pressure, increased thrombosis, increased insulin secretion and insulin resistance index [5, 6, 11]. The cardiovascular and nervous systems are most sensitive to the influence of heliogeophysical factors [8]. It is shown that the number of affective disorders, psychoses and psychosomatoses increases on the days of GMV [12, 15]. In auroral and subauroral latitudes, the characteristics of changes in geomagnetic factors differ significantly from the average latitudes. Under these conditions, their impact on Biosystems increases and the frequency and intensity of GMD changes in the wide frequency range increases [2, 12, 16]. Due to these circumstances the assessment of the psychophysiological status of people living in high latitudes is an urgent topic for determining the nature of the impact of space weather on human health.

The aim of the study

The aim of the work was to determine the influence of geomagnetic disturbance on the psychoemotional status of residents of polar and subpolar latitudes.

MATERIALS AND METHODS

As the territorial localization of this investigation, the village of Tiksi (auroral latitude) and Yakutsk (sub-auroral latitude), which in the spring of 2017 was held the next stage of the multi-latitude monitoring Geliomed-2, the aim of which is to study the impact of GMD on the nervous and cardiovascular system [7]. Among the relatively healthy volunteers, the number of which was 44 people, male persons predominated with 30 males and 14 females. The average age of the examined persons was 49.2 (41.7; 55.4) years. During March and April 2017, each volunteer was assessed daily for reactive anxiety levels by Ch. Spielberger–

Yu. Khanin [3]. Before the start of the monitoring phase, the persons under our supervision passed the test of A. Haym on the construction of stress-overcoming behavior with division by spheres (cognitive, emotional, behavioral) [14], the projective psychogeometric test by S. Delinger [1] and the second part of the questionnaire by Ch. Spielberger–Yu. Hanin to determine the levels of personal anxiety [3]. The choice of this combination of tests is explained in detail in one of our previous publications [4].

To assess the activity of space weather factors, the daily GMD — CR index was used-an index determined daily during a given observation period.

All participants in this work signed a voluntary informed consent.

Statistical processing of obtained results was performed using software package Statistica 6.0 and testing the null hypothesis on their normal distribution on the basis of calculation of the Shapiro-Wilk test and subsequent nonparametric and multivariate methods. The groups were compared using the Mann-Whitney U-test. The data were analyzed in the form of $M \pm \sigma$ for the mean and in the form of median (Me) with quartile range values (25%, 75%) for the samples. The reliability of the statistical estimates used was assumed to be at least 95%.

RESULTS

In the course of comparing the values of the Kr index and reactive anxiety indicators by Ch. Spielberger–Yu. Khanin, all the inhabitants of the subpolar latitudes involved in this stage of the project, were divided into two groups. The first group (14 males and 8 females) included respondents who had more than 66.7% of the peak values of these indicators in the dynamics of daily monitoring (psychologically sensitive to GMD), and the second group (16 males and 6 females) included those who had less or no matches (psychologically insensitive to GMD) [7]. Each group included 50% of the volunteers. Results of testing to determine the values of personal anxiety according to Ch. Spielberger–Yu. Hanin for individuals living in auroral and sub-auroral latitudes are shown in Fig. 1.

The data presented in Fig. 1 show that in the groups there was a significant difference between the average indicators of personal anxiety ($p<0.05$). In group I, anxiety as a disposition was close to a high level, while in group II, the level of personal anxiety was moderate.

When performing the test of A. Heim constructed for a stress-overcoming behavior with division by spheres, the results were obtained, illustrated in Fig. 2–4.

According to the data in Fig. 2 the volunteers with psychological sensitivity to changes in GMD

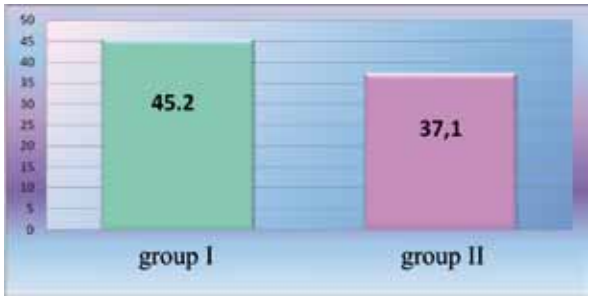

Fig. 1. *Averaged values of trait anxiety in the groups (in points)*

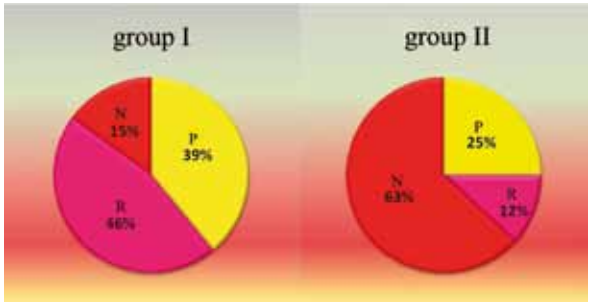

Fig. 2. *Distribution of coping-cognitions in the groups of volunteers*

Note: *Definitions for the types of coping-strategies: P — productive, R — relatively productive, N — non-productive*

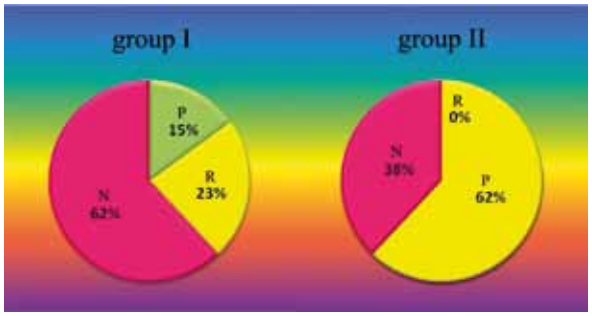

Fig. 3. *Distribution of emotional coping forms in the groups.*

Note: *Definitions for the types of coping-strategies: P — productive, R — relatively productive, N — non-productive*

(group I) chose productive coping cognitions almost twice as often as unproductive ones; and those who did not have this sensitivity (group II) — on the contrary (unproductive more often than productive), in the same ratio ($p<0.05$). The detailed analysis of the cognitive sphere in the groups revealed that the vast majority of people in group I chose to maintain self-control among the productive coping forms while the volunteers in group II preferred ignoring among the unproductive coping reactions.

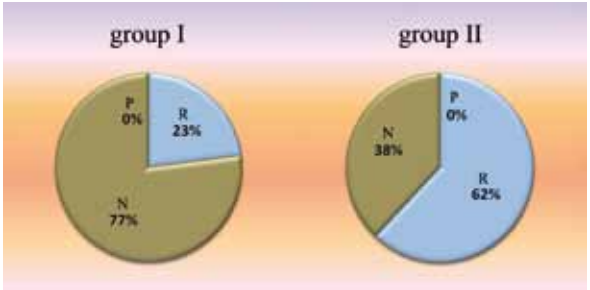

Fig. 4. *Distribution of behavioral coping-forms in the groups of volunteers*

Note: *Definitions for the types of coping-strategies: P — productive, R — relatively productive, N — non-productive*

The data illustrated in Fig. 3 show that the monitoring participants included in group I preferred non-productive forms of emotional coping strategies, namely, suppression of emotions, and the persons who made up group II chose productive emotional coping reactions: they were optimistic ($p<0.05$).

The data in Fig. 4 show us the following: the volunteers from both groups did not build their proper coping behavior effectively enough, preferring non-constructive forms (in group II — mainly active avoidance, and in group I — active avoidance and retreat, on a parity basis), while the choice of productive coping forms was completely absent. Note that the proportion of non-constructive coping styles in group I was almost twice as high as in group II ($p<0.05$).

When psychogeometric testing of volunteers with both psychological sensitivity to changes in GMV and without such sensitivity, the following was found: persons from group I gave equal preference to a triangle and a circle (27%, respectively), denying the zigzag (55%), and representatives of group II, preferring a square to other geometric shapes (37%), as well as persons from group I, rejected the zigzag (88%, $p\leq0.05$).

DISCUSSION

We noticed that at this stage of the Heliomed-2 project (spring 2017), among the volunteers living in high latitudes, the amount of those with and without psychological sensitivity to GMV was the same.

It was shown that individuals, who are psychologically sensitive to the effects of heliogeomagnetic factors, under stress conditions, were effective only in the cognitive sphere of stress-overcoming behavior, in contrast to the behavioral and emotional spheres. In conflict situations, they focused not so much on analyzing the problems that arose, but on suppressing their emotions and maintaining self-control, while actively avoiding open struggle with hostile circumstances or retreating before them (i.e., they were completely ineffective at coping with stress). People from Group I perceived a wide range of situations as threatening, were afraid of changes and conflicts, were sociable and friendly, but, at the same time, they could periodically be restrained, concentrated and purposeful. The presence of polar intrapsychic traits, a tendency to suppress emotions and increased anxiety of carriers of psychological sensitivity to the action of heliogeomagnetic factors allowed them to be attributed to the group of increased risk of neurosis and psychosomatic diseases [9, 17].

Volunteers who did not have psychological sensitivity to changing GMV were most effective in the emotional sphere of stress-overcoming behavior and least effective in behavioral, and the cognitive coping sphere occupied an intermediate position. The representatives of group II were moderately anxious, optimistic, hardworking, conservative, reserved and pedantic, preferring individual activities. However, in exclusive situations, they ignored problems or actively avoided them without even trying to deal with them.

CONCLUSION

Thus, despite the fact that all the inhabitants of the Northern latitudes observed by us were not sufficiently effective in constructing their stress-overcoming behavior, the risk of developing psychosomatic diseases was higher in the owners of psychological sensitivity to geomagnetic disturbance, taking into account their tendency to suppress emotions and significantly higher anxiety.

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ANALYSIS OF THE DISTRIBUTION OF GYNECOLOGIC DISEASES TREATED AT A DAY GYNECOLOGY UNIT

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ABSTRACT — Background: A gynecological day hospital is an alternative to hospitalization enabling to improve accessibility and avoid hospitalizations. Our study investigated the most common gynecologic issues treated in a day gynecology clinic. Methods: The distribution of attendances to a gynecology day hospital was studied in the period from 2015 to 2017. Data collected from the gynecologic diagnoses (a total of 2,908 cases) were standardized according to the International Classification of Diseases in its tenth revision. Results: Over the period from 2015 to 2017, noninflammatory disorders of the female genital tract (N80–N99) were predominant in the distribution of gynecologic conditions treated on an outpatient basis, that is, 69.0% in 2015, 78.6% in 2016, and 82.3% in 2017 of the total number of admissions. Among non-inflammatory disorders of the female genital tract, the most common were as follows: polyp of female genital tract (N84); other non-inflammatory disorders of uterus (N85), which include endometrial glandular hyperplasia (N85.0) and endometrial adenomatous hyperplasia (N85.1); erosion and ectropion of cervix uteri (N86); female infertility (N97). Conclusions: Our findings correspond to data obtained in other countries. The main group of diseases is represented by non-inflammatory disorders of the female genital tract. Thus, the data can be used in planning and organizing gynecological care for women undergoing treatment in day facilities.

KEYWORDS — distribution of gynecologic diseases, day hospital, noninflammatory disorders of the female genital tract, inflammatory diseases of the female pelvic organs.

INTRODUCTION

Hospital replacement forms and technologies are being developed actively worldwide. Admission in a day outpatient facility is an effective alternative to 24-h hospitalization [1].

Treatment in an ambulatory facility may include surgical interventions that require postoperative stay under medical supervision for several hours. Studies have confirmed that day clinics improve the comfort of patients' stay in a medical institution, increase the availability of medical care, and help decrease the number of repeated hospitalizations. The multidisciplinary day outpatient facility of a university hospital of the Andalusian Health Service illustrates that visits to a day clinic decreased inadequate hospitalization and repeated hospitalization by 93.3% and 4.2%, respectively [2].

In the Russian Federation, over the past 10 years, the number of gynecologic hospital beds has decreased by 32.2%. Therefore, outpatient facilities offering gynecologic services provide the female population with the necessary medical care, which positively affects the reproductive potential of the population [3, 4].

Thus, this study analyzed the distribution of gynecologic diseases in female patients treated in a day gynecology clinic operated at a multidisciplinary hospital in a large city.

MATERIAL AND METHODS

The distribution of attendances to the day gynecology clinic at a multidisciplinary hospital (Moscow Clinical Hospital No.15) was studied in the period from 2015 to 2017. A total of 2,908 hospitalization cases were analyzed (958 cases in 2015, 952 cases in 2016, and 998 cases in 2017). Data collected from the gynecologic diagnoses were standardized according to the International Classification of Diseases in its tenth revision.

RESULTS AND DISCUSSION

Over the period from 2015 to 2017, non-inflammatory disorders of the female genital tract (N80–N99) were predominant in the distribution of gynecological diseases treated on an outpatient basis, that is, 69.0% in 2015, 78.6% in 2016, and 82.3% in 2017 of the total number of admissions (Fig. 1).

In 2015 and 2016, inflammatory diseases of the female pelvic organs were the second most common (N70–77) and were diagnosed in 20.9% and 12.3% of the cases, respectively. In 2017, in total, 89.5% of the cases belonged to Class XIV "Diseases of the genitourinary system" (90.9% in 2016 and 89.9% in 2015).

In 2015, the remaining 10.1% of diseases were distributed into the following groups: submucosal uterine leiomyoma (Class II "Neoplasms," benign disorders of the uterus and ovaries, D10–D36) with 4.8%, pregnancy with abortive outcome (Class XV "Preg-

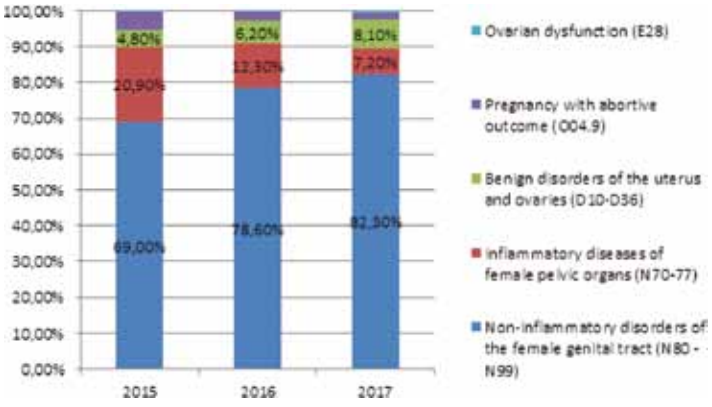

Fig.1. *Structure of gynecological diseases treated in a day inpatient facility in 2015–2017*

nancy, childbirth and the puerperium") with 4.9%, and ovarian dysfunction (Class IV "Endocrine, nutritional and metabolic diseases") with 0.4%. In 2016, the remaining 9.1% were distributed into groups, similar to those in 2015, namely, submucosal uterine leiomyoma (Class II "Neoplasms," benign disorders of the uterus and ovaries, D10–D36) with 6.2%, pregnancy with abortive outcome (Class XV "Pregnancy, childbirth and the puerperium") with 2.6%, and ovarian dysfunction (Class IV "Endocrine, nutritional and metabolic diseases") with 0.3%.

In 2017, as regards the structure of gynecological diseases, benign neoplasms (Class II "Neoplasms," benign neoplasms, D25, D26, and D28) ranked second and accounted for 8.1% of the cases, while inflammatory diseases of the female pelvic organs became the third most common (N70–77) and were present in 7.2% of the cases. Pregnancy with abortive outcome (Class XV "Pregnancy, childbirth and the puerperium") accounted for 1.9% of the cases, and ovarian dysfunction (Class IV "Endocrine, nutritional and metabolic diseases") were registered in 0.5% of the cases.

In 2017 the structure of gynecological diseases treated on an outpatient basis was characterized by a decrease in the number of pregnancy with abortive outcome, both in absolute and relative values compared with data obtained from 2015 to 2016.

Among non-inflammatory disorders of the female genital tract, the most common of such groups of diseases were as follows: polyp of female genital tract (N84); other non-inflammatory disorders of uterus (N85), which include endometrial glandular hyperplasia (N85.0) and endometrial adenomatous hyperplasia (N85.1); erosion and ectropion of cervix uteri (N86); female infertility (N97); and other diseases (Table 1).

In 2017, with regard to the distribution of inflammatory diseases of the female pelvic organs, 47.3% of the cases were diagnosed as chronic salpingitis and oophoritis (N70.1), 28.3% were chronic inflammatory disease of uterus (N71.1), and 3.8% cases were subacute and chronic vaginitis (N76.1), which is consistent with the distribution for this group in 2015–2016.

CONCLUSION

The analysis of the distribution of gynecological diseases treated in the day gynecological clinic corresponds to data obtained in other countries [3]. The main group of diseases is represented by non-inflammatory disorders of the female genital tract. Thus, results can be used in planning and organizing gynecologic care for women undergoing treatment in day outpatient facilities.

Table 1. *Non-inflammatory disorders of the female genital tract treated in the gynecologic day clinic in 2015–2017*

Diagnoses	Structure of visits, %		
	2015	2016	2017
Polyp of female genital tract (N84)	33.9	32.7	33.5
Other non-inflammatory disorders of uterus (N85)	17.3	19.5	20.0
Erosion and ectropion of cervix uteri (N86)	16.8	12.5	12.0
Female infertility (N97)	16.3	15.2	11.7
Dysplasia of cervix uteri (N87)	4.1	5.0	10.2
Menopausal and other perimenopausal disorders (N95)	3.9	0.7	0.7
Other non-inflammatory disorders of cervix uteri (N88)	2.5	4.5	8.1
Other non-inflammatory disorders of vulva and perineum (N90)	2.3	4.5	0.6
Excessive, frequent and irregular menstruation (N92)	1.4	2.3	1.5
Non-inflammatory disorders of ovary, fallopian tube and broad ligament (N83)	0.9	1.0	1.0
Pain and other conditions associated with female genital organs and menstrual cycle (N94)	0.6	2.1	0.7
All diagnoses	100.0	100.0	100.0

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EFFECT OF CHRONIC ALCOHOL INTOXICATION AND CONSTANT LIGHTING ON CARDIOVASCULAR PARAMETERS IN MALE RATS

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ABSTRACT — The aim of the research was to study the effect of chronic alcohol intoxication and constant il-lumination on the circadian rhythms (CR) of some parameters of the cardiovascular system in rats separately, as well as to study the rhythms of these parameters under the combined action of chronic alcohol intoxication (CAI) and constant illumination. It was found that chronic alcohol intoxication CAI at a fixed light regime causes a decrease in heart rate, an increase in SBP and PP; no changes were noted at CAI under constant lighting. At the same time, constant illumina-tion without ethanol exposure results in a decrease in heart rate and an increase in PP.
At the same time, CAI with a fixed light regime leads to the destruction of CR of all parameters, except for MBP; at constant illumination with CAI no circadian rhythms of HR, DBP, PP and MBP are detected. Constant illumination leads to the destruction of the CR of PP.
Among the remaining CRs, the heart rate rhythm, which is extant in the second group, persists practically unchanged, but the characteristics of all other CRs change significantly in comparison with control.

KEYWORDS — circadian rhythms, heart rate, blood pressure, desynchronosis.

INTRODUCTION

The rhythmicity of functioning is a fundamental, integral property of all living systems, which plays an important role in ensuring of normal vital functions. Based on biological rhythms, periodic programs are built that provide the necessary order for the course of bioprocesses, the optimal level of the functioning of organism at any given moment in time. Daily, or circadian rhythms (CR) are among the most significant rhythms for mammals. The cycles of life processes, which consequently replace each other, differ in their parameters, such as the duration of the period, amplitude, phase [3, 5, 16].

The temporal organization of the systems of mammalian organism is endogenous and ge-netically determined, but, nevertheless, it is modulated under the influence of periodic environmental factors — synchronizers, or pacemakers; and the light is one of the strongest synchronizers of daily biological rhythms in mammals. The rhythm of the course of adaptation processes is also of great practical importance, because it opens a reliable way to predict the dynamics of the state of the organism in acute and chronic stress induced by both internal and external causes. In cases of successful adaptation processes, the degree of influence of stressors on circadian rhythms is insignificant. Otherwise, the rhythmic processes of the organism lose their correctness, regularity, and state of desynchronosis occurs, which can lead to the development of one pathology or another, especially if there is a predisposition to it or the adaptive capabilities of the organism are weakened [9].

Currently, a fairly large number of people in the world are exposed to light pollution (in other words, lighting at night). Such impact may be related to the profession, may be due to habit and lifestyle [1]. Exposure to light at night has become an essential part of modern lifestyles and is associated with many serious behavioral and health conditions, including cardiovascular diseases and cancer [6, 7]. It is shown [10], that in the dynamics of the development of the diseases the general desynchronosis is one of the first disorders.

According to the hypothesis of *circadian destruction*, exposure to light at night disrupts the endogenous circadian rhythm, suppresses the nighttime secretion of melatonin by the pineal gland, which leads to a decrease in its concentration in the blood [14]. Disruption of CR during shift work leads to an increased risk of cardiovascular diseases, metabolic syndrome, type II diabetes mellitus [12, 15].

Another of the anthropogenic environmental factors to which the organism has to adapt is alcohol, or rather, alcohol intoxication. The chronotoxicity of alcohol and chronoesthesia to it were described in the works of Erhard Haus and Franz Halberg back in 1959. Even a single in-take of alcohol can cause significant chronobiological shifts: desynchronosis,

amplitude-phase rhythm disturbances. Signs of desynchronosis persist after complete elimination of alcohol for several days [11, 17].

In some patients with alcohol dependence, even with prolonged abstinence, the normali-zation of circadian biorhythms does not occur; in this regard, another hypothesis was put forward — about the primacy of desynchronosis itself in the pathogenesis of the development of alcoholism. Chronic alcohol consumption alters the normal functioning of both central and peripheral rhythm-organizing structures, disrupting the normal functioning of systems of organism [2, 13].

The toxic effect of alcohol directly on the myocardium is manifested in the appearance of functional heterogeneity - one part of the muscle fibers atrophies, and the other hypertrophies. Due to the melting of the Z-discs of sarcomeres by acetaldehyde, diffuse focal cardiosclerosis progresses, while the normal propagation of excitation through the myocardium is disrupted. Subsequently, fatty degeneration in the heart tissue and arteriosclerosis occur, which are accompanied by a decrease in vascular tone in the microvasculature against the background of a progressive decline of the cardiac contractile function [8].

The most important parameters of cardiac activity — heart rate (HR), blood pressure (BP), etc., have their own clear biological rhythms, synchronized in time in accordance with the period of wakefulness and sleep. The mismatch of biorhythms of various CVS parameters due to CAI can precede the development of pathological conditions with subsequent informational, energetic, metabolic and structural changes.

In this regard, we found it relevant to study the effect of chronic alcohol intoxication and constant illumination on the CR of some parameters of the cardiovascular system of rats separately, as well as to study the rhythms of these parameters under the combined action of CAI and constant illumination.

MATERIALS AND METHODS

Animals

The study was conducted on 160 male Wistar rats at age of 6 months, weighing 300±20 g. Animals were taken from the Stolbovaya nursery of laboratory animals (Moscow Region, Russia).

Design of experiment

All animals were kept in plastic cages with free access to food and water within 3 weeks. Animal were divided on 4 equal groups.

Control group was kept in standard laboratory conditions at fixed light regime (light:dark/10:14 hours, with lights on at 8:00 and off at 18:00).

1st group (n=40), was kept in the same conditions as control, but received as a drink a 15% aqueous solution of ethanol ad libitum.

2nd group (n=40), was kept in standard laboratory conditions at constant lighting (24 hours).

3rd group (n=40), was kept in standard laboratory conditions, but also at constant lighting (24 hours) and received as a drink a 15% aqueous solution of ethanol ad libitum.

The criterion for the selection of rats in the 1 and 3 groups, along with the absence of vis-ible deviations in the state and behavior, was the initial preference for a 15% solution of ethyl alcohol to a tap water. For this, a preliminary experiment was carried out for 3 days in individual cages with free access to both liquids.

Measurement of the parameters of the cardiovascular system was carried out at 9:00, 15:00, 21:00 and 3:00 using the "Systola" device (Neurobotics, Russian Federation). Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded directly. The pulse pressure (PP) was calculated by formula PP=SBP-DBP. For calculation of mean blood pressure (MBP) we used the formula: MBP= DBP+0,43PP; the index of energy costs was determined by the formula I=HR×SBP/1000.

All animal experiments were performed in according to the compliance with EC Directive 86/609/EEC and with the Russian law regulating experiments on animals.

Methods of statistical processing

The obtained data were analyzed using the GraphPad Prism 6.0 program by calculating average values, standard deviation, and arithmetic mean error. The numerical rows characterizing the diurnal fluctuations of the studied physiological rhythms of animals were subjected to mathematical processing, on the basis of which group chronograms were drawn. The statistical difference was determined using the Kruskal-Wallis test. Differences were considered statistical-ly significant at $p < 0.05$.

For statistical estimation of amplitude and acrophase of CR the cosinor analysis, which is an international, recognized method for the unified study of biological rhythms, was performed using the Cosinor-Ellipse2006-1.1 program.

Cosinor analysis is intended for the analysis of wave processes and the processing of chronobiological data. In the course of the analysis, the experimental data are approximated by the least squares sinusoidal parameter estimation. The presence of a reliable circadian rhythm, as well as its acrophase and amplitude, were determined. The output information of the cosinor analysis are the main parameters of the rhythms:

mesor, i.e. the value of the average level of the sinusoid (h), the amplitude of the sinusoid (A) and acrophase (Phi), that is the time of the onset of the maximum of the function. Mesor coincides in magnitude with the daily average value of the investigated function. Acrophase is a measure of the peak time of total rhythmic variability over a 24-hour period, i.e. the time when the function reaches its maximum. The amplitude corresponds to half of the total rhythmic variability in the cycle. Acrophase is expressed in hours; amplitude values are expressed in the same units as the studied variables.

The second stage is the construction of an error ellipse, which is necessary to determine the validity of the existence of rhythms at the accepted confidence level (for example, at the level of 0.95). A sinusoid is depicted on a plane by a point, the polar coordinates of which are amplitude and acrophase. All points obtained in this way in Cartesian coordinates are considered as realizations of a two-dimensional random variable with a hypothetically normal distribution law, and an ellipse of dispersion of errors of the general mean is constructed. The circadian rhythm is considered reliable when two conditions are met: the averaged sinusoid, approximating chronograms (depicted by a cross), must enter the ellipse, and the ellipse itself must not pass through the center of coordinates (because in this case, acrophase will fall on the entire 24 hour period) [4].

RESULTS

As a result of conducted study it is established that in 1st and 2nd experimental groups there is the decrease of HR in comparison with control, but the value of this parameter in the 3rd group is higher, than in other experimental groups, and does not reliably differ from the values of control. At the same time it is noted the reliable increase of SBP at 1st experimental group, and also the increase of PP in animals of 1st and 2nd experimental groups (Table 1, 2).

When considering the results of the cosinor analysis of the daily dynamics of the studied parameters, the presence of reliable CR for all parameters in the control was established. At the same time, CR of heart rate in groups 1 and 3 is destroyed, remaining in the 2nd group with char-acteristics practically indistinguishable from control (Table 3).

Reliable CR of SBP is not observed in 1st group, and the rhythm parameters in groups 2 and 3 differed significantly from control indicators. In the case of DBP, the rhythm, as in the case of HR, is maintained only in the second group, but at the same time the amplitude-phase characteristics of the rhythm differ significantly from the control.

CR of PP is observed only in the control, being destroyed in all three experimental groups, and CR of MAP is destroyed only in 3rd group, although CR of groups 1 and 2 differ in phase-amplitude characteristics from the control.

The CR of index of energy cost is destroyed in the 1st experimental group, while the acrophase of this rhythm occurs in the control at night hours, and in the second and third groups — in the daytime.

CONCLUSION

As a result of the study, it was found that chronic alcohol intoxication (CAI) at a fixed light regime causes a decrease in heart rate, an increase in SBP and PP; no changes were noted at CAI under constant lighting. At the same time, constant illumination without ethanol exposure results in a decrease in heart rate and an increase in PP.

At the same time, CAI with a fixed light regime leads to the destruction of CR of all pa-rameters, except for MBP; at constant illumination with CAI no circadian rhythms of HR, DBP, PP and MBP are detected. Constant illumination leads to the destruction of the CR of PP.

Among the remaining CRs, the heart rate rhythm, which is extant in the second group, persist practically unchanged, but the characteristics of all other CRs change significantly in comparison with control.

Table 1. *Parameters of cardiovascular system in rats*

	Control	1st group	2nd group	3rd group
HR, bpm	431.4±34.72	390.1±46.23	367.9±41.07	433.3±32.86
SBP, mm Hg	113.9±10.75	132.8±21.68	118.9±19.72	118.1±13.51
DBP, mm Hg	96.1±10.35	104.4±24.24	93.1±16.15	94.0±11.07
PP, mm Hg	17.75±9.53	28.40±11.68	25.74±10.35	24.26±9.68
MBP, mm Hg	108.6±25.27	166.6±22.44	104.2±17.02	104.3±11.22
Index of energy costs of heart	49.21±6.74	51.83±10.82	43.5±8.79	51.27±1.60

Table 2. *Significance of intergroup differences in the studied parameters of the cardio-vascular system in rats.*

	C×1EG	C×2EG	C×3EG	1EG×2EG	1EG×3EG	2EG×EG
HR, bpm	<0,005	<0,0001	>0,05	>0,05	<0,005	<0,0001
SBP, mm Hg	<0,005	>0,05	>0,05	>0,05	<0,05	>0,05
DBP, mm Hg	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05
PP, mm Hg	<0,005	<0,05	>0,05	>0,05	>0,05	>0,05
MBP, mm Hg	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05
Index of energy costs of heart	>0,05	>0,05	>0,05	<0,05	>0,05	<0,005

Table 3. *Results of the cosinor analysis of the diurnal dynamics of the cardiovascular pa-rameters in rats*

Group	HR			SBP		
	Acrophase	Amplitude	Mesor	Acrophase	Amplitude	Mesor
Control	1601	7.18	431.35	436	1.12	113.9
1st group	No reliable CR			No reliable CR		
2nd group	16.02	8.99	369.0	1424	21.34	117.0
3rd group	No reliable CR			11.18	7.98	117.82
Group	DBP			PP		
	Acrophase	Amplitude	Mesor	Acrophase	Amplitude	Mesor
Control	2144	4.22	96.10	1436	4.89	20.88
1st group	No reliable CR			No reliable CR		
2nd group	1408	15.05	91.22	No reliable CR		
3rd group	No reliable CR			No reliable CR		
Group	MBP			Index of energy costs of heart		
	Acrophase	Amplitude	Mesor	Acrophase	Amplitude	Mesor
Control	1418	18.01	102.23	136	1.67	48.57
1st group	1148	11.88	115.21	No reliable CR		
2nd group	342	14.35	102.32	1425	8.18	43.23
3rd group	No reliable CR			1207	5.90	51.07

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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MICROELEMENT PROFILE AND STRUCTURE OF REGIONAL LYMPH NODES DURING SENILE INVOLUTION OF LYMPHOID TISSUE

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ABSTRACT — The microelement profile and structure of lymph nodes were studied in experiment using old Wistar rats by means of a morphological method and the X-ray fluorescent analysis with synchrotron radiation. Their special qualitative and quantitative status is formed in regional lymph nodes that reflect age-related dynamics of lymphoid tissue. The content of trace elements and the size of compartments differ in lymph nodes of different localization. Age-related modifications in a microelement profile are characterized by proliferation of lymphoid cells, development of compartments and initiation of a corresponding immune response at the level of regional lymph nodes with different contact to external environment. Localization of lymph nodes is one of conditions for realization of the principle of a regional determinant (regional specifics).

KEYWORDS — morphology, lymph nodes, trace elements, gerontology.

INTRODUCTION

Expansion of knowledge of a role of chemical elements (bioelements) and lymphatic system became a basis for integration of a medical bioelementology [1] and a lymphology [2, 3]. Changes in homeostasis of trace elements and the lymphatic system accompany various physiological and pathologic conditions including aging of an organism [4, 5, 6]. Lymph nodes continue to be in the center of attention of lymphologists because of their protective function during the different periods of life. Studying the microelement profile of peripheral lymphoid organs as components of lymphatic regions is relevant. Assessment of participation of essential trace elements in forming of the immune status of lymph nodes belongs to unresolved questions though microelements have immunotropic properties [4, 7]. It is necessary to reveal relationships of cause and effect of trace elements content and structure of regional lymph nodes.

The purpose is to characterize modifications in content of trace elements and the structural organization of regional lymph nodes in aging.

MATERIALS AND METHODS

The experiment was carried out on white Wistar rats aged 1.5–2 years (old animals). Mesenteric, inguinal and tracheobronchial lymph nodes were investigated by a morphological method. Lymph nodes were fixed in 10% neutral formalin. After fixing we used the standard scheme of washing, dehydrating, embedding in xylene and paraffin. After that the microtome was operated to prepare histologic sections. Finally, the histologic sections of lymph nodes were stained with hematoxylin and eosine, azure-II-eosine and Masson's trichrome staining.

The choice of Se, Mn, Fe, Cu, Zn trace elements can be explained by the fact that they are essential bioelements which support the immune system in accordance with the modern classification [1]. The content of trace elements in lymph nodes was defined by the X-ray fluorescent method with the use of synchrotron radiation. The work was done on the equipment of Budker Institute of Nuclear Physics (Novosibirsk), supported by project RFMEFI62119X0022 [8].

The morphometric analysis of lymph node structures was carried out by means of a morphometric grid and the Image-Pro Plus 4.1 program. Statistical data processing was performed with licensed statistical software package StatPlus Pro 2009, AnalystSoft Inc. The semiquantitative method was used for assessment of data. A P-value < 0.05 was considered statistically significant.

RESULTS

It is established that there are age-dependent fluctuations of exchange of trace elements [4, 5, 9]. The concentration of bioelements varies not only in organs, but also in regional lymph nodes. In majority of trace elements concentration reduces by 1.2–1.5 times ($p < 0.05$–0.01) compared to the maximum possible

value at young age [6]. We noted that the differences in bioelements content of lymphoid tissue depend on the extent of their accumulation of different localization (regional specifics) in lymph nodes. There are higher rates of content of Mn, Fe, Zn and minimum for Se in an inguinal lymph node. There is a high value concentration of Se (1.14±0.06 mkg/g) in the mesenteric lymph node. The content of selenium exceeds by 1.4–1.5 times concentration in tracheobronchial ($p < 0.001$) and inguinal ($p < 0.05$) lymph nodes. There are low values of content of Mn, Fe, Zn and Se in the tracheobronchial lymph node.

Level the content of Cu lies in the interval 4.68±0.27–5.37±0.14 mkg/g in lymph nodes of different topographical groups. Within this interval the smallest content of Cu is observed an inguinal lymph node, the greatest one is noted in the tracheobronchial lymph node (Table 1). Comparison of microelements content revealed reliable differences between lymph nodes, belonging to lymphatic regions that are located in different contact with the external environment. Accumulation and removal of microelements happens unequally in lymph nodes that leads to forming individual qualitative and quantitative microelement profile in aging.

Table 1. *The Microelement Status of Lymph Nodes in old age period*

Trace elements	Inguinal lymph node	Mesenteric lymph node	Tracheobronchial lymph node	P
	1	2	3	
Mn	+++	+	++	$P_{1-2} < 0{,}001$ $P_{1-3,\,2-3} < 0{,}05$
Fe	+++	+	++	$P_{1-2,\,2-3} < 0{,}05$ $P_{1-3} > 0{,}05$
Zn	+++	++	+	$P_{1-3} < 0{,}001$ $P_{1-2,\,2-3} < 0{,}01$
Cu	+	++	+++	$P_{1-3} < 0{,}05$ $P_{1-2,\,2-3} > 0{,}05$
Se	+	+++	++	$P_{1-2} < 0{,}001$ $P_{1-3,\,2-3} < 0{,}05$ $P_{2-3} > 0{,}05$

The bioelemental composition reflects specific features of the structural and cellular organization of lymph nodes in aging. There is a prevalence of medullary substance mainly at the expense of a B-dependent zone (medullary cords) and evenly expanded lymphatic sines at minimization of lymphoid compartments in the mesenteric lymph node (Table 2). Such structure of a lymph node defines the immune response of humoral type. Trace elements together with enzymes make a certain contribution to proliferation of lymphoid (immune) cells and to antioxidant protection [1, 4, 7]. It is provided with the different level of accumulation of trace elements. We noted the maximum contents Se, an average — Cu, Zn and minimum — Fe, Mn (Table 1). The distinction of concentration of trace elements defines extent of proliferative processes, development of compartments and leads to formation of the immune response of humoral type in the mesenteric lymph node.

Table 2. *The morphological status of lymph nodes in old age period*

Lymph nodes sructures	Inguinal lymph node	Mesenteric lymph node	Tracheobronchial lymph node	P
	1	2	3	
Lymphoid follicles	+	+	+	$P_{1-2,\,1-3,\,2-3} > 0{,}05$
Cortex plateau	++	+	+++	$P_{1-2,\,1-3} < 0{,}05$ $P_{2-3} < 0{,}01$
Paracortex	+++	+(+)	++	$P_{1-2,\,1-3} < 0{,}01$ $P_{2-3} > 0{,}05$
Medullary cords	++	+++	++	$P_{1-2,\,2-3} < 0{,}01$ $P_{1-3} > 0{,}05$
Lymphatic sinus	+++	++	+	$P_{1-2,\,2-3} < 0{,}05$ $P_{1-3} < 0{,}001$

There is an expansion of the area of an interfollicular part of cortex and medullary cords (B-zone), a paracortex (T-zone) against the background of narrow lymphatic sine in the tracheobronchial lymph node (Table 2). The immune response of the mixed type is formed at simultaneous representation of cortical and medullary substances at a limited drainage function. The morphoimmune status of a tracheobronchial lymph node is combined with the maximum contents of Cu, an average — Se, Mn, Fe, minimum — Zn (Table 1).

There is a rather wide T-dependent zone at the expense of a paracortex and an interfollicular part of cortex at wide lymphatic sines in an inguinal lymph node (Table 2). The immune response of cellular type is formed in an inguinal lymph node. The inguinal lymph node distinguishes the maximum content of Mn, Fe, Zn and minimum — Se, Cu (Table 1). The

content of Zn Fe is a priority. These trace elements are essential for normal division, proliferation and a differentiation of T-cells [10, 11] and for further development of a paracortex with the immune response of cellular type.

The discretization of structural units of lymph nodes defines vulnerability of elements of a system at age-dependent changes. In old animals there is a reduced number of lymphocytes, lymphoblasts in compartments of lymph nodes including in lymphoid follicles. It is necessary to assume that the micronutrient deficiency, in aging, affects the activity of enzymes that results in decrease of cellular proliferation and a reduction of lymphoid follicles [4, 5, 7].

Lymphoid follicles reach the smallest sizes within 4.79±0.27%–5.84±0.36% without demonstration of statistically reliable difference between lymph nodes ($p > 0.05$). There is a reduction of a lymphocytic pool due to decrease of immunogenesis. It is obvious that forming of a certain microelement profile and morphotype of lymph nodes depend on localization of the lymphatic region and features of contact with external environment. Lymphoid follicles are a systemically important element and as reactive structures are responsible for a lymphopoiesis and forming of compartments. Trace elements enter cofactors of many enzymes and they are necessary for proliferation and functioning of lymphoid (immune) cells. Age-dependent changes are characterized by correlation ratios between the content of microelements and the area of lymphoid follicles.

Thus, lymphoid follicles without the germinative center show positive correlation concerning Mn ($r=0.34$, $p < 0.05$) and Se ($r=0.52$, $p < 0.01$) in the tracheobronchial lymph node. There is negative correlation concerning Fe ($r=-0.30$, $p < 0.05$) and Zn ($r=-0.45$, $p < 0.01$) in an inguinal lymph node. There is a positive correlation with Mn ($r=0.65$, $p < 0.001$) and Fe ($r=0.48$, $p < 0.01$) in the mesenteric lymph node. Lymphoid follicles with the germinative center are most indicative. There is a positive correlation of lymphoid follicles with the germinative center concerning Cu ($r=0.33$, $p <0.05$) in the tracheobronchial lymph node. We noted weak degree of correlation ($r <0.30$, $p> 0.05$) for all trace elements in inguinal and mesenteric lymph nodes. The correlation between trace elements and lymphoid follicles does not allow to speak about existence of steady lymphoid-microelement association.

We, for the first time, described the formation of lymphoid-microelement association during the maximum development of lymphoid tissue [6, 9]. Reduction of activity of lymphoid follicles and decrease of correlation with microelements can disrupt lymphoid-microelement association during age-related changes of lymphoid tissue. Possible deviations are the result of temporary disadaptation or a readaptation of a structurally functional condition of lymph nodes connected with their localization and age.

DISCUSSION

Aging of an organism affects all organs and systems including lymphoid tissue. Pathognomonic sign of aging is involution of lymphoid tissue with its replacement by fatty or connective tissue [2]. Nevertheless many peripheral lymphoid organs (lymph nodes) keep the structure, but it has features of transformation in aging [6, 9]. We noted interrelation of microelements with the morphoimmune status of lymph nodes of different localization. Immune function of lymph nodes is reflection of development of compartments in the course of proliferation and a differentiation of immunocompetent cells. Trace elements influence cells of the lymphocytopoietic system of lymph nodes and as a response modify the area of compartments of lymph nodes.

The immunogenesis is reduced and there is a reduction of a lymphocytic pool in combination with the low content of trace elements in old animals [7, 9]. Concentration of separate trace elements differs in regional lymph nodes. A certain microelement profile and the corresponding morphotype in each of the studied lymph nodes provide the immune response of humoral type in the mesenteric lymph node, the mixed type in the tracheobronchial lymph node and cellular type in an inguinal lymph node (regional specifics). The principle of a regional determinant is implemented according to the concept of the lymphatic region by Yu.I. Borodin [3], there are reliable differences between lymph nodes, belonging to various lymphatic regions. Each of lymphatic regions differently contacts to external environment, as causes age-dependent originality of lymph nodes.

CONCLUSION

The obtained results demonstrate specifics of trace element exchange and the structural organization of the regional lymph nodes natural aged. The principle of a regional determinant is the basic in formations a microelement profile and a morphoimmune status of lymph nodes of different localization according to the concept of the lymphatic region. The indispensable condition of functioning of lymph nodes is existence of trace elements in a certain concentration. Trace elements influence process of proliferation and a differentiation of immunocompetent cells, development of compartments and variant of the immune response in lymph nodes of different lymphatic regions. Structural features and a microelement profile of lymph nodes

serve as a prognostic tool for aging of peripheral lymphoid organs. The results can be employed to correct balance of trace elements and to increase the protective function of lymph nodes at the stage of senile involution in lymphoid tissue.

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MACROMICROSCOPIC CHARACTERISTICS OF INDIVIDUAL AND AGED VARIABILITY OF THE GLANDS OF THE VAGINAL VESTIBULE

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ABSTRACT — Our study aimed to obtain data on the age and individual characteristics of the glands of the vaginal vestibule in postnatal human ontogenesis.
MATERIAL AND RESEARCH METHODS. By the macromicroscopic way, the small glands of the vaginal vestibule wall were investigated in cadavers of 163 women of different ages without pathology of the urogenital system. The total number, length, width, density of location, the area of the initial section, the diameter of the common excretory duct of the glands, the number of glands with ampoule-widened excretory ducts, and glands were determined.
THE RESULTS OF THE STUDY. The conducted macromicroscopic examination made it possible to reveal that the maximum number and size of small vestibular glands are determined in the 1st period of adulthood. Starting from the 2nd period of adulthood and up to old age inclusive, there is a decrease in these indicators. The minimum level of individual variability in the size and number of small glands of the vestibule is characteristic in ontogeny for the neonatal period.

KEYWORDS — Glands, vaginal vestibule, sample preparations, common excretory duct, initial parts.

INTRODUCTION

Morphological exocrinology is in the focus of the attention of anatomists, histologists, pathologists, and clinicians of various specialties. This is due not only to the need to expand theoretical knowledge, but also to decipher the pathogenesis of numerous nosological forms, in the development of which the small glands of hollow organs are involved [1].

As is known, the source of adenogenic vaginal cancer is the epithelium of the small vaginal glands [2]. The glands of the vaginal vestibule are also affected by fibroadenomatous pathology [3], they are exposed to abscesses, diverticulitis [4], and polyps of the vestibule of the vagina are not uncommon [5].

Despite this, among the meager work carried out on the study of the glands of the genitourinary apparatus, there is almost no work on the topic of the glands of the vaginal vestibule. The only targeted research on the macromicroscopic anatomy of the vestibular small glands was carried out only in the middle of the XX century [6].

The study aimed to obtain data on the aged and individual characteristics of the glands of the vaginal vestibule in human postnatal ontogenesis.

MATERIAL AND METHODS

By the macromicroscopic way, the small glands of the vaginal vestibule wall were investigated in 163 women of different ages who died or died from accidental causes, without pathology of the urogenital system. On the cadavers, the area of the vaginal vestibule was excised by dissection. On the preparations obtained, the vaginal vestibules were stained according to the method of R.D. Sinelnikov [7]. For this, the vaginal area was excised from the cadaver by dissection. To make an anatomic resection, the actual material was placed in a 0.5% solution of acetic acid with 0.05% methylene blue solution in tap water. The glands in this solution were stained for 24–36 hours. Then, within 24–30 hours, the vaginal preparation was fixed in a saturated solution of ammonium molybdate. Then the preparation was placed in glycerol and fixative solution, where the bleached preparation was preserved.

After that the glands were examined in transmitted and reflected light using a forehead magnifier and an MBS-9 microscope (magnification 8–64×). The vaginal vestibule was preliminarily divided by transverse threads into anterior, middle, and posterior thirds. All measurements of the study were taken separately in the above zones.

During the macromicroscopic study, the total number of glands, the number of glands with ampoule-widened excretory ducts, the number of glands with ampoule-widened excretory ducts, and the density of the glands were counted.

The length, width, area of the initial department and the diameter of the common excretory duct were measured. We also analyzed the percentage of glands with a different number of initial departments (the total set of glands on the total preparation was taken as 100%).

The digital data obtained in the course of the study were subjected to statistical processing. The mean

values of the obtained samples (M), standard errors (m), minimum (min), maximum (max) values of the series were calculated. A comparison was made between groups (P), sequentially within a group (P_0), within a group with the first parameter (P_1), within a group with a maximum (P_2). For a preliminary assessment of the difference between the variation series, the parametric Student's t-test was used. Further, to compare and determine the reliability of quantitative differences in groups and subgroups, the nonparametric rank U-Wilcoxon (Mann-Whitney) test was used [8].

The calculations were carried out in the programs of the statistical package MS EXCEL-2016 and SPSS-22.

RESEARCH RESULTS

Glands on total preparations are defined as dark anatomical formations located on a lighter background of the surrounding wall. The contours of the glands are well defined. They are present both in the anterior (closest to the external opening of the urethra) and in the middle and posterior (closer to the anus) thirds of the wall of the vaginal vestibule. The glands are located singly or in groups and do not form longitudinal rows.

At the macro-microscopic level, the initial departments and excretory ducts are revealed in the glands. The shape of the initial departments of the glands is diverse, more often ovoid or rounded.

Initial departments of various numbers are identified in the composition of glands. Their number varies from one up to four or six and more. According to our data, the maximum number of initial departments of a single gland reaches 15.

The results of a study of the age characteristics of the glands of the vaginal vestibule in women normally showed that the glands are constantly (in 100% of cases) determined already in newborns.

The number of glands of the vaginal vestibule in early childhood by 1.5 times (P <0.05), in adolescence by 2.0 times (P <0.05), and in the 1st period of adulthood by 2.8 times (P <0.05) is more than in newborns. This parameter in elderly age is 1.4 times (P <0.05), in senile age, it is 1.7 times (P <0.05) less than in the 1st period of adulthood (Table 1).

The length of the initial section of the glands in girls of early childhood is 1.4 times (P <0.05), at puberty 2.6 times (P <0.05), and in women at the 1st period of adulthood, 3.7 times (P <0.05) more than in newborns. This indicator for the glands of the vaginal vestibule at the elderly age is 1.3 times (P <0.05), at senile age is 1.6 times (P <0.05) less than in women at the 1st period of adulthood (Table 2).

According to the data obtained, the width of the initial department in early childhood is 1.4 times (P <0.05), at puberty — 2.6 times (P <0.05), at the 1st period adulthood 3.5 times (P <0.05) more than newborn girls. This indicator at the elderly age 1.3 times (P <0.05), at senile age 1.4 times (P <0.05) is less than in the 1st period adulthood.

The area of the initial department of glands increases in early childhood by 1.2 times (P> 0.05), at puberty by 1.7 times (P1> 0.05), at the 1st period adulthood by 2.2 times (P> 0.05), compared with newborn girls. In comparison with the 1st period adulthood, the considered indicator at elderly aged women decreases 1.4 times (P> 0.05), at senile age — 1.4 times (P> 0.05).

We have identified age-related variability in the percentage of glands with different numbers of initial departments of the glands of the vaginal vestibule. So, the percentage of glands with one initial department in early childhood decreases by 1.1 times (P <0.05), at puberty by 1.4 times (P <0.05), at the 1st period adulthood 1.7 times (p <0.05), compared with newborn girls. In senile age, the percentage of such glands increases by 1.4 times (P <0.05), compared with the 1st period of adulthood. The relative number of glands with two initial departments in early childhood increases 1.6 times (P <0.05), at puberty — 2.5 times (P <0.05), at the 1st period of adulthood — 4.7 times (P <0.05), compared with newborn girls. This indicator in senile age is 1.4 times less (P <0.05) than in the 1st period of adulthood. The percentage of glands with three initial departments in early childhood increases by 2.2 times (P <0.05), at puberty — 3.4 times (p <0.05), at the 1st period of adulthood — 4.6 times (P <0.05). In senile age, the content of such glands in the area under consideration decreases by 1.3 times (P <0.05), compared with the 1st period of adulthood. The percentage of glands with four or more initial departments in early childhood increases by 1.1 times (P <0.05), at puberty — 3.3 times (P <0.05), at the 1st period of adulthood — 5.0 times (P <0.05), compared with newborns. The number of these glands at senile age is 1.9 times less (P <0.05), compared with the 1st period of adulthood.

We have found that the number and size of the glands of the vaginal vestibule are individually variable. The level of variability (the amplitude of the variation series of indicators) in the glands predominantly increases during postnatal ontogenesis. For example, compared with newborn girls, the maximum and minimum individual values of the length of the initial department of the small glands of the vaginal vestibule at 22–35 years 1.7 times (P <0.05), the width of the initial department are 1.6 and 1.8 times respectively (P <0.05), the diameter of the common excretory duct are 1.4 and 1.9 times (P <0.05) are larger.

The individual minimum and maximum size-quantitative indicators of the glands in the walls of

Table 1. *The total number of small glands of the vaginal vestibule (the number of orifices of the excretory ducts on the surface of the mucous membrane) in women of different ages*

Age	N	Part of the vaginal vestibule, the number of the small glands			
		Anterior third	Middle third	Posterior third	The vaginal vestibule in general
Newborns (from 1 to 10 days)	7	14±0,81 8–18	18±0,54 16–22	22±0,56 16–26	54±1,74 41–62
Infancy (from 10 days to 1 year)	5	18±0,62 12–23	24± 0,75 16–29	26± 0,87 18–33	68± 1,74 48–77
Early childhood (1–3 years)	5	22±1,09 15–26	28± 1,18 21–33	32± 1,50 24–39	82± 4,62* 69–111
1st childhood (4–7 years)	6	23±0,87 17–26	30± 1,09* 24–35	36± 1,61 26–42	89± 5,35* 73–126
2nd childhood (8–11 years)	6	25±1,1* 19–28	35±1,45* 25–39	42±1,31* 35–49	102±5,12* 79–128
Puberty (12–15 years)	5	28±1,11* 22–35	36±1,02* 32–42	44±1,11* 36–49	108±4,50* 81–133
Adolescence (16–20 years)	6	30±0,35* 26–34	38±0,47* 33–45	47±0,65* 38–54	115±2,75* 92–157
1st adulthood (22–35 years)	8	36±0,55* 28–42	52±0,46* 45–56	64±0,72* 52–69	152±2,70* 121–185
2nd adulthood (36–55 years)	8	32±0,37* 25–36	43±0,41* 37–49	54±0,75* 46–67	129±1,16* 111–142
Elderly (56–74 years)	9	24±0,41 18–31	36±0,42* 28–43	45±0,50* 35–52	105±1,16* 86–124
Senile (75–90 years)	9	18±0,36 13–24	32±0,41* 26–38	39±0,63* 30–48	89±1,61* 68–113

Note. *Here and in the following table means: 1. n — number of observations; 2. Statistically significant difference within the group with the first parameter: * — P <0.05*

Table 2. *The length of the initial department of the small glands of the vaginal vestibule of the vagina in women of different ages (mm)*

Age	N	Part of the vaginal vestibule, the length of the initial department of the glands			
		Anterior third	Middle third	Posterior Third	The vaginal vestibule in general
Newborns(from 1 to 10 days)	7	0,11±0,01 0,08–0,14	0,22±0,01 0,17–0,26	0,25±0,01 0,20–0,29	0,19±0,01 0,16–0,22
Infancy (from 10 days to 1 year)	5	0,16±0,01 0,11–0,21	0,24±0,01 0,17–0,28	0,28±0,01 0,21–0,33	0,23±0,01 0,18–0,29
Early childhood (1–3 years)	5	0,19± 0,01* 0,14–0,25	0,29± 0,01 0,22–0,35	0,35± 0,01 0,27–0,38	0,27± 0,01* 0,23–0,35
1st childhood (4–7 years)	6	0,24± 0,010,33–0,18 *	0,33± 0,01 0,26–0,38	0,45± 0,01* 0,31–0,54	0,34± 0,01* 0,27–0,41
2nd childhood (8–11 years)	6	0,30± 0,010,43–0,22 *	0,40± 0,01* 0,27–0,48	0,55± 0,01* 0,37–0,61	0,42± 0,01* 0,30–0,48
Puberty (12–15 years)	5	0,35± 0,01*0,42–0,27 *	0,48± 0,01* 0,36–0,55	0,64± 0,01* 0,50–0,76	0,49± 0,01* 0,37–0,59
Adolescence (16–20 years)	6	0,41± 0,010,48–0,33 *	0,55± 0,01* 0,37–0,66	0,80± 0,01* 0,64–0,96	0,59± 0,01* 0,37–0,72
1st adulthood (22–35 years)	8	0,46± 0,01*0,54–0,35 *	0,76± 0,01* 0,54–0,97	0,92± 0,01* 0,68–1,12	0,71± 0,01* 0,55–0,95
2nd adulthood (36–55 years)	8	0,33± 0,010,52–0,22 *	0,70± 0,01* 0,51–0,87	0,84± 0,01* 0,68–1,03	0,62± 0,01* 0,51–0,85
Elderly (56–74 years)	9	0,28±0,010,46–0,18 *	0,57±0,01* 0,26–0,71	0,75±0,02* 0,37–0,85	0,53±0,01* 0,31–0,73
Senile (75–90 years)	9	0,26±0,010,42–0,16 *	0,45±0,01* 0,25–0,60	0,63±0,03* 0,33–0,83	0,45±0,02* 0,26–0,63

both the vaginal vestibule as a whole, and the anterior, middle, and posterior thirds of it, increase from the neonatal period to the 1st period of adulthood and then decrease to the elderly, senile age.

The amplitude of the variation series of this sign of lymphoid structures in newborn girls, in early childhood, in most cases, is greater than in senile age.

DISCUSSION

So, at the macro-microscopic level, the initial departments (one or more) and excretory ducts are revealed in the glands of the vaginal vestibule.

M.R.Sapin, D.B. D. B. Nikityuk, V. B. Shadlinski, N. T. Movsumov et al. (2001) indicate that the excretory duct of the small glands of the walls of hollow internal organs can be preformed anatomically. At the same time, given the asynchronous nature of the secretory process, periodic weakening of secretion (for example, with involution of the glands), and antigenic materials are not always washed out from the lumen of the gland [9].

The analysis showed that the small glands of the vaginal vestibule are fully formed by the time the child is born and is capable of active secretion. This is due to a qualitative change in vital activity immediately after birth, the need to implement a protective function to the integumentary epithelium of the vestibule of the vagina (from mechanical damage, microorganisms, etc.). The study on total preparations of the age characteris-

tics of the glands of the vaginal vestibule showed that from the neonatal period to the 1st period of adulthood, the number of glands, length, width, and area of the initial departments increase. At this age, the shape of the glands is the most diverse, which is also typical for the glands of the majority of the mucous membranes of the hollow organs of the genitourinary apparatus, respiratory and digestive systems [10, 11, 12].

Starting from the 2nd period of adulthood and up to senile age, inclusive, there is a decrease in the indicated size-quantitative indicators of the glands of the vaginal vestibule.

In senile age, the shape of the glands (their exterior) is also simplified — the percentage of glands with three, four, or more initial departments (complex-shaped glands) decreases, and the content of simple-shaped glands increases (i.e. with one initial department).

Simplification of the *exterior* of the glandular apparatus is also typical for the walls of other hollow internal organs of the genitourinary apparatus, digestive and respiratory systems [9].

The variability of the dimensional and quantitative indicators revealed by us is also characteristic of other glands of hollow organs. So, according to M.K. Allahverdiyev (2007), B.M. Huseynov (2011), G.A. Huseynova (2013), on the shape, size, and the number of glands in the walls of the biliary tract, urinary bladder, female urethra, trachea, and main bronchi is also characterized by significant individual anatomical variability. According to these researchers, the individual structural features of the glands are least pronounced during the neonatal period, and most - in the elderly and senile age [10, 11, 12].

Significant individual variability in the shape and size of the glands of the mucous membranes of hollow internal organs is one of the patterns of their morphogenesis. The lower level of individual variability of the dimensional parameters of the glands in newborn girls and early childhood is possibly associated with the uniformity of the child's living conditions (hygiene, use of diapers, bed rest). The maximum level of these indicators, perhaps, depends on the characteristics of personal hygiene, the level of intimate relationships, past diseases, and other factors [1].

CONCLUSION

Thus, the performed macro-microscopic analysis made it possible to reveal previously unknown facts about the morphogenesis of the small glands of the vestibule and the individual variability of the glandular apparatus.

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PHARMACOGENETIC PROFILE AND PERSONALIZATION POSSIBILITIES IN TREATMENT OF PATIENTS WITH CHRONIC PELVIC PAIN SYNDROME

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ABSTRACT — Chronic pelvic pain syndrome (CPPS) is equally common in both men and women, causes worsening quality of life, social isolation and disability. The treatment of CPPS requires long-term pharmacotherapy associated with the development of class-specific side effects of nonsteroidal anti-inflammatory drugs (NSAIDs).
Genetic study of the carriage of polymorphic alleles of the CYP2C9 gene involved in the metabolism of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed to patients with CPPS is an urgent and in-demand task of modern healthcare.
This study allows us not only to determine the genotypes of patients with CPPS but also to identify ways of personalized approach to therapy.

KEYWORDS — chronic pelvic pain syndrome, non-steroidal anti-inflammatory drugs, pharmacogenetics, CYP2C9, personalized algorithms.

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) has a relatively equal prevalence throughout the world. According to the WHO, every fifth person on the planet suffers from chronic pelvic pain caused by diseases of various body organs and systems. More than 60% of women and 70% of men go to specialists because of CPPS. [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) efficacy in CPPS can be explained by the intracellular enzyme cyclooxygenase (COX) inhibition, which is involved in the synthesis of a variety of prostaglandins and leukotrienes regulating development of the inflammatory response. However, drugs from this group have serious class-specific adverse reactions (ADR) [1, 4].

NSAIDs are metabolized by cytochrome P450 enzymes, among which CYP2C9 plays a major role. The CYP2C9 gene is characterized by significant polymorphism. The most clinically important alleles are CYP2C9*2 and CYP2C9*3, which are associated with a slow rate of metabolic reactions of NSAIDs [8]. These genetic features facilitate the accumulation of drugs, increase the area under the concentration curve and as result lead to ADR. On the other hand, active metabolizers are able to eliminate NSAIDs in a shorter time what may reduce the clinical efficacy of drugs.

Therefore, the aim of this study was to study the frequency of polymorphic alleles of the CYP2C9 gene and to develop approaches for the personalized administration of NSAIDs in patients with CPPS.

MATERIALS AND METHODS

The research was carried out at the Department of Pharmacology and the Department of Nervous Diseases of the Astrakhan State Medical University (Russia). The ethical principles of Helsinki Declaration of the World Medical Association (1964, 2000) were observed in the work with patients. Informed consent was obtained from all patients that participated in our study. The study involved 102 patients with CPPS. They underwent a comprehensive clinical, laboratory and genetic testing based on which events for personalized therapy were developed.

Inclusion criteria were patient's informed consent; established diagnosis of CPPS; adverse drug reaction on NSAIDs in the medical history; the age from 18 to 70 years; for women: absence of pregnancy and contraceptive usage.

Exclusion criteria were: severe concomitant liver and renal diseases; the presence of decompensated concomitant diseases, including cancer, requiring constant intake of drugs from other groups; CHD. Angina pectoris, functional class III-IV; administration of drugs-substrates of CYP2C9, including warfarin; presence of diabetes mellitus and metabolic syndrome; presence of strokes and heart attacks in the anamnesis; hypotrophy, cachexia, severe asthenic syndrome; presence of genetic and mental illnesses; age under 18 and over 70 years; lack of compliance to therapy.

The intensity of pain syndrome and clinical, instrumental, laboratory and pharmacogenetic tests of the CYP2C9 gene were evaluated in all patients of the main observation group (n=102) enabling to develop their personalized therapies.

The polymorphism of CYP2C9 gene was determined by polymerase chain reaction after first DNA isolating from blood samples according to generally accepted methods at the D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg.

The average age of the patients was 49.7±13.43 years. There were 46 men (46%) and 54 women (54%). In accordance with the visual-analog scale (VAS) the pain intensity index was used for a comprehensive evaluation of the pain syndrome

Statistical processing of the results was carried out by the methods of parametric and nonparametric statistics. Correspondence of the genotype frequencies in the populations to the Hardy-Weinberg equilibrium was determined by the χ^2 method. The reliability of group differences for the parameters following the normal distribution was evaluated using the Student's test (T). The differences were considered significant at $p < 0.05$. To study the causal relationship between the phenomena, the regression analysis method was used using the Excel package of additional statistical programs. There was applied regression analysis using Excel package of additional statistic software to study the cause-effect relationship between the events.

RESULTS

In the study of CYP2C9 genotypes equilibrium distribution at the polymorphic markers C43OT and A1075C according to the Hardy-Weinberg proportion it was found that the distribution frequencies of polymorphic genotypes in the total study group (n=100) were equally distributed — χ^2=0,2445; p=0,6210 (p>0.05).

According to the results of conducted genotyping *2/n (rs1799853 CYP2C9*2 (C43OT)) phenotype was found in 10% of cases which according to the consortium's Guidelines (CPIC) for CYP2C9, has an activity index of 1.5 and corresponds to the concept of *intermediate metabolism* — Intermediate metabolizer.

The polymorphic slow allele rs1057910 CYP2C9*3 (A1075C) with an activity index of 0.5 was detected in 22% of cases. Since intermediate metabolizers are phenotypically individuals with reduced CYP2C9 function, it was decided to combine them into one general subgroup — individuals with reduced function. Which in the total sample of the study (n=102) was 32%. In patients with CPPS, 68% were found to be normal metabolizers with the wt/wt genotype.

When comparing patient's complaints, anamnesis of the disease, life history with concomitant pathology, the efficacy and tolerability of NSAIDs in outpatient practice of the anamnesis and finally taking into account the identified genotypes there were identified interesting features which in our opinion require understanding, systematization and further large-scale studies.

There were patients with CPPS who had mainly a long *experience* of the disease — 10 or more years in the group of slow metabolizers. While in the group of normal metabolizers this number was much lower: 57.5% VS 89% (Table 1).

90.6% of slow metabolizers with HTB on admission had a pain intensity value on a visual-analog scale (VAS) of 8 or more points. The pain intensity in the group of normal metabolizers was less marked — 7 points (57.5 %).

According to the materials of medical documentation and medical history of the disease, 46% of patients with CPPS who are normal metabolizers have weak efficacy of NSAIDs taken on an outpatient basis. On the other hand, in the group of patients with slow CYP2C9 allele more patients showed the effectiveness of NSAIDs in anamnesis, however, 31% of them had ADR of the gastrointestinal tract that contributed to the discontinuation or replacement of drugs in this group.

Character of the concomitant pathology depending on the CYP2C9 genotype carrier also requires attention. Among the concomitant pathologies, CVS diseases took first place in the frequency of prevalence (42.9%) in patients with CPP who are normal metabolizers. The second most important were gastrointestinal diseases — 12.5%. Among the cardiovascular pathologies, the leading ones were stage II hypertension (20.4%), secondary hypertension (10%) and CHD. Angina pectoris (functional class II) was observed in 7.5% of patients, atrial fibrillation — in 5%.

In the group of CPPS patients with the slow CYP2C9 allele, gastrointestinal tract pathology was most common, among which erosive and ulcerative lesions were recorded in the history of 24% patients, and the symptoms of the last exacerbation were noted less than 5 months ago. It was found by the method of regression analysis that in slow metabolizers there is a relationship between the intensity of pain in CPPS according to the VAS and the frequency of erosive and ulcerative diseases in the history — determination coefficient R^2=2,22.

It can be assumed that, in addition to the well-known *vicious circles* of the CPPS pathogenesis formation there is a mutual conditioning and aggravating effect of NSAIDs on the gastrointestinal mucosa, on the one hand, and NSAIDs *tolerance* depending on the initial state of the gastrointestinal tract, on the other. Patients with CPPS carrying the slow CYP2C9 allele,

Table 1. *Clinical and pharmacogenetic features of the examined patients with CPPS (n=102)*

№	Clinical and anamnestic parameters.	Normal CYP2C9 wt/wt metabolizers (n=70)	Poor metabolizers rs1057910 CYP2C9*3 (A1075C) rs1799853 CYP2C9*2 (C430T)/(n=32)
1	Duration of the disease		
	More than 10 years	57,5%	84%
	More than 5 years	22,5%	12,5%
	More than 1 year	30,4%	3,5%
2	Assessment of pain intensity (VAS)		
	≥8 points	25%	90,6%*
	7 points	57,5%	9,4%
	≤6 points	17,5%	-
3	Efficacy and tolerability of NSAIDs in medical history		
	NSAIDs in tablet form, taken in outpatient treatment	Low efficiency 46%	Significantly high efficiency
	ADR when taking NSAIDs at any time in the anamnesis (dyspepsia, epigastric pain, heartburn, flatulence)	5,5%	31%
4.	Concomitant pathology		
	Gastrointestinal tract	11%	30%*
	Erosive-peptic ulcer disease of the gastrointestinal tract with an exacerbation less than three months ago	-	24%
	Erosive-peptic ulcer disease of the gastrointestinal tract with exacerbation more than 2 years ago	6,5%	2%*
	Chronic colitis	2,5%	1%
	Chronic gastritis	3%	5%
	CVS	42,9%	12,5%
	Stage II hypertension	20,4%	-
	Secondary arterial hypertension	10%	12,5%
	Coronary artery disease. I functional class angina pectoris II functional class, NC0	7,5%	-
	Atrial fibrillation	5%	-
	Gynecological diseases (fibroids, adnexitis)	5,5%	9,3%
	Prostate adenoma, chronic prostatitis	8,6%	6,2%
	Chronic pyelonephritis	4,5%	-

** — Statistically significant relationship between the studied parameters, determined by the method of regression analysis. Determination coefficient R2>0.8*

when taking NSAIDs, experience gastrointestinal complications, are forced to refuse to take NSAIDs group drugs, which leads to the inflammatory reaction persistence, prolongation of the pathological process and even cause chronicity of pain syndrome.

Cardiovascular system pathology in this group of patients was significantly less frequent than the pathology of the gastrointestinal tract and was diagnosed in 12.5% of patients, mainly in the form of secondary hypertension.

Gynecological diseases in women carrying the slow CYP2C9 allele were registered slightly more often than in the group of conventional metabolizers of 9.3%VS5.5%. Urological symptoms in men of both clinical observation subgroups were recorded with the approximately same frequency of 8.6%VS6.2%.

DISCUSSION

Since NSAIDs are prescribed for long-term treatment of CPPS and the majority of patients are elderly people with unfavorable comorbid diseases, the development of methodological approaches which take into account the risk factors for the ADR development, the presence of concomitant pathology and genetic characteristics of the NSAIDs metabolism is a serious medical and social task.

Therapeutic recommendations for NSAIDs prescribing depending on the carriage of CYP2C9

genotypes were developed for CYP2C9 and NSAIDs at the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) [3].

These Consortium recommendations for celecoxib, flurbiprofen, lornoxicam, ibuprofen and meloxicam based on the CYP2C9 phenotype provide recommendations for normal (Activity score 2), intermediate (Activity score 1.5; 1.0) and slow metabolizers (Activity score 0.5) for the choice of NSAIDs [3]. These approaches are based on the carriage of the CYP2C9 genotype, pharmacokinetic and pharmacodynamic characteristics of NSAIDs.

The therapeutic recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) for NSAIDs can be applied for both short-term and long-term pharmacotherapy.

These recommendations are most stringent for intermediate (IM) and slow metabolizers (PM) of CYP2C9. Recommendations relate both to the choice of drugs — the possibility of treatment with alternative drugs, most of which are not metabolized by CYP2C9 (for example, naproxen, aceclofenac, sulindac, etc.) and suggestions for the prescribed NSAIDs dose titrating.

Considering the broad therapeutic index of NSAIDs, reducing the dose of drugs for normal metabolizers is not recommended. Meanwhile, for intermediate and slow metabolizers it is recommended to prescribe therapy with the lowest initial dose with next titrating it to the clinical effect. For celecoxib and flurbiprofen, the FDA recommends that in slow CYP2C9 (PM) metabolizers the initial dose should be reduced by 75–50%, followed by titration to clinical effect.

Previous clinical studies have shown the least adverse effects of celecoxib and naproxen on the CVS. [7].

These results are shown in the Russian clinical guidelines for the rational use of NSAIDs. Therefore, when developing events for personalized therapy of CPPS in patients with risk for cardiovascular complications, we recommend to use celecoxib selecting an individual dose based on the CYP2C9 genotype. [5, 6].

With the slow CYP2C9*1/3* and CYP2C9*3/3* genotype carriage the area under the curve AUC of celecoxib and flurbiprofen increases, and the FDA has made warnings in the instructions for these drugs and recommendations for dose reduction [3]. Therefore, in the case of CYP2C9*3 carriage and the risk of gastrointestinal complications, aceclofenac (aertal) may be prescribed, the pharmacokinetics of which are not significantly affected by the genetic variants of CYP2C9 in vivo and /or there is insufficient evidence to make a recommendation to present clinical practice guide (CPIC).

According to the results of our research, it might be concluded that the pharmacogenetic study of CYP2C9 gene polymorphic alleles carriage is an informative, accessible and non-invasive method that helps to determine the pharmacogenetic profile of patients with CPPS and identify ways of pharmacotherapy personalization taking in account a particular comorbid pathology.

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PRIMARY HYPERPARATHYROIDISM. A CLINICAL OBSERVATION

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ABSTRACT — Background. Primary hyperparathyroidism is an endocrine disease resulting from a primary pathology of the parathyroid gland, characterized by increased secretion of parathyroid hormone and increased blood calcium levels. Among the endocrine diseases, primary hyperparathyroidism is the third most common after diabetes mellitus and thyroid disease. Without timely diagnosis, primary hyperparathyroidism causes systemic damage to internal organs: renal impairment, nephrolithiasis, esophageal affection, cardiovascular and nervous system and affects bones.
The aim of the work was to present a clinical case of a patient with primary hyperparathyroidism and to analyze the stages of its diagnosis and treatment.
Material and methods. We reviewed the relevant literature and analyzed the patient's medical records.
Results and Discussion. The patient had a complicated course of primary hyperparathyroidism of bone and visceral form. Despite of the slow progression and availability of screening methods, hyperparathyroidism was detected at the stage of complications. The efficacy of the therapy has been assessed. The underlying reasons that made it difficult to diagnose PHPT at an early stage, before the development of serious complications of internal organs were investigated.
Conclusions: It can be assumed that our clinical case will increase the awareness of physicians, especially therapists, about the primary manifestations of this pathology and the challenges of its detecting and avoiding diagnostic errors.

KEYWORDS — primary hyperparathyroidism, parathyroid gland adenoma, hypercalcemia, parathyroid hormone, bone and visceral form.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease resulting from underlying disease of the parathyroid gland, characterized by increased secretion of parathyroid hormone and high blood calcium levels [1], which leads to increased osteolysis and calcium release from bone tissue, as well as increased intestinal calcium absorption. As a result, hypercalcemia, hypercalciuria, and hyperphosphaturia develop [2]. Among endocrine diseases, PHPT is the third most common after diabetes mellitus and thyroid disease [1]. Its incidence increases with aging; women suffer 2 times more often than men; the average age of diagnosis is 54–59 years [4].

Hypercalcemia is dangerous because it has a negative effect on all systems in the body and entails dysfunction of the kidneys (nephrolithiasis, hypecalciuria), the digestive system (nausea, vomiting, constipation, peptic ulcer of the stomach, or duodenal ulcer), cardiovascular system (tachycardia, arterial hypertension, arrhythmias), nervous system (hyporeflexia, muscle weakening, headache, drowsiness, depression) [2].

The first diagnostic step on the way to a diagnosis is to identify hypercalcemia, then to determine the PTH level, calciuria, as well as niveau diagnosis, including ultrasound examination of the parathyroid glands, computed tomography of the neck and mediastinum with contrast enhancement, and scintigraphy [1].

Currently, surgical intervention is the most effective method of treatment with a low risk of complications [1].

Despite the high prevalence of the disease and the availability of information about PHPT, patients with this pathology receive ineffective treatment for years due to misinterpretation of symptoms that mask the true cause of the condition.

The objective of the research is to demonstrate a clinical case of a patient with PHPT, and, using this example, to analyze the stages of the disease diagnosis and treatment.

MATERIALS AND METHODS

The authors have reviewed the medical literature on the problem of diagnosis and treatment of PHPT, as well as medical records of a female patient with this pathology.

RESULTS AND DISCUSSION

Patient Sh., born on 07.07.1982 (38 years old). On October 28, 2020 she was admitted to the Parathyroid Gland Pathology Unit of the National Medical Research Center of Endocrinology in Moscow (Russia) by referral of Tver Regional Clinical Hospital (Russia) to choose further treatment management.

On admission, the patient complained of recurrent convulsions, paresthesia and pain in the lower extremities, pain in the lower extremities while walking for a long time. History of the disease states the first

symptom of the disease was periodical convulsions in the lower extremities which appeared in 2005, and decreased during therapy with vitamin D analogs (alfacalcidol at a dose of 0.25 μg per day). For 10 years, the patient was not observed by either an endocrinologist or a therapist. The general state was satisfactory. In 2016, she was diagnosed with urolithiasis and bilateral nephrolithiasis. In 2017, she was diagnosed with secondary chronic pyelonephritis, which in 2018 was complicated by an abscess of the right kidney. The patient was urgently operated on.

Since 2020, the patient underwent magnetic resonance imaging of the spine in connection with an episode of an acute pain syndrome in the thoracic spine while tilting the trunk, which showed a visible mass in the cervical region. According to the results of the study, she was examined by an endocrinologist with the first suspect of PHPT.

On an outpatient basis, the patient was diagnosed with hypercalcemia (total calcium — 2.76 mmol/l, ionized calcium — 1.49 mmol/l), a low level of vitamin D (46.4 nmol/l), a tenfold increase in blood parathyroid hormone (76.7 pmol/l). On September 10, 2020, scintigraphy of the parathyroid glands revealed scintigraphic signs of adenoma of the lower right parathyroid gland. On September 15, 2020, osteodensitometry determined the total T criterion at the level of the femoral neck equal to 1.0; at the level of the lumbar spine — 0. Kidney ultrasound examination found diffuse changes in the renal parenchyma and signs of bilateral nephrolithiasis.

To decide on further management and referral to a specialized institution outside the Tver Region for surgical treatment, the patient was admitted to the specialized endocrinology unit of Tver Regional Clinical Hospital.

Positive family history of cardiovascular diseases and kidney stone disease.

During inpatient examination, a complete blood count revealed no pathology. Laboratory tests showed a slight decrease in GFR (73 ml/min and phosphorus — 0.70 mmol/L), an increase in total (2.74 mmol/L) and ionized calcium (1.50 mmol/L). The decrease in GFR was consistent with the development of such kidney complications as stage 2 chronic kidney disease. Thyroid hormone examination: free T-4 — 10.0 pmol/l, TSH — 1.50 mIU/l; free T-3 — 6.8 pmol/L, that is, free T-3 was above the norm, the rest were within its limits. Esophagogastroduodenoscopy (EGDS) revealed no pathology of the esophagus, stomach and first parts of the duodenum. Ultrasound of the thyroid gland revealed diffuse changes in the thyroid tissue with the presence of nodes in both lobes of the thyroid gland. TI-RADS 3. Scintigraphy revealed a parathyroid adenoma.

According to the results of the examination, the patient was diagnosed with primary osteo-visceral hyperparathyroidism.

The patient started treatment with Cholecalciferol 5000 IU daily. On the background of therapy, the patient had no significant changes in her state of health.

On October 2, 2020, the patient was admitted to the parathyroid gland pathology unit of National Medical Research Center of Endocrinology in Moscow, to decide on further management and possible surgical treatment.

During the examination, all values of complete blood count were within normal limits. Blood chemistry, 05.11.2020: total calcium — 2.79 mmol/l (hypercalcemia), albumin — 44 g/l, albumin-adjusted calcium — 2.71 mmol/l. Blood PTH, 28.10.2020 is significantly increased and amounts to 295.8 pg/ml. Common urine analysis — 1016, acidic reaction, no protein, leukocytes 2–3 in the field of view, no bacteria. Electrocardiogram within normal limits.

Considering the young age of the patient and periodic rises in blood pressure to exclude the hereditary nature of PHPT, an extended examination was carried out: insulin-like growth factor-1 — 244.9 ng/ml, cortisol of evening saliva — 2.31 nmol/ml, daily urine — 137 nmol/day, aldosterone-renin ratio — 58.7 (pg/ml). Evaluation of the indicators found a high level of insulin-like growth factor-1, while the rest of the indicators were within normal limits. The daily urinary calcium excretion was 12.1275 mmol/day, which was almost 2 times higher than the standard. Ultrasound examination of the thyroid and parathyroid glands revealed sonographic signs of multinodular goiter with focal changes, EU-TIRADS 2, signs of adenoma of the right lower parathyroid gland. Densitometry of the right proximal femur: -0.8; lumbar spine: -0.4; and distal radius: -2.0. Contrast-enhanced multispiral computed tomography of the neck, abdomen, and retroperitoneal space revealed signs of adenoma/hyperplasia of the parathyroid gland in the lower third of the neck, signs of multinodular goiter, enlarged liver and spleen, and a cystic mass in S4 liver. There were calculi in the calixes of both kidneys, signs of postischemic changes in the right kidney.

Based on the history, clinical findings, laboratory and instrumental results, the patient was clinically diagnosed with: Primary diagnosis: Primary osteo-visceral hyperparathyroidism. A mass lesion of the right parathyroid gland. Complications of the underlying disease: Recurrent urolithiasis, bilateral nephrolithiasis, chronic secondary pyelonephritis, non-acute. Chronic kidney disease, stage 2. Osteopenia (low mineral density -2.0 SD by Z-criterion) of the radius.

Concomitant diseases: Multinodular colloid goiter, 1 degree (WHO), euthyroidism. Liver cyst.

Surgeon consultation, 05.11.2020: a 38-year-old patient with confirmed primary hyperparathyroidism (albumin-adjusted calcium — 2.81 mmol/l, PTH — 295.8 pg/ml, calcium in daily urine 12.1 mmol/day), a mass lesion of the right lower parathyroid gland 2.8x0.9x0.8 cm. Indications for scheduled surgical treatment.

Prior to the scheduled operation, on 02.11.2020 the patient started treatment with a calcium mimetic drug to lower the PTH level — Cinacalcet, 30 mg, evenings. The patient was discharged from the hospital on 05.11.2020 in a satisfactory condition, with improvement, under the local outpatient supervision of specialists. Recommendations for the continuation of drug therapy with Cinacalcet 30 mg once a day, evenings; after 1 month, testing of laboratory parameters, namely, total blood calcium, ionized, albumin, phosphorus, creatinine, PTH, followed by consultation with an endocrinologist, at least once every 3 months. The patient needs to receive the results of a genetic test (MENI). Recommendations for routine surgical treatment of primary hyperparathyroidism in a specialized endocrinological hospital in 2–3 months.

Analyzing this clinical case, we should note that a total of 15 years passed from the onset of early primary manifestations of the disease (2005) to the diagnosis of complicated hyperparathyroidism. Late diagnosis of the disease prevented the patient from receiving effective therapy before the complications developed. The burdened family history of kidney stone disease could somewhat confuse the doctors and be also the reason for the late diagnosis. It can be assumed that the search for the cause of the development of kidney stone disease would allow to diagnose PHPT a little earlier.

During the examination, the clinicians should have to consider the complaints (periodic cramps in the lower extremities) and the relationship of their relief with the course of taking vitamin D, to timely conduct laboratory tests to confirm the diagnosis of PHPT, namely to determine the blood level of PTH and calcium. An additional examination: to determine the level of vitamin D, perform densitometry, kidney ultrasound, EGDS has to be performed.

After the diagnosis, it was necessary to adjust the diet to limit calcium intake to 800–1000 mg/day and increase fluid intake to 1.5–2.0 l/day. [3]. Then, monitor the following parameters: the level of calcium in the blood — 2–4 times a year; blood creatinine, GFR — 1 time in 6 months, PTH — 1 time in 6 months; daily excretion of calcium in the urine — 1 time in 6 months; ultrasound of the kidneys — once a year; measurement of BMD in the radius, femur, vertebrae; lateral radiographs of the spine with suspected fractures of the vertebral bodies (decreased growth, the appearance of back pain); EGDS — once a year [1]. In the case of indications, prompt surgical treatment is indicated — selective parathyroidectomy.

It can be assumed that the parathyroidectomy will significantly improve the condition of the patient. At the same time, she will still need to monitor the state of bone tissue and kidneys by an endocrinologist, urologist and nephrologist. Timely nephroprotective therapy will slow down the progression of chronic kidney disease.

CONCLUSIONS

Late diagnosis of PHPT in the patient at the stage of severe complications indicates a lack of awareness among practitioners about the pathogenesis of hyperparathyroidism, the variety of its clinical signs and options for screening examination. It can be assumed that raising the awareness of primary care specialists about the features of diagnosis and treatment of PHPT will allow timely identification of this pathology and effective therapy, before the development of serious complications.

Conflict of Interest Statement:

The authors declare no conflict of interest.

Author Contributions:

Danila Vasiliev — literature review, text writing. *Anastasia Kulish* — research design, text writing; *Olga Poselyugina* — collection and processing of materials, research concept, editing; *Elena Andreeva* — literature review, editing.

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TOXIN-INDUCED ACUTE KIDNEY INJURY. CLINICAL OBSERVATION

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ABSTRACT — The article presents a clinical case of toxin-induced acute kidney injury. The authors analyzed the cause of the event, revealed the pathogenesis of toxin injury of the kidneys, and described the main principles of treatment. The authors used this clinical case to show the importance of timely renal replacement therapy and the influence of comorbid pathology on disease development. The onset of acute kidney injury in patients with surrogate alcohol intoxication manifested as combined kidney and liver injury was described.
The article may be of interest to doctors of all specialties, especially for therapists and surgeons who are the first to reveal acute kidney injury and their choice of adequate management ultimately determines the outcome.

KEYWORDS — acute kidney injury, surrogate alcohol, hemodialysis.

INTRODUCTION

Acute kidney injury (AKI) is a complex of symptoms that develops due to a sharp decrease in the glomerular filtration rate (GFR) that leads to an increase in the concentration of nitrogen and non-nitrogen metabolites in the blood with the disturbances in the levels of electrolytes, pH, and fluid volume excreted by the kidneys [1]. The mortality rate in patients with AKI was around 20–30% during the past years. In intensive care units, it reached 70% [2]. Prognostically unfavorable factors in patients with AKI are oligoanuria, persistent hypotension, hepatitis, a necessity for artificial lung ventilation, and impaired consciousness. One of the most significant risk factors of the mortality in AKI is sepsis. The lethal outcome rate from this complication is 75% [3]. It should be noted that in 75% of cases, renal AKI is provided by acute tubular necrosis (ATN) that can be of two types: ischemic ATN, which complicates shock of different genesis, comatose conditions, and dehydration, and nephrotoxic ATN that develops as a result of a direct toxic effect of chemical compounds and pharmaceutical drugs [4]. The most important role in the pathogenesis of toxin-induced AKI belongs to vasoconstriction caused by the effect of nephrotoxins that leads to alterations in renal microcirculation [5]. Nephrotoxic AKI is diagnosed in every tenth patient with AKI admitted to hospital for acute hemodialysis [6]. Timely diagnostics of AKI is crucial for the provision of specialized medical care. The treatment of AKI includes etiotropic therapy that aims to resolve or decrease the effect of the causal factors. Pathogenetic therapy targets the stabilization of systemic and regional hemodynamics, correction of electrolyte and pH disturbances, resolution of anemia and hyperhydration, limitation of protein diet, and also includes extracorporeal methods of treatment [4]. Often, timely diagnosis of AKI determines disease outcome.

The study aimed to present a clinical case of a patient with toxin-induced AKI and characteristics of disease p, its diagnosis, and treatment.

MATERIALS AND METHODS

A review of the literature on AKI was performed, clinical recommendations on the management of patients with AKI were analyzed, and the clinical case of a patient with AKI was presented.

RESULTS

Patient M. aged 65 years was admitted to the nephrology unit of the Tver Regional Clinical Hospital (Russia). The patient complained of pronounced leg weakness, inability to walk, decreased volume of the excreted urine to 100 ml per day, constipation for three days, whole body trembling, respiratory difficulty, loss of appetite, and dry mouth.

The anamnesis, collected from the patient's relatives, showed that the patient abused alcohol and surrogate alcohol for 12 days before the disease onset. The disease onset was sudden and started with fainting and a fall in blood pressure to 70/40 mmHg. The ambulance team started pre-hospital vasopressor support with dopamine. Considering the severity of the patient's condition, he was admitted to the Anesthesiology and Resuscitation Unit of the Tver Municipal Clinical Hospital No. 7 with the diagnosis *poisoning by unspecified substance*. At the pre-hospital stage, cerebral infarction was excluded by the results of computed tomography (CT) of the head. During the patient's stay at the intensive care unit for three days, laboratory tests were made. Biochemical blood

assay showed an increase in the concentration of urea nitrogen (from 8.1 mmol/L to 19.3 mmol/L) and creatinine (from 234 μmol/L to 380 μmol/L). The patient was examined by a nephrologist who diagnosed severe toxin-induced AKI (pre-renal combined with renal) at the stage of anuria. Ultrasonic examination of the abdominal cavity and kidneys revealed diffuse lesions of the parenchyma, pancreas, and kidneys. Thoracic CT revealed disc-like collapses in the inferior lobe of the left lung. Electrocardiography showed sinus node tachycardia, left axis deviation, signs of both ventricles overload, cicatricial changes of the myocardium of the left ventricle posterior wall. Echocardiography revealed diffuse hypokinesia of the left ventricle walls. The ejection fraction was reduced to 50%. Areas of hypokinesia of the left ventricle posterior wall were visualized. Conservative therapy was chosen that included cytoflavin, ademetionine, omeprazole, dexamethasone, Ringer's solution, and semisynthetic penicillins (Klamosar, levofloxacin hemihydrate, and furosemide). Despite the treatment, negative dynamics was observed: the level of azotemia increased and oliguria persisted. Considering the necessity to start hemodialysis, the patient was transferred to the nephrology unit of the Tver regional clinical hospital.

Within the first five days in the unit, the patient underwent renal replacement therapy with acute hemodialysis, which resulted in positive dynamics in biochemical blood parameters that reflect kidneys functioning: the level of urea nitrogen decreased from 28.0 mmol/L to 15.7 mmol/L; the level of creatinine decreased from 416.0 μmol/L to 240.0 μmol/L; GFR increased from 5.45 ml/min to 29.8 ml/min. The levels of potassium in the blood normalized from 3.4 mmol/L to 4.00 mmol/L. In the same period, hyperglycemia was observed (the level of glucose was up to 8.6 mmol/L). A decreased tolerance to glucose was revealed. Besides, pathological values of biochemical blood parameters that characterize kidney functioning were observed: an elevated level of total bilirubin to 36.2 μmol/L and its direct fraction to 9.0 μmol; a decrease in the total protein to 54 g/L; an increase in the activity of hepatic enzymes, hypoalbuminemia, and hypertriglyceridemia. From the first day of hospitalization, blood coagulation disturbances were revealed: prothrombin index — 36%, international normalized ratio — 1.86 units, D-dimer — 9.68 mg/L. At the beginning of the observation, clinical blood assay showed I degree anemia, leukocytosis, lymphopenia, neutrophilia, thrombocytopenia, erythrocyte sedimentation rate (ESR) up to 60 mm/hour. A common urine test revealed alterations typical for this pathology: low specific gravity, proteinuria to 0.26 g/L, leukocyturia 10–15 in the field of vision, microhematuria, bacteriuria, flat epithelium 3–5 in the field of vision, nebulous urine.

To control the status of vital organs and to reveal comorbid pathology, the patient underwent different instrumental investigations. Thoracic, abdominal, and brain CT revealed hepatomegaly, signs of fatty hepatosis, and dyscirculatory encephalopathy associated with cerebral atherosclerosis. An electrocardiogram showed sinus node tachycardia, horizontal axis deviation, and disturbance of repolarization in the inferior wall of the left ventricle. Abdominal and kidney ultrasonic examination revealed diffuse lesions of hepatic parenchyma and pancreas, diffuse lesions of both kidneys, and kidney cysts. The patient was examined by a gastroenterologist who diagnosed nonspecific reactive hepatitis associated with moderate steatosis and pancreatic lipomatosis. A psychiatrist diagnosed toxic encephalopathy.

Within the period of hospitalization (two weeks), apart from renal replacement therapy, the patient received multicomponent pharmacotherapy: losartan 50 mg in the morning daily; omeprazole 20 mg twice a day; insulin therapy when the level of glucose elevates higher than 11 mmol/L 3–4 units s/c; aminophylline 2.4–10.0% i.v. by drop infusion of 250 ml of saline solution daily; choline alfoscerate 4.0 i.v. by drop infusion of 250 ml of saline solution daily; furosemide 60 mg i.v. bolus daily with a decrease in the dose to 20 mg; Remaxol 400 mg i.v. by drop infusion daily, potassium chloride 4–30.0% i.v. by drop infusion of 250 ml of saline solution daily, Meldonium 5.0 i.v. by drop infusion N. 10; saline solution 500 ml i.v. by drop infusion daily for the first ten days.

Within two weeks, the indicated therapy led to the normalization of the level of blood urea nitrogen. The level of creatinine decreased to 141 μmol/L, GFR increased to 56.42 ml/min/1.73m^2. The level of transaminases also normalized. However, hypopotassaemia, hypoalbuminemia, hypoproteinemia, hyperglycemia, and a decrease in the tolerance to glucose remained. The level of glycated hemoglobin was 6% and there were disturbances in the blood coagulation system. Clinical blood assay still showed II-degree anemia and an increase in the ESR to 79 mm/hour. Clinical restoration of diuretic activity was observed. Further, the patient was transferred to the therapeutic unit of the Tver municipal clinical hospital No. 7 for the correction of anemia and treatment of comorbid pathology. The patient was transferred to the hospital with the diagnosis of severe toxin-induced acute kidney injury at the stage of restoration of diuresis. Renal replacement therapy with hemodialysis was performed daily from June 6, 2020 to June 10, 2020. Stage II anemia.

Comorbid diseases: moderate non-specific reactive hepatitis associated with liver steatosis. Pancreatic lipomatosis. Stage III hypertensive disease, II-degree arterial hypertension, risk 4. Ischemic heart disease: postinfarction cardiosclerosis of undetermined time of onset. Diabetes mellitus type II with multiple complications. Recommended level of glycated hemoglobin is less than 7.5%. Stage II encephalopathy of complex (toxin-induced and dyscirculatory) genesis with moderately expressed vestibular impairments and psychoorganic syndrome.

DISCUSSION

On the one hand, the described clinical case demonstrates classic development of toxin-induced AKI with anuria when conservative therapy was ineffective. On the other hand, it shows that timely indicated hemodialysis led to the restoration of the kidney functioning. It should be noted that the patient had numerous comorbid diseases that were not controlled by the patient. This was an aggravating factor for the development of the main disease. Besides, this clinical case shows that in patients with surrogate alcohol intoxication, kidney injury is combined with toxin-induced liver injury.

Up to now, the diagnosis and treatment of AKI remain a challenging task. The severity of AKI and its complications are determined by the timely diagnosis and complete volume of treatment measures, including renal replacement therapy. Patients with the developed AKI can be placed under the care of doctors practicing in a few specialties because its manifestations are diverse. We believe that dissemination of the knowledge and experience in the diagnosis and treatment of AKI will help doctors of primary care timely recognize patients at risk.

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ENDOPROSTHETIC REPLACEMENT IN PATIENTS WITH TUMORS OF BONES AND JOINTS: REVISION SURGERY

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ABSTRACT — The article analyzes complications after individual oncological endoprosthesis replacement in tumor lesions of bones and joints, which led to repeated endoprosthesis replacement. After operations of endoprosthesis replacement of bones and joints with tumor lesions, the following complications were observed: periprosthetic infection — 7.4%, aseptic instability of the stem of endoprosthesis —13.1%, destruction of the endoprosthesis structure - 2.3%, wear of polyethylene inserts — 1.7%. Revision endoprosthesis replacement due to complications after endoprosthesis replacement of bones and joints for tumors was performed in 38 (21.7%) cases. Repeated endoprosthesis replacement of knee joint was performed in 22 cases, repeated endoprosthesis replacement of hip joint was performed in 6 cases, repeated endoprosthesis replacement of elbow joint was performed in 4 cases, repeated endoprosthesis replacement of shoulder joint was performed in 3 cases, repeated endoprosthesis replacement of tibial shaft was performed in 2 cases, repeated endoprosthesis replacement of ankle joint was performed in 1 case. The factors that led to complications and repeated endoprosthesis replacement were presented. In case of an infectious complication, it was recommended to install a metal-on-cement *spacer*, followed by repeated endoprosthesis replacement; in case of aseptic instability of the stem of endoprosthesis, repeated endoprosthesis replacement was performed with replacement of only one (loose) component of the endoprosthesis using a long intramedullary nail or replacement of the entire endoprosthesis; in case of the destruction of endoprosthesis structure, the repeated endoprosthesis replacement of the joint was effected with replacement of the entire endoprosthesis structure; when the polyethylene inserts were worn out, the repeated endoprosthesis replacement was performed with the replacement of the polyethylene inserts. After repeated endoprosthesis replacement, repeated revision operations were performed in 10 (26.3%) cases.

KEYWORDS — endoprosthetic replacement of bones and joints, complications, periprosthetic infection, aseptic loosening of the stem of endoprosthesis, destruction of the endoprosthesis structure, wear of polyethylene inserts, repeated endoprosthesis replacement.

INTRODUCTION

Over the past 30–40 years, the progress of onco-orthopedics has allowed to perform organ-sparing operations on the extremities in cases of bone tumors in most circumstances. Nowadays, in 90% of patients with bone tumors, the standard of organ-sparing surgery represents endoprosthesis replacement of joints and bones, which became possible due to the improvement of endoprosthesis replacement systems and surgical techniques of reparative surgery. Endoprosthesis reconstruction in patients with malignant tumors and bony spread improves the quality of life and allows timely giving of chemotherapy treatment cycles [1].

According to the references, this has been facilitated by the success of combined and complex treatment of malignant bone tumors [2, 3, 4]. As a result of endoprosthesis replacement, the development of various complications is possible, which leads to repeated operations in the scope of a revision endoprosthetic replacement. According to various authors, reoperations were performed in 13.68–50% of cases after joint endoprosthesis replacement for bone tumors [4, 5].

Depending on the model of the endoprosthesis, the reasons for revision endoprosthesis replacement included: deep infection in 7.3–17% of cases, aseptic instability in 1–12% of cases, destruction of the endoprosthesis structure in 1.5–10.6% of cases, wear of polyethylene components of the endoprosthesis in 3.1–35.6% of cases. Infectious complications after endoprosthetic reconstruction in oncology patients according to the current information range from 5% to 66% [6, 9, 18]. According to some researchers [7], in general, in reparative surgery on the extremities in patients with bone tumors, infectious complications amounted to 32%, 17% of these patients underwent amputations. According to Myers et al. [18] out of 32 patients with endoprosthesis bed infection, 7 patients underwent primary amputation, and 25 patients underwent a two-stage reoperation, of which 8 patients eventually underwent amputation. According to Capanna et al. [9] in 5% of cases, patients who underwent endoprosthesis replacement were subjected to repeated endoprosthesis replacement. Subsequent analysis revealed that 6% of patients had recurrent infections of the endoprosthesis bed and, accordingly, these patients were subjected to repeated endoprosthesis replacement.

Instability of the stem of endoprosthesis is the second frequent complication of endoprosthesis replacement of bones and joints. In almost half of the cases (44–47%) the cause of the revision operation is the mechanical instability of the implant stem [4, 8, 10]. According to the references, aseptic instability of oncological endoprostheses occurred in 6–27% of cases with a follow-up period of 1 to 15 years [19, 20]. Therefore, complications that occur after bone and joint endoprosthesis replacement performed in bone tumors are a factor that determines the prognosis of survival of endoprostheses and may represent indications for revision endoprosthetic replacement. In turn, revision endoprosthetic replacement has a much higher complication rate than primary endoprosthesis replacement. The need for re-intervention after revision replacement occurs within 5 years in 20–56% of cases [4, 11]. The risk of repeated endoprosthetic replacement according to Myers et al. [18] is 12% amounts to 32% in five years after surgery, 25% to 61% in 10 years, and 30% to 75% in 15 years.

In this article, we analyze the results of joint and bone endoprosthesis replacement in tumor lesions and provide data on the reasons that led to repeated endoprosthesis replacement in this category of patients.

MATHERIALS AND METHODS

During the period from 2009 to 2020, 175 operations of endoprosthesis replacement of bone and joint in cases of bone tumors were performed at the clinic of Institute of Traumatology and Orthopedics of the NAMS Ukraine, Kyiv. Among the patients, there were 96 women (54.9%) and 79 men (45.1%). The mean age of patients was 39.6 ± 1.3 years. Different models of endoprostheses were used: individual oncological endoprostheses, produced by Inmed (Ukraine) in 112 cases, by Beznoska (the Czech Republic) in 5 cases, by Zimmer (USA) in 4 cases, by Prospon (the Czech Republic) in 1 case, and individual modular oncological endoprostheses produced by V. Link (Germany) in 37 cases, by Stryker (USA) in 15 cases, by Implantcast (Germany) in 1 case. The indications for endoprosthetic replacement were: giant cell tumor — 56 cases, osteogenic sarcoma — 47, chondrosarcoma — 27, metastatic tumors — 18, bone fibrosarcoma — 9, giant-cell sarcoma — 6, lymphosarcoma — 3, malignant fibrous histiocytoma of bone — 2, myeloma – 2; adamantinoma — 2, Ewing's sarcoma — 2, fibrous histiocytoma of bone — 1.

Endoprosthetic reconstruction of the knee joint, after resection of the distal femur with a tumor, occurred in 64 (36.6%) patients; of the knee joint, after resection of the proximal tibia, occured in 31 (17.7%) patients; of hip joint, after resection of the proximal femur occured in 24 (13.7%) patients; of shoulder joint, after resection of the proximal humerus, was performed in 24 (13.7%) patients; of elbow joint, after resection of the distal humerus or proximal humerus, was performed in 13 (7.4%) patients; of ankle joint, after resection of the distal tibia, was performed in 6 (3.4%) patients, of humeral diaphysis was performed in 5 (2.9%) patients, of tibial shaft was performed in 4 (2.3%) patients, of femoral shaft was performed in 3 (1.7%) patients, of radial shaft was performed in 1 (0.6%) patient.

Before endoprosthesis replacement, a comprehensive examination of patients was performed, which included both general clinical studies (studies of values of blood, urine, ECG, ultrasound of internal organs, etc.), and X-ray radiological methods of examination. X-ray examination allowed to reveal a tumor of the skeleton, the length of the bone lesion, the malignant invasion in the soft tissues surrounding the bone. Computed tomography allowed to determine the degree of bone destruction, the condition of the bone medullary canal and tumor extension in it. Functional magnetic resonance tomography allowed to assess the soft tissue component of the tumor, the condition of the muscle envelope. Angiography was used to determine the source of blood supply to the tumor, the connection with the great vessels. With the help of osteoscintigraphy tumor lesions in other parts of the skeleton were revealed. Positron emission tomography was used to detect distant metastases in bone and visceral organs.

The morphological examination of the tumor, of course, was the main criterion for examining the patient. The technique of trepan or open tumor biopsy was used to obtain material for histological examination. The scope of surgery consisted of resection of the joint segment or bone segment with an *en block* tumor and replacement of the bone defect with an individual oncological or individual modular oncological endoprosthesis. The functional result of the operated limb was calculated according to the MSTS scale (Musculo-Sceletal Tumor Staging /System/). Quality of life was determined by the EORTC-QLQ-C30 questionnaire. The 10-year survival of endoprostheses was studied using the Kaplan-Meier multiple estimation method. Survival in patients was also assessed by the Kaplan-Meier method.

OBTAINED RESULTS

As a result of endoprosthetic replacement for bone and joint tumors, the following complications were revealed: after resection of the distal femur and knee joint endoprosthesis replacement (64 patients):

aseptic instability of the stem of endoprosthesis occured in 11 (17.2%) patients (Fig. 1), periprosthetic infection occured in 5 (7.8%) patients, destruction of the endoprosthesis structure occured in 2 (3.1%) patients, wear of polyethylene inserts occured in 1 (1.6%) patient.

After resection of the proximal tibia and endoprosthetic replacement of knee joint (31 patients) the following complications were revealed: periprosthetic infection was observed in 4 (12.9%) patients, aseptic instability of the stem of endoprosthesis was observed in 2 (6.5%) patients, destruction of the endoprosthesis structure was observed in 1 (3.2%) patient.

After resection of the proximal femur and endoprosthetic replacement of hip joint (24 patients) the following complications were revealed: aseptic instability of the stem of endoprosthesis was observed in 3 (12.5%) patients, wear of polyethylene inserts was observed in 2 (8.3%) patients, periprosthetic infection was observed in 1 (4.2%) patient (Fig. 2).

After resection of the proximal humerus and endoprosthesis replacement of the shoulder joint (24 patients) the following complications were revealed: aseptic instability of the stem of endoprosthesis was observed in 2 (8.4%) patients (Fig. 3), perirothic infection was observed in 1 (4.2%) patient. After resection of the distal humerus or proximal ulna and elbow joint endoprosthesis replacement (13 patients) the following complications were revealed: aseptic instability of the stem of endoprosthesis was observed in 2 (15.4%) patients, periprosthetic infection was observed in 1 (7.7%) patient, destruction of the endoprosthesis structure was observed in 1 (7.7%) patient. After resection of the distal tibia and ankle joint endoprosthesis replacement (6 patients) the following complications were revealed: aseptic instability of the stem of endoprosthesis was observed in 1 (16.7%) patient, periprosthetic infection was observed in 1 (16.7%) patient. After resection of the tibial shaft and endoprosthesis replacement of the bone defect (4 patients) the following complication was revealed: aseptic instability of stem of the implant was observed in 2 (50%) patients. According to our observations, overweight, which was observed in 9 (30%) cases, and increased patient activity in the post-surgery period, which was observed in 6 (20%) cases, were the main causes of aseptic instability of the stem of endoprosthesis, destruction of the endoprosthesis structure, and destruction of polyethylene inserts. In cases of periprosthetic infection the following measures were taken: non-surgical treatment with application of dialysis and administrations of antibiotics and antiseptics into a joint cavity in combination with systemic antibiotic therapy in 4 patients, surgical sanitation of an endoprosthesis bed in an amount of excision of necrotic and infected tissues with removal of the endoprosthesis and subsequent repeated endoprosthesis replacement after reduction of the infection process (two-stage repeated endoprosthesis replacement) in 7 patients, limb amputation in 1 patient. In case of instability of the stem of endoprosthesis, repeated endoprosthesis replacement was performed in 25 patients, including replacement of the stem of endoprosthesis with a longer one in 17 patients. In case of destruction of the endoprosthesis structure, repeated endoprosthesis replacement with replacement of all the structure of an endoprosthesis in 5 patients was carried out. In case of wear (destruction) of polyethylene inserts, repeated endoprosthesis replacement with replacement of inserts in 3 patients was executed. Repeated endoprosthesis replacement of a knee joint in patients with a tumor of the distal femur was performed in 17 patients, repeated endoprosthesis replacement of a knee joint in patients with a tumor of the proximal tibia was performed in 5 patients, repeated endoprosthesis replacement of a hip joint was performed in 6 patients, repeated endoprosthesis replacement of a shoulder joint was performed in 3 patients, repeated endoprosthesis replacement of an elbow joint was performed in 4 patients, repeated endoprosthesis replacement of an ankle joint was performed in 1 patient, repeated endoprosthesis replacement of tibial shaft was performed in 2 patients. The functional outcome of the operated limb (according to the MSTS scale) amounted to: 75–85% after knee joint endoprosthesis replacement, 70–80% after hip joint endoprosthesis replacement, 65–70% after shoulder joint endoprosthesis replacement, 75–80% after elbow joint endoprosthesis replacement, 70–72% after ankle joint endoprosthesis replacement, 85–90% after femoral shaft endoprosthesis replacement, 80–85% after tibial shaft endoprosthesis replacement, 85–95% after the endoprosthesis replacement of diaphysis of humerus, 96% after the endoprosthesis replacement of diaphysis of ulnar bone.

The functional outcome of the operated limb (according to the MSTS scale) amounted to: 70–80% after knee joint repeated endoprosthesis replacement, 65–75% after hip joint repeated endoprosthesis replacement, 60–65% after shoulder joint repeated endoprosthesis replacement, 70–75% after elbow joint repeated endoprosthesis replacement, 65–67% after ankle joint repeated endoprosthesis replacement, 80–85% after femoral shaft repeated endoprosthesis replacement, 75–80% after tibial shaft repeated endoprosthesis replacement, 80–90% after the repeated endoprosthesis replacement of diaphysis of humerus, 85% after the repeated endoprosthesis replacement of diaphysis of ulnar bone.

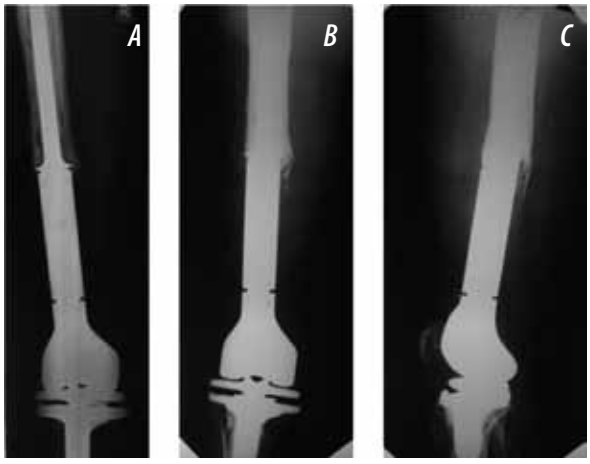

Fig. 1. *A — photoprint of the radiograph of the patient G. — aseptic loosening of the stem of knee joint endoprosthesis, produced by Stryker; B, C — photoprints of radiographs of the patient G. — a state after repeated endoprosthesis replacement of a knee joint*

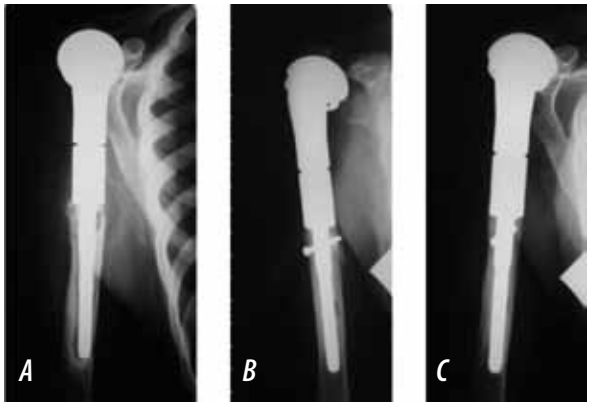

Fig. 3. *A — photoprint of the radiograph of the patient S. — aseptic loosening of the stem of endoprosthesis of the shoulder joint, produced by Inmed; B, C - photoprints of radiographs of the patient S. — a state after repeated endoprosthesis replacement of the shoulder joint with the installation of a anti-rotation screw*

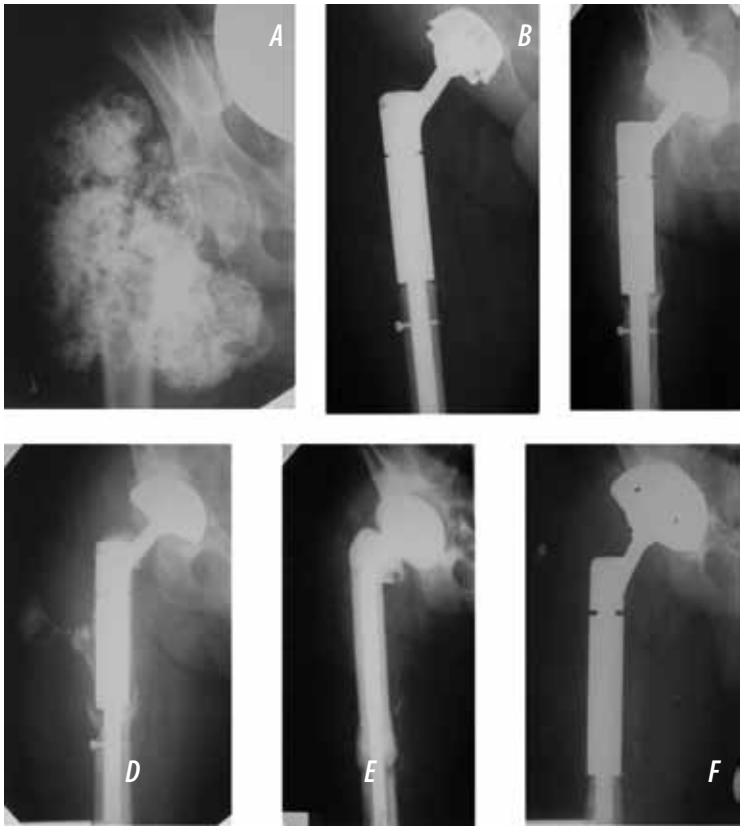

Fig. 2. *A — photoprint of the radiograph of the patient S. — primary chondrosarcoma of the proximal part of right femur; B — photoprint of the radiograph of the patient S. — a state after resection of the proximal femur with a tumor and hip endoprosthesis replacement with an endoprosthesis, produced by Inmed; C — photoprint of the radiograph of the patient S. — a state after repeated endoprosthesis replacement with replacement of the metallopolymer hip joint cup due to loosening of the cup; D — photoprint of the radiograph of the patient S. — periprosthetic infection with fistulous tract; E — photoprint of the radiograph of the patient S. — a state after removal of the endoprosthesis and installation of a metal-on-cement spacer; F — photoprint of the radiograph of the patient S. — a state after repeated endoprosthesis replacement*

The quality of life in patients (EORTC-QLQ-C30 questionnaire) before endoprosthesis replacement amounted to 20–40 points, after endoprosthesis replacement it amounted to 75–80 points, and after repeated endoprosthesis replacement it amounted to 65–75 points. The 10-year survival of the most frequently used endoprostheses in our sampling, calculated by the Kaplan-Meier method, amounted to 75% for Inmed (Ukraine) endoprostheses (70-80%), and 83% for V.Link endoprostheses (Germany) (80–90%), 92% for endoprostheses "Stryker" (USA) (85–95%), taking into account the totality of all revisions.

The overall three-year survival of operated and treated patients amounted to 68.2 ± 2.4%, and the overall five-year survival of operated and treated patients amounted to 51.8 ± 3.2%.

RESULTS AND DISCUSSION

Revision endoprosthesis replacement due to complications after bone and joint endoprosthesis replacement was performed by us in 38/175 (21.7%) cases. After repeated endoprosthesis replacement, repeated revision operations were performed in 10/38 (26.3%) cases.

According to the results, occurrence rate of instability of the stem of endoprosthesis during hip

endoprosthesis replacement was 12.5%, and according to the references, the occurrence rate of instability of the stem of endoprosthesis in patients, who undergone endoprosthesis replacement of the proximal femur ranged from 2.2 to 24.5%, i.e. our indicator was consistent with the data of other researchers [12].

Occurrence rate of instability of the stem of endoprosthesis in endoprosthesis replacement of the distal femur in our study was 17.2%, according to the references it is 6–14%, and in some studies — up to 27% [12], which is also consistents with our results.

Occurrence rate of instability of the stem of endoprosthesis during endoprosthesis replacement of the proximal tibia in our study was 6.5%, and according to the references it ranged from 6 to 27% [19, 20], and in some studies up to 31% [12], which practically coincides with our results.

According to our data, destruction of the endoprosthesis structure ranged from 3.2% to 7.7%, depending on the applied model of the endoprosthesis and the location of the endoprosthesis replacement. Destruction of the endoprosthesis structure (fracture of the stems of endoprosthesis) according to some researchers [13] was observed in 1.8% of cases, according to other researchers [9] in total of 95 cases of endoprosthetic replacement in 6 (6.3%) cases there was a fracture of the stems of endoprosthesis, and according to Myers et al. [18] fracture of the endoprosthesis structure occurred in 2% of cases, respectively, all patients underwent repeated endoprosthesis replacement.

In our study, the occurrence rate of destruction of polyethylene inserts was observed in 1.6% of cases in knee joint endoprosthesis replacement, and in 8.3% in hip endoprosthesis replacement. According to the references [9], destruction of polyethylene inserts amounted to up to 41%, of which in 30% of cases repeated endoprosthesis replacement was performed, and in some studies [5] it ranged from 3.1% to 35.6%. Myers et al. [18] in total of 194 cases of endoprosthesis replacement there are 36 (18.6%) patients with a destruction of polyethylene inserts. It should also be noted that of the 36 patients, who undergone repeated endoprosthesis replacement, in 16 cases a repeated destruction of inserts was reported.

Infectious complications that led to repeated endoprosthesis replacement in our study ranged from 4.2 to 16.7%, and based on the references, infectious complications amounted to 7.2% [16].

After endoprosthesis replacement of the shoulder joint, the complications in our study included the following: aseptic instability of the stem of endoprosthesis in 2 (8.4%) patients, periprosthetic infection in 1 (4.2%) patient. In the references [15], the authors analyze 60 cases of endoprosthesis replacement of shoulder joint, where complications amounted to 32%, repeated endoprosthesis replacement because of aseptic instability was performed in 2 patients (3%), because of infection of the endoprosthesis bed it was performed in 2 (3%) patients, because of shoulder joint instability it was performed in 6 (10%) patients, 3 patients underwent amputation due to tumor recurrence. According to the authors [14] complications of endoprosthesis replacement of the shoulder joint were observed in 60% of cases, including fractures of the endoprosthesis in 7 patients and infectious complications in the bed of the endoprosthesis in 3 patients, repeated endoprosthesis replacement was performed in 10 patients.

The distal part of the humerus was affected in 1% of cases of tumor lesions of the skeleton.

According to our studies, during endoprosthesis replacement of elbow joint in 13 patients, aseptic instability of the stem of endoprosthesis was observed in 2 (15.4%) patients, periprosthetic infection was observed in 1 (7.7%) patient, destruction of the endoprosthesis structure was observed in 1 (7.7%) patient.

The authors [17] report the experience of performing endoprosthesis replacement of the distal humerus in 18 patients, where aseptic instability of the endoprosthesis was observed in 3 (16.6%) patients, local tumor recurrence was observed in 2 (11%) patients, periprosthetic infection was observed in 2 (11%) patients, radial nerve neuritis was observed in 1 (5.5%) patient, fracture of the endoprosthesis structure was observed in 1 (5.5%) patient, due to complications repeated endoprosthesis replacement was performed in 4 cases.

Survival of the endoprosthesis amounted to 78% during monitoring of up to 4.5 years. According to our study, in endoprosthesis replacement of the ankle joint (6 patients), aseptic instability of the stem of endoprosthesis was observed in 1 (16.7%) patient, periprosthetic infection was observed in 1 (16.7%) patient, and according to the references [21], of 9 patients operated for tumors of the distal tibia, complication in the form of periprosthetic infection was observed in 2 (22.2%) patients.

The authors [22] report that out of 280 knee joint endoprosthesis replacement operations for tumor lesions of the distal femur, 52 (18.6%) repeated endoprosthesis replacement operations were performed in this area, of which they were performed in 8 (2.9%) cases due to infection of the endoprosthesis bed, and in 44 (15.7%) cases they were performed due to instability.

According to our studies, during resection of the distal femur and knee joint endoprosthesis replace-

ment, aseptic instability of the stem of endoprosthesis was observed in 11 (17.2%) patients, periprosthetic infection was observed in 5 (7.8%) patients, which is slightly higher than in the above authors. According to the references [22], of 117 primary knee joint endoprosthesis replacement in patients with proximal tibial tumor, repeated endoprosthesis replacement was performed in 32 (27.3%) cases, due to periprosthetic infection repeated endoprosthesis replacement was performed in 13 (11.1%) cases, due to aseptic instability repeated endoprosthesis replacement was performed in 19 (16.2%) cases. According to our data, after resection of the proximal tibia and knee joint endoprosthesis replacement, periprosthetic infection was observed in 4 (12.9%) patients, aseptic instability of the stem of endoprosthesis was observed in 2 (6.5%) patients, which is slightly higher regarding peripheral infection, and much lower regarding aseptic instability of the stem of endoprosthesis. Some researchers [22] report that repeated endoprosthesis replacement was performed in 6 (7.1%) cases out of 84 primary hip endoprosthesis replacement, due to periprosthetic infection in 3 (3.6%) cases, and due to aseptic instability repeated endoprosthesis replacement was performed in 3 (3.6%) cases.

According to our study, after resection of the proximal femur and hip endoprosthesis replacement, aseptic instability of the stem of endoprosthesis was observed in 3 (12.5%) patients, periprosthetic infection was observed in 1 (4.2%) patient, which is higher than the values, provided by the above authors.

In the references [22] the results were reported of 81 endoprosthesis replacement of the shoulder joint, where repeated endoprosthesis replacement was performed in 4 (4.9%) cases, of which due to aseptic instability — in 2 (2.45%) cases, and due to periprosthetic infection — in 2 (2,45%) cases.

According to our study, after resection of the proximal humerus and shoulder joint endoprosthesis replacement, aseptic instability of the stem of endoprosthesis was observed in 2 (8.4%) patients, and periprosthetic infection was observed in 1 (4.2%) patient, which is also higher than these researchers reported. Thus, after comparing the results obtained by us and the results of other researchers, we can conclude that some complications after primary endoprosthesis replacement in our study are more numerous, due to the use of imperfect model of endoprosthesis or violation of the technique of endoprosthesis replacement.

FINDINGS

1. Revision endoprosthesis replacement due to complications after bone and joint endoprosthesis replacement for tumors was performed in 38 (21.7%) cases.

2. Repeated endoprosthesis replacement due to periprosthetic infection was performed in 7.4% of cases, due to aseptic instability of the stem of endoprosthesis it was performed in 13.1% of cases, due to destruction of the endoprosthesis structure it was performed in 2.3% of cases, due to wear of polyethylene inserts it was performed in 1.7% of cases.

3. Repeated endoprosthesis replacement was required 1.2 times more often than after primary endoprosthesis replacement and amounted to 26.3%.

4. The overweight of the patient which was observed in 9 (30%) cases, and increased patient activity in the postoperative period, which was observed in 6 (20%) cases, were the main cause of aseptic instability of the stem of endoprosthesis, and of destruction of the endoprosthesis structure, and of destruction of polyethylene inserts.

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LOCAL NODULAR PROCESSES AFTER BREAST CANCER SURGERY

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ABSTRACT — The present study is based on treatment outcomes in 140 women who underwent operative treatment in the volume of oncoplastic radical resection (main group, n = 70) and Madden's radical mastectomy (comparison group, n = 70) for 1st to 2nd stages of breast cancer. When examined during the first year after surgery, no progression (local and distant) of the disease was observed, both after oncoplastic radical resections and Madden's radical mastectomy. Nodal processes in the surgical area were identified in 7.1% of patients in the main group and 10.0% in the comparison group. No significant difference was found between the groups. We noted that after oncoplastic radical resection, oleogranulomas were more common, whereas after Madden's radical mastectomy — organized lymphoceles were observed more often.

KEYWORDS — breast cancer, radical mastectomy, oncoplastic radical resection, nodular processes.

INTRODUCTION

Breast cancer (BC) has a leading position in the structure of general oncological incidence and the first place in the structure of oncopathology in women [1]. The treatment of BC should always be comprehensive and comprise such activities as surgery followed by hormonal, targeted, radiation therapy [2]. Surgery is a strong stress for a person, which can adversely affect the course and outcome of the disease. Malignant breast neoplasms are significant medical and social problems of the modern society. Removal of the breast is a crippling operation, leads to loss of attractiveness, loss of femininity and sexuality, a decrease of self-esteem. Therefore, in the last decades classical mastectomy has shifted to organ saving treatment of breast cancer, if it does not violate oncological radicality and lead to deterioration of long-term results [3, 4]. Numerous methods of oncoplastic surgery have been developed combining the principles of radical oncological surgical treatment and plastic surgery [5]. Achieving a satisfactory aesthetic result with the adherence to oncological radicality is most problematic in central localizations (due to loss of the nipple) and medial localizations (reduction of the subcutaneous fat layer) of the tumor, which makes it relevant, to study of the treatment outcomes in patients with central or medial localization of the tumor in the mammary gland [6]. Surgery should be executed with minimal local complications, such as nodular processes and surgical site infections [5, 7].

The aim was to assess the immediate results of breast cancer surgery when localizing the tumor in the central and medial quadrants.

MATERIALS AND METHODS

The study was carried out in the Department of Breast Pathology of Tver Regional Clinical Oncology Centre in 2017–2019. The study included 140 women who underwent oncoplastic radical resection in various modifications or radical mastectomy by Madden, for 1st to 2nd stages of BC. The patient age varied from 30 to 89 years.

The main group included 70 women diagnosed with 1st to 2nd stages of BC, who had oncoplastic radical resections (OPRR) with various modifications. The tumor was located in the lower-medial quadrant — in 20 cases, in the upper-medial quadrant — in 38 patients, and in the central quadrant — in 11 patients, on the border of medial quadrants — in 1 case. OPRR were done in all cases. The modification of OPRR by Hall-Findlay's technique was used in 11 cases, the upper lateral glandular flap was used in 8 patients, and the lower flap was used in 3 patients. The T-invers version of OPRR was used in 12 patients: in 7 cases — using the upper glandular flap and in 5 cases — the lower one. Round-block OPRR was done in 13 patients, Batwing mammoplasty — in 9 cases, the S-technique of OPRR — in 3 patients, the sliding dermo-glandular flap with Z-shaped incision — in 16 patients, the Grisotti technique — in 5 patients and thoraco-epigastric flap was used in 1 case. The average length of hospital stay was about 21 days. All patients were recommended to undergo the radiation therapy and chemotherapy in the postoperative period depending on the stage of the disease and the immunohistochemical subtype of the tumor.

The comparison group included 70 women with 1st to 2nd stages of BC in whom Madden's radical mas-

tectomy was performed. The tumor was localized in lower-medial quadrant — in 13 cases, in upper-medial quadrant — in 22 patients, in central quadrant — in 31 patients and in the border between medial quadrants — in 4 cases.

Following the design of the study, all women in both groups had a follow-up examination within one year after surgery. The patients underwent a comprehensive medical check-up: clinical and the biochemical blood tests, oncomarkers (CEA, Ca 15-3), ultrasound of the mammary glands and regional lymph nodes — once every 3 months, then mammography, ultrasound of the abdominal organs, computed tomography of the chest organs every 6 months after the surgical treatment.

RESULTS

In the period of observation after oncoplastic radical resection 3 patients (4.3% of cases) had marginal skin necrosis. One patient (1.4%) after T-inverted type of OPRR with lower glandular flap had marginal necrosis of areola.

The appearance of nodular formations in the postoperative scar region and soft tissues of the remaining breast tissue with a diameter of more than 2.0 cm was observed in 5 patients (7.1%) 6–9 months after surgery. Thin-needle aspiration puncture of these formations was performed. Unpalpable entities were not identified during this period even with ultrasound.

According to the results of a cytological study, 4 (5.7%) women had cytological signs of oleogranuloma and 1 (1.4%) patient had a lymphocele. Since there were doubts on the local recurrence of BC and the efficacy of conservative treatment of these malformations, we removed them with the use of local anesthesia. Histological examination confirmed the diagnosis of oleogranulema. Thus, there were no locoregional recurrences of BC after oncoplastic breast resections in central and medial tumor localization of tumor. We explain development of such the malformations as consequences of local trophic disruptions in the form of fibrotic-sclerotic processes after radiation therapy and decompensation of local hemodynamics in the early post-operative period. Hepatotoxicity, induced by anticancer therapy, presents an additional challenge. No significant changes in the liver and mammary gland were revealed by ultrasound and examination of oncomarkers.

In the comparison group, nodular formations in the postoperative scar zone on the thoracic wall were detected in 7 (10.0%) patients within 3–6 months after surgery. All of them were unpalpable and detected with ultrasound study. The tactics of treatment were identical to the main group. These formations were punctured under ultrasound navigation. Cytological examination of aspirates diagnosed lymphoceles in 6 (85.7%) patients and an oleogranuloma — in 1 (14.3%) patient.

CONCLUSIONS

Our findings showed no progression of BC (local and distant) within a year after either oncoplastic radical resections or Madden's radical mastectomy. Nodular processes in the surgical zone were represented by development of lymphocele and oleogranulomas. The most common local nodular complications, we observed after oncoplastic radical resections, were oleogranulomas, whereas lymphoceles were more common after Madden's radical mastectomy.

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SURGICAL CORRECTION OF FOOT DEFORMITY IN CHILDREN UNDER 3 YEARS OF AGE

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ABSTRACT — Aim. The study aimed to improve the outcomes for surgical correction of talipes equinovarus in children using the Ponseti method, as well as vertical talus correction using the Dobbs method combined with massage, physiotherapy and therapeutic exercise. Material and methods. In the period from 2015 to 2020, 109 children were examined and treated at the Filatov City Children's Hospital, Moscow. Results. The study has revealed that without timely correction the orthopedic foot pathology in children is often accompanied by pain, functional changes and a high risk of developing disability in a child, which determines a high social significance of this nosology. After a comprehensive assessment and a combination of conservative and surgical correction techniques, the congenital foot deformity in all children was completely eliminated. Conclusion. The Ponseti method is required to be carefully adhered to in order to achieve a complete pes equino-varus correction. Early start of correction of changes is effective.

KEYWORDS — clubfoot, pes equino-varus, metatarsus varus, vertical talus, congenital foot deformity, the Ponseti method, pes varus, pes planovalgus, pes cavus.

INTRODUCTION

Congenital foot deformities are represented by such nosologies as pes equino-varus (clubfoot), metatarsus varus, vertical talus, pes varus, pes planovalgus, pes cavus, as per ICD-10 code Q66.5. The epidemiology of pes equino-varus is 1 per 1000 newborns [1], while vertical talus and metatarsus varus are met quite rare [2].

The mentioned nosologies are accompanied by severe pain syndrome, functional changes in the foot, thus forcing the patient to use orthopedic shoes. In the absence of proper surgical correction, the risk of disability is high. Functional disorders affect the patient's quality of life and determine the high social significance of the mentioned nosologies [1].

Today, there is a range of congenital foot pathology classifications. According to Zatsepin-Bohm, there are two clinical forms of pes equino-varus: typical and atypical. According to the literature, the typical deformity accounts for 80% of cases. This type of deformity responds well to such treatment methods as bandaging and plastering.

There are also three types of soft tissue component involvement — soft tissue and bone (rigid). Attributing to a particular type of pathology is distinguished by the possibility and efficacy of a conservative treatment option. The literature describes a number of soft tissue types of deformity as the most common [3].

The aim of the study was to improve outcomes of pes equino-varus correction using Ponseti method, and vertical talus correction using the Dobbs method in children combining it with massage, physiotherapy and therapeutic exercise.

MATERIAL AND METHODS

In the period from 2015 to 2020, a double prospective cohort study was conducted at the Filatov City Clinical Children's Hospital, Moscow. 109 children with congenital foot deformities were enrolled for the proposed treatment.

During examination of 102 children (93.6%) were diagnosed with the typical form and 7 children (6.4%) were diagnosed the atypical form of pes equino-varus. The soft tissue form was found in 51.4% of cases (in 56 children), and the bone form was found in 48.6% of cases (53 children). We identified the left-sided type in 24 children (22.1% of cases); the right-sided type in 20 children (18.3% of cases) and bilateral type of deformity in 65 children (59.6% of cases).

In terms of the age in which the deformity was diagnosed, the patients were distributed as follows: in 73.4% of cases, the deformity was diagnosed under 3 months (80 children), in 6.4% of cases — from 3 to 6 months (7 children), and in 20.2% of cases — at the age of 6 months and older (22 children).

On average, the clinical observations and treatment began at the age of one month. The surgical intervention period was 3.0 (±1.25) months, on average.

Surgical correction was performed in all 103 patients with pes equino-varus and in 3 patients with vertical talus. Metatarsus varus was treated conservatively in all patients. Surgical treatment was performed in 106 children (achillotomy was performed in 103 children with pes equino-varus and in 3 children with vertical talus).

The Ponseti method was used in all children with pes equino-varus and in 11 children (91.7%) of 12 children with metatarsus varus. This is a conservative technique for plastering congenital clubfoot, which consists of the stage-by-stage brining of all the deformity components into the correction position, and is based on the ankle joint biomechanics and supplemented with percutaneous achillotomy.

The Dobbs method was used in all children with vertical talus. This is a conservative technique for plastering congenital equinovalgus deformity of feet, which implies a gradual bringing all deformity components to the correct position, and is based on the ankle joint biomechanics, supplemented with percutaneous achillotomy and, in some cases, by fixing the first ray using a Kirschner's wire.

The comprehensive treatment of children with metatarsus varus included massage procedures. Massage was used in five children (83.3%) out of six with vertical talus. A massage was not administered to the children with pes equino-varus. Physiotherapy procedure courses were used in two cases (16.7%) out of twelve in children with metatarsus varus. Comprehensive physical therapy exercises for metatarsus varus were carried out in 70.3% of cases (64 out of 91 children) and in 33.3% of cases for vertical talus (4 out of 6 children). Comprehensive physical therapy exercises were not administered to the children with pes equino-varus.

Treatment outcomes were assessed according to the Pirani scale (1995). The classification includes the analysis of 6 described clinical signs, while their value is determined in the maximum foot correction position.

Each of the signs is assessed based on a point scale: 0, 0.5 and 1 point (depending on the severity).

Statistical assessment of the study results was carried out using a laptop and "Statistica" Software (for Windows, version 6.0).

The study result data were assessed by the variation statistics method.

The study used the following statistical research methods:

1. Wilcoxon's signed rank test (to assess statistically significant differences before and after treatment in each clinical group of patients);
2. Mann-Whitney test (to assess statistically significant differences in inpatient and outpatient groups);
3. Fisher's exact test (to assess statistically significant differences in patients with dorsiflexion> 15° and <15°
4. Friedman's two-way analysis (to assess statistically significant differences before and after treatment according to the Pirani classification).

RESULTS

The treatment efficacy criteria were the following: heel cavus, degree of cavus rigidity, assessment of the medial fold, shape of the foot lateral arch, foot equinus and dorsiflexion degree. Changes in the foot were determined according to the Pirani classification (1995):

1. The hindfoot condition according to Pirani classification before treatment had more pronounced statistical differences than after correction (according to Wilcoxon test = -8.955, p <0.001);
2. The cavus rigidity degree according to the Pirani classification before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -9.125; p <0.001);
3. Assessment of the foot medial fold before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -9.105; p <0.001);
4. Bend of the foot fibular margin before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -9.364; p <0.001);
5. Foot equinus before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -8.879; p<0.001); 5. Assessment of the posterior fold of the heel according to the Pirani system before treatment had more pronounced statistical differences than after correction (Wilcoxon test = 8,791; p<0,001).

The total points according to the Pirani criteria before treatment were 4.5 (3.0; 6.0), after correction they amounted to 0 (0; 0) point.

The obtained differences were considered significant at p <0.001 level (Friedman rank analysis of variance was used for related samples).

Among the children enrolled in our study, 61 children underwent surgery on an outpatient basis whereas 45 patients were hospitalized (n = 106) and the remaining 3 children were treated as a case follow-up.

OUTPATIENT SURGICAL TREATMENT RESULTS

According to the Pirani classification, changes in the foot were distributed as follows: 1. Heel cavus according to Pirani classification before treatment revealed statistically significant differences at p <0.001 than after correction (Wilcoxon test = -6.705,1.0 (0.5; 1.0) before treatment versus 0.0 (0.0; 0.0) after correction); 2. Cavus rigidity according to Pirani classification before treatment had more pronounced-statistical differences than after correction (Wilcoxon test = -6.628; p <0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0.0) after correction); 3. Assessment of the foot medial fold before treatment had more

pronounced statistical differences than after correction (Wilcoxon test = -6.628; p <0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0 , 0) after correction); 4. Bend of the foot fibular margin before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -6.683; p <0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0 , 0) after correction); 5. The foot equinus before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -6.753; p <0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0.0) after correction); 6. Assessment of the posterior fold of the heel according to the Pirani classification before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -6.662; p <0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0, 0; 0.0) after correction).

Thus, the total point according to the Pirani classification before treatment was 5.0 (4.0; 6.0), after correction it was 0 (0; 0). The obtained differences were considered significant at p <0.001 (according to Friedman rank analysis of variance).

RESULTS OF INPATIENT SURGICAL TREATMENT

According to the Pirani classification, changes in the foot were distributed as follows: 1. Heel cavus according to the Pirani classification before treatment had more pronounced statistical differences than after correction (Wilcoxon test= -5.665, p<0.001, 1.0 (0.5;1.0) before treatment versus 0.0 (0.0; 0.0) after correction); 2. Cavus rigidity according to Pirani classification before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -5.557; p<0.001, 1.0 (0.5, 1,0) before treatment versus 0.0 (0.0; 0.0) after correction); 3. Assessment of the foot medial fold before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -5.516; p<0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0 , 0) after correction); 4. Bend of the foot fibular margin before treatment had more pronounced statistical differences than after correction (Wilcoxon test = -5.631; p<0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0 , 0) after correction); 5. The foot equinus before treatment had more pronounced statistical differences than after correction (Wilcoxon test= -5.674; p<0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0.0; 0.0) after correction); 6. Assessment of the posterior fold of the heel according to the Pirani classification before treatment had more pronounced statistical differences than after correction (Wilcoxon test= -5.631; p<0.001, 1.0 (0.5, 1.0) before treatment versus 0.0 (0, 0; 0.0) after correction).

Thus, the total point according to the Pirani classification before correction was 5.5 (4.0; 6.0), after correction it was 0 (0; 0). Differences were considered statistically significant at p <0.001 (according to Friedman's two-way analysis).

COMPARISON OF INPATIENT AND OUTPATIENT GROUPS

Before treatment, the inpatient and outpatient treatment groups were comparable in all Pirani classification criteria: 1. Heel cavus (Mann-Whitney test, p = 0.466); 2. Cavus rigidity (Mann-Whitney test, p = 0.611); 3. Medial fold of the foot (Mann-Whitney test, p = 0.986); 4. Bend of the foot fibular margin (Mann-Whitney test, p = 0.978); 5. Foot equinus (Mann-Whitney test, p = 0.663); 6. Posterior fold of the heel (Mann-Whitney test, p = 0.671).

Based on the treatment efficacy criteria according to the Pirani classification, it is possible to compare the clinical comparison groups according to the achieved dorsiflexion degree.

Achieved dorsiflexion exceeding 15° was observed in 57 cases of surgical treatment (93.4 ± 10.9%) in hospital environment and in 39 cases (86.6 ± 11.2%) of surgical treatment in the inpatient setting (Table 1).

From the above table it follows that the differences between the groups are statistically insignificant (Fisher's exact test, exact significance (2-sided) = 0.139). By the overall point — Mann-Whitney test, p = 0.917. Thus, the groups are comparable with each other in terms of these indicators.

UNFAVORABLE OUTCOMES OF INPATIENT AND OUTPATIENT TREATMENT

After surgical correction in hospital environment, one child required a second surgical intervention due to relapse (an additional achillotomy was performed).

Based on the accumulated experience, early detection of the recurrent pathology is the key to successful elimination of recurrent deformities. They are usually caused by a failure to follow the rules of using rehabilitation orthoses, braces and orthopedic shoes at the end of the main surgical correction stage. Relapse, as a rule, is detected during the period of the foot intensive growth — before 10–13 years of age. Therefore, at the juvenile onset, such children should be regularly followed up by an orthopedist [4].

In 6 (9.8%) of 61 children who were undergoing outpatient treatment, the limited motion range was observed in the distal part of the lower leg, while the same complication in the hospital was observed in 3 (6.6%) of 45 patients. There were no statistical differences in the compared groups (Fisher's test, exact significance (2-sided) = 0.387).

Table 1. *Achieved dorsiflexion in comparison groups*

			Comparison groups			
			Outpatient n=61	Inpatient n=45	p1	p2
Achieved dorsiflexion	< 15°	Number, people	4	6	0.178	0.664
		Incidences, %	6.5±7.5%	13.3±6.2%		
	> 15°	Number, people	57	39	0.038	0.120
		Incidences, %	93.4±10.9%	86.6±11.2%		

Note: *p1 is the level of statistical significance of differences in pairwise comparison of outpatient and inpatient groups of patients; p2 — the level of statistical significance of differences in pairwise comparison of groups of patients, depending on the degree of achieved dorsiflexion.*

Thus, both outpatient and inpatient treatment options for children with foot pathology had the same effect on the evaluation criteria for treatment success. Satisfactory results were achieved in 100% of cases of surgical correction. When choosing a treatment method (outpatient or inpatient), not only the degree of social adaptation of the patient should be considered as the principal criteria, but also economic factors, since the clinical effectiveness of these treatment approaches was the same.

DISCUSSION

In the modern pediatric orthopedic practice, pes equino-varus treatment according to the Ponseti method is the *gold standard* correction

To achieve a successful pes equino-varus correction with the prevention of relapses or other deformities, careful adherence to the Ponseti protocol is required. Initially, the Ponseti procedure was used only in the children under two years of age, but modern studies demonstrate the success of pes equino-varus correction in the older age groups [5].

According to the authors, the proposed protocol employment for treating foot deformity is effective and consistent with the data obtained by other authors. The Ponseti procedure is successful and relapse-free in 94–96% [6].

In our opinion, the most preferred age for deformity correction is an early age and we adhere to the position of early treatment of deformities (immediately after diagnosis). Based on the studied literature available to us, the late correction start is directly proportional to the likelihood of repulse and treatment duration [1].

CONCLUSION

Based on the obtained data we recommend treating pes equino-varus as early as possible after birth (3–5 months) to prevent recurrence and ensure the complete deformity correction. In addition, a strict adherence to the Ponseti protocol is required for such patients.

In cases of vertical talus correction, conservative correction in combination with minimally invasive surgical techniques can prevent the development of complications previously observed during extensive surgical procedures.

The Dobbs correction method used by us is simpler and more effective in infants. Our data are consistent with reports of other authors' excellent results. The Dobbs correction method is less invasive and allows avoiding the risks associated with more extensive surgeries [7].

We have not found significant differences in the choice of an outpatient or inpatient treatment regimen. Considering the economic factor, in conditions of statistically significant similar clinical outcomes, the outpatient treatment regimen is most preferable.

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PLASMA LEVELS OF SERUM METALLOPROTEINASES MMP-9, MMP-2 AND TISSUE INHIBITORS TIMP-2 IN NEWBORNS WITH NECROTIZING ENTEROCOLITIS

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ABSTRACT — The analysis of the balance of elastase (MMP-2, MMP-9) and TIMP-4 was performed in order to determine its involvement in the pathogenesis of NEC. A progressive duration of NEC with sepsis is accompanied by increased serum concentrations of MMP-9, MMP-2 and TIMP-4. Increases in concentrations of MMP-2>503 ng/ml, MMP-9>812 ng/ml TIMP-4>1404 ng/ml can be regarded as statistically significant predictors of fatal outcome of NEC. The proposed method for determination of the outcomes of NEC in newborns is characterized by high sensitivity (94%) and specificity (87%).

KEYWORDS — necrotizing enterocolitis (NEC), newborns, sepsis, matrix metalloproteinase MMP-9, matrix metalloproteinase MMP-2, tissue inhibitors of /matrix metalloproteinase TIMP-2.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating disease found primarily in premature infants. NEC is characterized by rapid coagulation necrosis of distal ileum resulting in severe cases of intestinal perforation. The spectrum of clinical manifestations is presented by reversible intestinal disorders to fulminant forms, accompanied by gangrene of the intestinal wall perforation, development of abdominal sepsis and septic shock [1, 2]. One of the primary directions in the study of the pathogenesis of NEC is a search for reliable molecular markers, which help identifying the severity of the disease and help to determine the prognosis and selection of individual treatment strategies [3]. Currently, the prognosis of the duration of the disease is based on the use of standard criteria including clinical symptoms, laboratory parameters and morphological characteristics of the disease. Matrix metalloproteinases (MMPs), zinc endopeptidase are synthesized in a latent form and activated by proteolytic cleavage of the amino-terminal domain or conformational changes induced by oxidative stress. They take a part in the degradation of collagen type IV, which is the main component of the basal membrane as it contributes to the destruction of gastrointestinal perforation [4, 5].

Aim of research

To study the role of matrix metalloproteinases MMP-9, MMP-2 and TIMP-2 tissue inhibitors in newborns with NEC.

MATERIALS AND METHODS

The study was approved by the local medical ethics committee. The patients were divided into two groups. Group I (n=25) was defined as premature infants (≤ 37 completed weeks) without NEC, sepsis, septic shock, or systemic inflammatory response syndrome. Group II (control group, n=30) included infants with proven NEC (Bell's stage III) who were treated in the intensive care unit of the University Medical Center (Volgograd, Russia) between September 2012 and June 2019. The distribution of gestational age, birth weight, and gender was similar in patients with NEC and control groups. Concentrations of elastase (MMP-9, MMP-2) and tissue inhibitors of metalloproteinases (TIMP-2) in blood plasma were determined twice in Group II: during the first clinical presentation and 7 days after the surgery. In Group I, concentrations of elastase (MMP-9, MMP-2) and tissue inhibitors of metalloproteinases (TIMP-2) in blood plasma were determined once during the first clinical presentation. Blood was sampled by venipuncture and serum harvested by centrifugation and stored at -20° C. Plasma enzyme concentration was quantified via kits commercially used for ELISA (Human Human MMP-9 Quantikine ELISA Kit, Human Human MMP-9 Quantikine ELISA Kit Human Human TIMR-1 Quantikine ELISA Kit, R & D Systems, USA) by the ELISA analyzer ANTHOS 2020 (Austria). The methods of correlation and discriminant analysis were used to perform statistical analysis via SPSS 17.0 software. All data were presented as mean ± SD. Links between continuous variables were examined using Spearman rank correlation. Statistical

differences between the two groups were evaluated using unpaired Student's t-test or Kruskal-Wallis test. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Significant differences ($p < 0.05$) were observed for MMP-2, TIMP-4 in all patients with NEC. The value of MMP-9 did not differ significantly between the groups. Average values of MMP-9 and TIMP-4 were higher among patients with a fatal outcome than among surviving patients by a factor 2-times ($p < 0.01$). Strong positive correlation between TIMP-4 and MMP-2 ($r = 0.81$; $p < 0.01$) was detected. In patients with gastrointestinal perforation, the average concentrations of MMP-2 were increased ($p < 0.01$) by 8 times, TIMP-4 by 5.8 times when compared to Group II. In patients with sepsis, production of MMP-9 and TIMP-4 was increased by 2.3-times ($p < 0.01$) when compared to patients without sepsis. The deaths of patients with signs of sepsis were accompanied by a significant ($p < 0.01$) increase in the average concentration of TIMP-4 (2085 ng/ml) and MMP-9 (1032 ng/ml). In patients without signs of lethal sepsis, average concentrations of TIMP-4 (1306 ng/ml) and MMP-9 (668 ng/ml) were elevated. After operations on recovered patients, average concentrations of MMP-2 decreased by 1.5-times ($p < 0.01$) and TIMP-4 by 1.5 times ($p < 0.05$) respectively. However, they remained significantly higher than control values. In addition, in Group II, the average concentrations of MMP-9 were still elevated before and 7 days after the start of treatment. The ROC analysis showed that predictors of mortality in newborn with NEC were the following: TIMP-4 (AUC = 0.74, 95% CI = 0.62 to 0.97; $P < 0.001$), MMP-2 (AUC = 0.95, 95% CI = 0.9 to 0.99; $P < 0.001$), MMP-9 (AUC = 0.68, 95% CI = 0.52 to 0.84; $P < 0.003$). Optimal values for each predictor of mortality were MMP-2>503 ng/ml, MMP-9> 812 ng/ml, TIMP-4>1404 ng/ml. Sensitivity of the test was 94%, specificity was 87%, which proves the high quality of our proposed method for determining the basis of NEC.

DISCUSSION

According to some investigations, in samples of removed intestinal tissue of patients with NEC, the levels of expression of MMP-2, MMP-9 and TIMP-2 remained unchanged [6]. The role of MMP-2, MMP-9 and TIMP-4 in sepsis remains unclear, but some studies indicate that MMP plays a certain role in the migration of leukocytes from the blood in inflammation by MMP-mediated proteolysis of the basement membrane [7]. High levels of MMP-9 and TIMP-4 in blood serum were found in patients with sepsis and fatal outcome, which may be important for understanding the pathophysiology of sepsis in patients with NEC. The development of endotoxemia might lead to the release of MMP-9, MMP-2 and TIMP-4, which explains the significant correlation differences between these parameters in patients with sepsis. In addition, while MMP-9 is mainly released by activated leukocytes, the observed differences cannot be explained by the presence of leukocytosis, as the values were approximately the same in surviving and deceased patients with NEC. Having analyzed the characteristics of the ROC curve, we found that serum levels of TIMP-4 and MMP-2 had high sensitivity and specificity and were good predictors for mortality in patients with NEC. From a clinical point of view, a highly sensitive test may lead to over-diagnosis, but it minimizes the risk of leaving the disease undetected, because development of complications leads to high mortality.

CONCLUSION

A progressive duration of NEC with sepsis is accompanied by increased concentrations of MMP-9, MMP-2 and TIMP-4 in blood serum. Increases in the concentrations of MMP-2>503 ng/ml, MMP-9>812 ng/ml, TIMP-4>1404 ng/ml can be regarded as statistically significant predictors of fatal outcome of NEC. The proposed method of determination of the outcomes of NEC in newborns is characterized by high sensitivity (94%) and specificity (87%).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Concept and design of the study — I.N. Khvorostov; Data collection and processing — I.N. Khvorostov; Text writing — I.N. Khvorostov, I.E. Smirnov; Editing — I.N. Khvorostov, I.E. Smirnov.

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IDENTIFICATION OF C-TERMINAL TELOPEPTIDES AS MARKERS OF CONNECTIVE TISSUE DYSPLASIA IN BIOCHEMICAL BLOOD TESTS IN ADOLSCENTS WITH A HERNIATED DISC

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ABSTRACT — Juvenile osteochondrosis, which can be complicated by a herniated disc, is a common disease in the pediatric population. Currently, this nosology is considered as one of the forms of manifestation of connective tissue dysplasia syndrome. A clinical study was conducted to identify dysplastic processes among 34 adolescents operated on for a herniated disc. Based on the characteristic phenotypic features, it was revealed that 15.36 % of the subjects had grade 1 connective tissue dysplasia, 74.47% — grade 2, and 10.17% — grade 3. The diagnosis was supplemented by a biochemical blood test for C-terminal telopeptides of type I collagen Beta-Cross Laps. In 18 patients (52,94%), the biochemical blood test exceeded the reference values, indicating consistency in the ongoing systemic catabolic reactions associated with the prevalent destruction of the collagen fibers of the tissues of the body.

KEYWORDS — osteochondrosis, herniation of the intervertebral disc, C-terminal telopeptides Beta-Cross Laps.

INTRODUCTION

In the structure of morbidity in children and adolescents, nosologies associated with the pathology of the musculoskeletal system occupy the 3rd place. One of these diseases is juvenile osteochondrosis, which can be complicated by a herniated disc [3, 5, 9]. According to modern concepts, juvenile osteochondrosis is considered as a manifestation of the syndrome of connective tissue dysplasia (mesenchymal insufficiency) [2, 4, 7]. A study was conducted to identify dysplastic processes in adolescents with a herniated disc on the background of juvenile osteochondrosis.

Objective:
to assess the state of connective tissue structures based on the study of venous blood markers (C-terminal telopeptides) in children with a herniated disc.

MATERIALS AND METHODS

From 2013 to 2020, 34 children with juvenile osteochondrosis complicated by IVD hernia underwent surgical treatment at the Neurosurgical Department of the Children's Regional Clinical Hospital in Tver. The study group consisted of adolescents aged 12 to 17 years (13 boys and 21 girls). All adolescents underwent microdiscectomy with video endoscopic assistance. The postoperative period was smooth. All children were examined for phenotypic signs of connective tissue dysplasia using a specially developed table by T. Milkovskaya-Dimitrova [1]. The degree of mesenchymal insufficiency was determined by the number of signs evaluated in this table. The following phenotypic signs of connective tissue dysplasia were more common in the studied patients: scoliosis (32.35%), joint hypermobility (29.41%), nasal septum asymmetry (23.52%), visual pathology (23.52%). (Fig. 1)

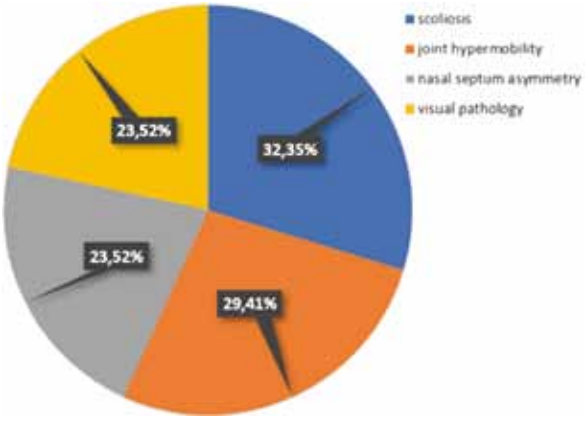

Fig. 1. *Distribution of phenotypic signs of connective tissue dysplasia in the group of treated patients*

According to the diagnostic criteria developed by Abbakova L.N. [1] we detected:

I degree of connective tissue dysplasia in 15.36%, II degree — 74.47%, III degree — 10.17%. To identify the systemic nature of mesenchymal immaturity of the body's tissues, the examination was supplemented by

a study of biochemical blood analysis for C-terminal telopeptides of type I collagen Beta-Cross laps. The reference values were: 0.276–1.546 ng/ml for males, 0.167–0.933 ng/ml for females [1, 5, 6, 11].

RESULTS

Excess rates of beta-Cross Laps of telopeptides from the norm was seen as the presence of systemic catabolic processes from the connective tissue in the body [7, 10]. In 18 patients (52,94%), the biochemical blood test exceeded the reference values, indicating consistency in the ongoing systemic catabolic reactions associated with the prevalent destruction of the collagen fibers of the tissues of the body.

This group of children was prescribed vitamins, chondroprotectors, antioxidants as well as observation of an endocrinologist, orthopedist [3, 6, 8, 9, 11].

CONCLUSIONS

1. In the treatment of juvenile osteochondrosis complicated by IVD hernia, it is necessary to take into account the features of the clinical picture associated with the manifestation of connective tissue dysplasia syndrome for better and more complete treatment and rehabilitation events.
2. Biochemical blood parameters, such as Beta-Cross Laps, can be markers of hidden catabolic processes associated with the breakdown of collagen fibers, which then manifest themselves in clinical practice in the form of mesenchymal insufficiency syndrome.
3. To compensate for dysplastic processes, it is important to follow up such children by specialist doctors, to determine the intake of vitamins, antioxidants, chondroprotectors, to monitor their nutrition and physical activity.

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CAPABILITIES OF AN INFORMATION-ANALYTICAL SYSTEM FOR ASSESSING MOTOR ACTIVITY IN PARKINSON'S DISEASE DURING SLEEP

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ABSTRACT — The research aimed to study motor activity in Parkinson's disease during sleep using a data analytical system developed by authors. The study included 8 patients (4 men and 4 women) diagnosed with Parkinson's disease at the age from 59 to 89 years. All patients were clinically evaluated for motor deficit (UPDRS Part III), motor fluctuations (UPDRS Part IV), functional activity (UPDRS Part I), non-motor symptoms (UPDRS Part II) and the clinical global impression. Using our information-analytical system we obtained data on motor activity during sleep and processed it on the following parameters: number of movements, maximum value of the jerk and motor activity coefficient. For the number of movements, the average value for men was 56.7, for women — 47.2. For the maximum value of the jerk, the average value for men was 22.1 g/s, for women — 16.7 g/s. For motor activity coefficient, the average value for men was 27.7%, for women — 22.3%. Thus, the feasibility of using the information analytical system for assessment of motor activity in Parkinson's disease during sleep and the necessity of studying hypokinetic tremors during sleep has been shown.

KEYWORDS — Motor activity during sleep, Parkinson's disease, hyperkinesis, information analytical system.

INTRODUCTION

According to the World Health Organization (WHO), there is a high rate of nervous system diseases in the world. The world prognosis for Parkinson's disease is also unfavorable — the morbidity has increased among the population, thus, in Russia, from 2010 to 2017 it increased by 5.9% [1].

To diagnose, monitor the course and determine the prognosis of Parkinson's disease, neurologists around the world use the Movement Disorder Society unified Parkinson's disease rating scale (MDS-UPDRS). MDS-UPDS is quite well established in clinical neurology; however, there is still a significant demand in the practice of outpatient neurologists and doctors of related specialties for instrumental methods of diagnosing Parkinson's disease and various forms of tremors. The development of innovative and affordable diagnostic systems for Parkinson's disease and multiple forms of hyperkinetic tremors will help clinicians to perform early verification and a reliable prognosis in the so far incurable diseases.

Long-term monitoring of Parkinson's disease and its evaluation with the use of new information parameters has still remained on a poor level. Research into motor activity in Parkinson's disease using the information analytical system (IAS) has been insufficient [2, 3]. Upon review of existing research, the number of movements, the jerk value and motor activity coefficient were not considered and investigated as information parameters.

Purpose of the study is to study motor activity in Parkinson's disease during sleep using the proposed information analytical system.

MATERIAL AND RESEARCH METHODS

The study was conducted on 8 patients (4 men and 4 women) diagnosed with Parkinson's disease at the age from 59 to 89 years. All subjects gave informed consent for participation in the study. All patients were clinically evaluated for motor deficit (UPDRS Part III), motor fluctuations (UPDRS Part IV), functional activity (UPDRS Part I), non-motor symptoms (UPDRS Part II), clinical global impression. The study was conducted during the night sleep period: with the activation of the information analytical system (IAS) from the moment of going to bed with subsequent falling asleep until the moment of waking with the IAS turned off [4, 5]. The IAS device was fixed on the wrist of the hand of the sub-dominant hemisphere (for right-handed persons — on the left hand, for left-handed persons — on the right hand). The duration of a single study was 8 hours. For each subject, motor activity registration using IAS was conducted over three consecutive nights. At the end of the procedure, information about the subject's motor activity was stored in the memory of the IAS device. The obtained data was processed and presented for further analysis of the following parameters using special software:

1 — Number of movements — the highest number of hand movements out of the total number of movements on each axis during the whole study (dimensionless quantity);

2 — Jerk — the maximum value of the acceleration change rate modules during data recording (g/s);

3 — Motor activity coefficient (MAC) — the ratio of the number of files with significant motor activity to the total number of files (%).

RESEARCH RESULTS AND THEIR DISCUSSION

As a result of the research, the following data was obtained. For the number of movements, the average value for men was 56.7; for women — 47.2; maximum values for men — from 10 to 113, for women — from 30 to 70. For the jerk, the average value for men was 22.1 g/s, for women — 16.7 g/s; the maximum values for men were from 10 to 59 g/s, for women — from 9 to 26 g/s. For motor activity coefficient, the average value for men was 27.7%, for women — 22.3%; maximum values for men — from 8.4 to 41.7%, for women — from 11.8 to 34.8%.

The data show relatively large average values of the analyzed parameters of the number of movements, maximum jerk value and motor activity coefficient in men compared to women.

Fig. 1 shows motor activity indicators in the form of a histogram in a selected study subject.

Fig. 2 shows motor activity graphs in the three axes in a selected study subject.

Due to the analysis of the study of patients with Parkinson's disease using the number of movements, the jerk value and the motor activity coefficient as information parameters, it was demonstrated that it is possible not only to diagnose, but also to correct treatment with the help of our information analytical system for assessing motor activity in Parkinson's disease during sleep.

The revealed parametric information with a difference between the male and female genders can indicate sexual dimorphism during Parkinson's disease and requires further research and comprehensive analysis.

It is also possible to have multiple diagnostics available at outpatient conditions and clarification of clinical features of the course of different nosological entities of hyperkinesis during sleep.

The obtained results, primarily, have practical value with scientific novelty and originality in the form of application of innovative methods of registration of motor activity during sleep with the following analysis for diagnostics, treatment and prognosis of diseases of extrapyramidal system.

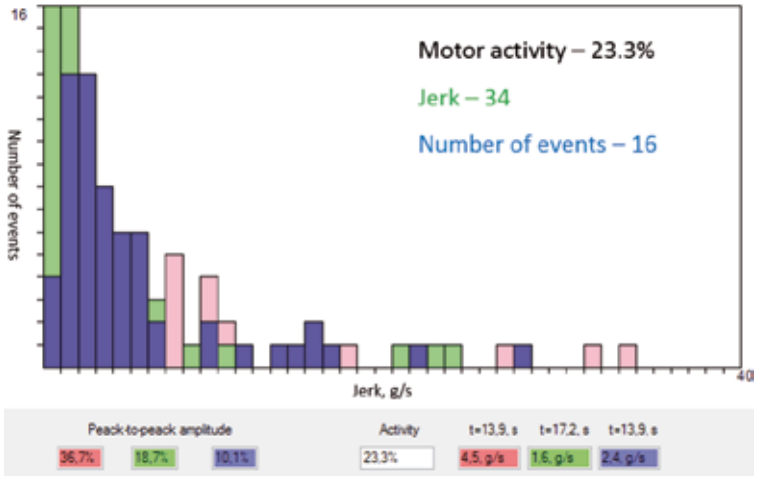

Fig. 1. *Night-time motor activity histogram in Parkinson's disease*

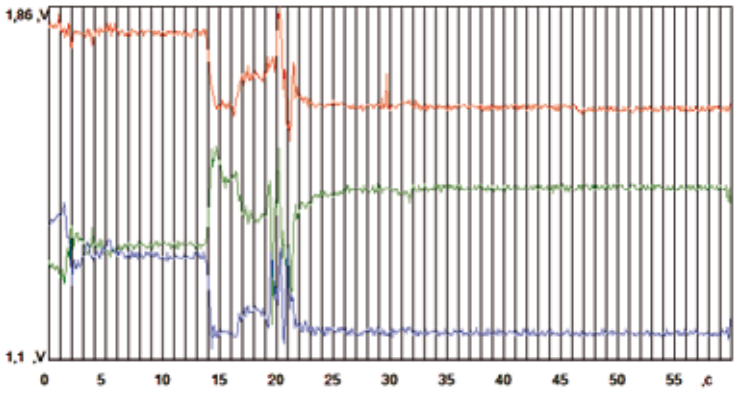

Fig. 2. *Graphs of motor activity on three axes at night in Parkinson's disease*

CONCLUSION

The feasibility of our findings should be extrapolated on further researches of motor activity during sleep using the proposed information-analytical system.

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CHARACTERISTICS OF HUMAN MOTOR ACTIVITY DURING SLEEP IN YOUNG ADULTS (18–21 YEARS) USING INFORMATION-ANALYTICAL SYSTEM

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ABSTRACT — The study of human motor activity during sleep in the period of adolescence/early adulthood was carried out. The study involved 35 healthy people — 18 women (51.5%) and 17 men (49.5%) aged 18 to 21 years. The data was obtained and processed with the employment of an original information-analytical system developed by the authors. When analyzing the data, we identified and used the following parameters: the number of movements, the maximum value of jerk and the coefficient of motor activity. For the number of movements, the average value was 9.6 and 10.2 for men and women, respectively. For the maximum value of jerk, the average value was 26.4 g/s and 24.3 g/s for men and women, respectively. For the coefficient of physical activity, the average value was 10.3% and 12.7% for men and for women, respectively. Thus, the results of the study are fundamental for understanding the adolescent period of postnatal human ontogenesis, indicate sexual dimorphism, and can also be used in research and practice in the field of physiology, neurology, neurosurgery, psychiatry and functional diagnostics with account of the specific age interval, as well as for prognosis.

KEYWORDS — motor activity in sleep; ontogenetic development, adolescence/young adulthood; information-analytical system.

INTRODUCTION

Currently, despite the intensive development of methods and tools for clinical observation, insufficient attention is paid to the organization and conducting preventive and screening diagnostic studies. However, the development of such technologies makes it possible to identify diseases at an early stage of their onset and, what is extremely important, to predict a patient's condition. Today, one of the most challenging and poorly studied issues in terms of development of medical diagnostics is the dynamic analysis of physiological and pathological conditions. Improvement of diagnostic methods inevitably requires to introduce new information parameters into research [1, 2, 3]. As such information parameters, we introduced and studied: the number of movements, the maximum value of jerk and the coefficient of motor activity.

Purpose of the study is to investigate motor activity during sleep in young adults (human ontogenesis of the period of young adulthood).

MATERIAL AND RESEARCH METHODS

The study involved 35 people — 17 women (51.5%) and 18 men (49.5%) aged 18–21 years (average age 19.6 years). All participants were students of the Tambov State Technical University, practically healthy people who gave informed consent to participate in the study. The study was carried out during the period of night sleep. The information-analytical system (IAS) developed by us [5] performed the monitoring from the moment of going to bed, followed by falling asleep until the moment of awakening with the IAS turning off. The IAS device was fixed on the wrist of the subdominant hemisphere (in right-handers — on the left hand, in left-handers — on the right hand). The duration of an experiment was 8 hours. The motor activity in each participant was recorded using the IAS for three consecutive nights. On completion of the experiment, the data on the motor activity of each individual was saved in the memory of the IAS device. Then, using special software, the obtained data were processed and presented for subsequent analysis of the following parameters:

1. Number of movements: the largest number of hand movements out of the total number of movements along each axis for the entire study period (dimensionless value);
2. Maximum value of jerk: the maximum value of the modules of the acceleration rate changes during data recording (g / s);
3. Coefficient of motor activity (CMA): the ratio of the number of files with significant motor activity to the total number of files (%).

RESEARCH RESULTS AND THEIR DISCUSSION

The findings of the study are as follows. The average value for the number of movements was 9.6 and 10.2 for men and women, respectively; the maximum values for men were from 4 to 19, while those for women were from 5 to 22. For the maximum value of jerk, the average value was 26.4 g/s for men and 24.3 g/s for women; the maximum values were from 13 to 40 g/s for men and from 8 to 38 g/s for women. For the coefficient of motor activity, the average values were 10.3% and 12.7% for men and women, respectively; while the maximum values were from 4.3 to 19.3% for men and from 3.9 to 23.0% for women.

Fig. 1 shows the histogram of indicators of the motor activity in a selected study subject.

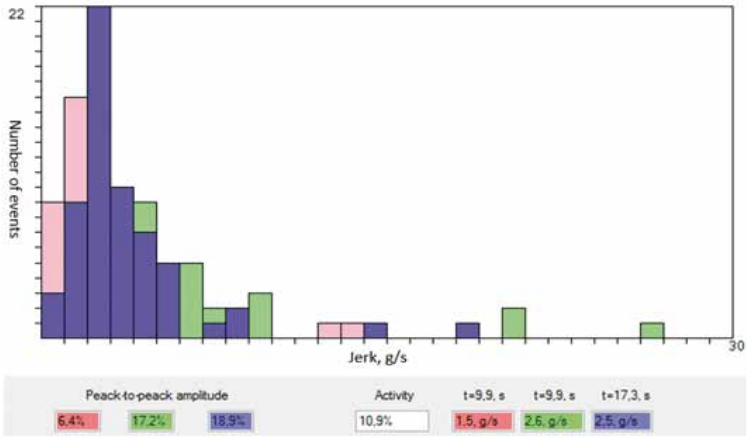

Fig. 1. Motor activity histogram

Fig. 2 shows graphs of motor activity along three axes in a selected study subject.

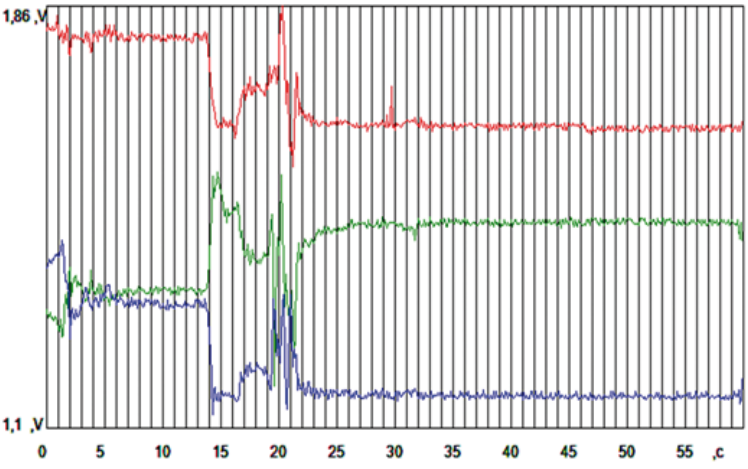

Fig 2. Three-axis motor activity graphs

This study makes it possible to form the regulatory framework of healthy people in the period of young adulthood (18–21 years of age). This will help to assess normal motor activity in order to subsequently use the obtained values for the analysis and diagnosis of patients with hyperkinetic movements and tremor in various pathological conditions.

Our research offers simplification and greater accessibility of clinical analysis and interpretation of patient's data when rendering diagnostic and/or therapeutic medical care or medical services in various conditions.

Our findings show that there is a slight deviation in the parameters of the motor activity in healthy people. This deviation can be explained by individual physiological characteristics, by the influence of certain external factors, and by sexual dimorphism.

The results of the research are practically applicable; they have scientific novelty and originality due to the use of an innovative technique, which enables to register and analyze the motor activity [4, 5].

CONCLUSION

We intend to employ the information-analytical system for further researches on the following directions:

— Searching for further system upgrades to improve diagnostics and treatment;

— Improving data accuracy and this will result in a better quality of future research.

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EFFECTIVENESS OF SCREENING TOOLS EMPLOYED FOR IDENTIFYING HEARING LOSS IN OLDER ADULTS

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ABSTRACT — The study evaluated the effectiveness of screening tests by identifying hearing loss in 127 adults of the older age groups (aged 60–87). We performed a quantitative assessment of the HHIE-S questionnaire (accuracy, sensitivity, specificity) comparing to the pure-tone threshold audiometry (the gold standard for detecting hearing loss). The analysis of hearing impairment prevalence in the target population relied on both methods. We have observed a high rate of hearing loss — 81% in the patients of the older age group, of which 30% had mild hearing loss, 38% — moderate hearing loss, 9% — severe hearing loss, the remaining 4% with profound hearing loss. We have evaluated the average accuracy (62.2%), sensitivity (64.0%), specificity (54.0%) as well as the positive predictive value (85.7%) of the HHIE-S questionnaire, whereas it was the negative predictive value only that revealed a low rate (26%). The study outcomes confirm the possibility of using HHIE-S questionnaire as a screening tool for hearing loss in the older age group. HHIE-S can prove particularly useful for primary care physicians as well as for physical examination due to its reliable accuracy and ease of use. The probability of a false positive outcome and an overestimated hearing impairment in the older age group is relatively low. However, pure-tone threshold audiometry is required in patients with detected hearing loss.

KEYWORDS — audiological screening, hearing loss, chronic sensorineural hearing loss, older age group, questionnaire survey.

INTRODUCTION

In the context of the modern development of medical science and practice, diagnostics is one of the rapidly developing areas [1–3]. Computerization and integration of high-tech research methods into medicine contributes to the active development of functional diagnostics, an annual increase in research methods and the number of functional tests performed. Functional diagnostics is widely used for the early detection of pathology, differential diagnosis of various diseases and monitoring the effectiveness of treatment [4, 5].

One of the most discussed issues within practical healthcare is that of aging as well as the growing rate of chronic diseases that are entailed naturally [6]. According to the World Health Organization (WHO), the total number of people suffering from socially significant hearing loss in 2012 was 360 million people (5.3% of the world population), of which 328 million (91%) were adults, with the remaining 32 million (9%) being children [7]. The prevalence of hearing loss increases over age and, along with other sensory issues, there is a growing risk of developing and progressing dementia, degenerative diseases, and, consequently, disability affecting the populations within the older age group. Hearing disorders in geriatric patients reveal their own specific features — initial changes in speech intelligibility, especially in noisy contexts; frequent increase in sensitivity to sounds (hyperacusis), as well as complaints of tinnitus. All this points at the need to undergo audiometry within an extended frequency range, speech tests as well as getting the auditory evoked potentials registered, if necessary. At the same time, there are a number of questionnaires for hearing self-assessment, as well as primary screening tools [8,9]. Correct interpretation of the questionnaire results is of extreme importance in terms of forecasting possible audiometric changes and designing an individual patient examination plan.

A number of studies focused on the discrepancy between the self-report data on the hearing status and the tonal threshold audiometry outcomes [10]. The reasons for this discrepancy, according to a number of authors, may be several underlying factors, the age being a major one. In view of this, the older age group reveals a higher discrepancy rate between audiometry and self-report [11] due to the earlier existing hearing problems or the patient's personality factor [12].

Aim of study

to evaluate the effectiveness of screening tools used to detect hearing loss in older age groups through quantitative evaluation of the HHIE-S questionnaire (accuracy, sensitivity, specificity) as compared to tonal threshold audiometry (the gold standard for detecting hearing loss).

MATERIALS AND METHODS

The study focused on patients belonging to the older age group (60+) who were undergoing treatment at the Regional Clinical Hospital for War Veterans in the City of Samara (Russia). Since this clinic is not a specialized one, people who had their appointments scheduled randomly through the week, did not always present hearing complaints.

The study excluded all patients using hearing aids as well as patients who were already going through the process of audiological rehabilitation, those who failed to reveal a minimum level of listening to qualify for the testing procedures, and persons with active inflammatory issues and tumors diagnosed during the otoscopic examination. Of the 135 participants who were found to have normal eardrums, 127 completed the survey fully. The study was carried out as a weekly targeted screening with ENT endoscopy. The participants' age fell within the range of 60 to 87 (median age — 79.7±5.2), of them the share of males was 46.5% (59 people), females accounting for 53.5% (68 persons). The majority of the patients were elderly people (over 81) who made up 57% (72 persons); people aged 60–70 made up 25% (32 persons); aged 71–80 accounted for 18% only (23 persons). The prevailing part of the target group was the people with a degree in specialized technical training (80%), while holders of university degrees were 37%.

Written informed consent was obtained from each participant prior to completing the questionnaire and tonal threshold audiometry. The study was carried out within a project run jointly by the Chair and the ENT University Clinic (Samara, Russia) in accordance with the principles of the Helsinki Declaration for Biomedical Research, and was approved by the University's Bioethics Committee.

The perceived hearing impairment was assessed with the HHIE-S questionnaire (Hearing Handicap Inventory for the Elderly – Screening Version) for elderly people with hearing issues [13]. We used a shortened screening version of the questionnaire, which includes 10 questions, 5 of them implying socio-situational assessment (scale S), and another 5 — emotional assessment (scale E). The T scale combines the data from both scales. Following the survey outcomes, there were three groups identified: lack of issues (0-8 points); mild/moderate disorders (10–24 points); severe disorders affecting the patient (26–40 points), which are associated with hearing loss. The questionnaire was always used by the same researcher, whereas the average interview time varied from 5 to 10 minutes, considering the patient's individual features.

Upon filling in the HHIE-S questionnaire form, a hearing test was held using the tonal threshold audiometry method. The audiometric examination was carried out in a sound-proof booth with an audiometer (AC-40, Interacustic, Denmark) used (Fig. 1). In order to analyze the tonal threshold audiometry results (Fig. 2, 3), the patients were divided into three groups based on their hearing capacity levels. The hearing capacity level was defined as the average threshold value for air conductivity at frequencies of 500, 1000, 2000 and 4000 Hz in the better ear. Subject to the WHO classification, the following groups were identified: persons with normal hearing (hearing threshold below 25 dB); persons with mild hearing loss (threshold between 26 dB and 40 dB); persons with moderate hearing loss (threshold between 41 dB and 60 dB); persons with severe hearing loss (hearing threshold within the range of 61 dB and 80 dB); persons with deafness (hearing threshold exceeding 81 dB). The number of patients in the groups was 24, 39, 48, 11, and 5, respectively, while the average hearing loss was 18, 35, 56, 74, and 83 dB. 115 patients of the first three groups featured symmetric audiometry data with an accuracy of ±10 dB; 15 patients with severe hearing loss could hear better with their right ears, while in 7 listeners with deafness, the difference between the ears' hearing capacity was more than 10 dB, the left ear functioning better.

The accuracy of the HHIE-S questionnaire was determined through calculating its sensitivity and specificity, as well as by matching the results that were

Fig. 1. *Tonal threshold audiometry procedure*

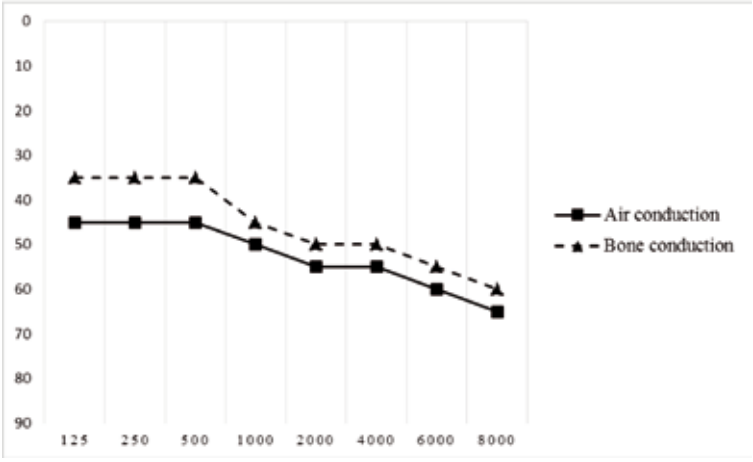

Fig. 2. Tonal threshold audiometry blank form (right ear)

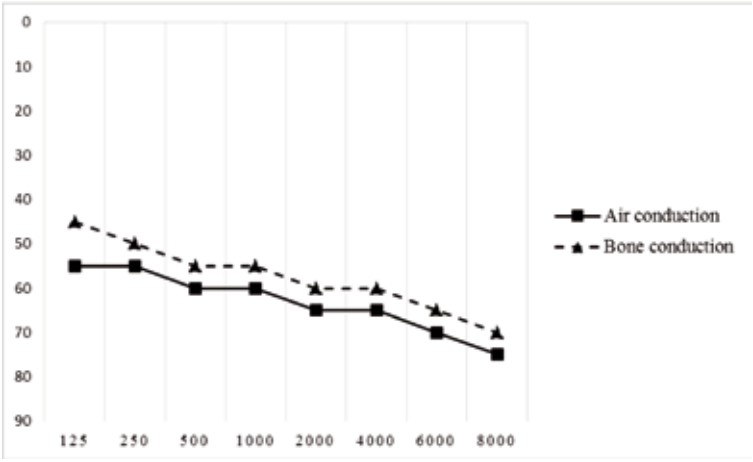

Fig. 3. Tonal threshold audiometry blank form (left ear)

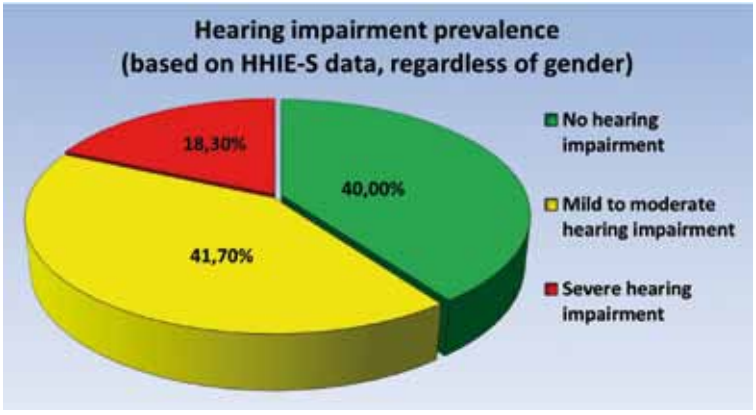

Fig. 4. Hearing impairment prevalence (based on HHIE-S data, regardless of gender)

true positive, false positive, true negative, and false negative with the average hearing thresholds. The respective confidence intervals were calculated using the Clopper-Pearson method in order to evaluate the sensitivity, specificity, positive predictive value, and the negative predictive value. The analysis was carried out using the Microsoft Excel application package and the Statistica 9.0 software.

RESULTS AND DISCUSSION

The HHIE-S outcomes revealed that 51 elderly patients (40.0%) had no hearing impairment; 53 patients (41.7%) had mild/moderate impairment, while 23 (18.3%) had severe impairment (Fig. 4). Given that, the prevalence of hearing impairment based on the HHIE-S questionnaire (in view of the lack or presence of any hearing impairment perception) was 60% (76/127).

The analysis of the survey outcomes, taking into account the patients' gender (Fig. 5), showed a hearing decrease of 61.8% (n = 42) in males based on self-assessment, while in females the rate was 57.6% (n = 34). The number of males and females with hearing impairment was almost equal — 38.2% (n = 26) and 42.4% (n = 25), respectively. As far as severe hearing impairment was concerned, both males and females featured almost the same rate — 17.6% (n=12) and 18.6% (n=11), respectively. Mild and moderate hearing impairment prevailed in males — 44.2% (n=30), whereas in females the rate was 39% (n=23).

The audiometric assessment of the patients, taking into account the general level of hearing (Table 1), showed the following rates: normal hearing was diagnosed in 24 patients (19.0%); mild hearing loss was to be observed in 39 patients (30.0%); moderate hearing loss — in another 48 persons (38.0%); severe hearing loss — in 11 patients (9.0%), with another 5 patients (4.0%) accounting for profound hearing loss. The hearing impairment prevalence identified through audiometric testing, in view of the overall result and including all its intensity degrees, was 81.0% (103/127).

A comparison of the data obtained through the HHIE-S survey with the audiometry results, we could note that of 51 patients in the older age group who had normal hearing (according to the survey data) only 24 (19%) showed no issue through the audiometric examination. As for 76 patients with hearing impairments (according to the questionnaire), 87 patients (68%) had mild to moderate hearing loss, while another 16 patients (13%) had severe hearing loss. Table 2 offers a view at the results received by the matching the two diagnostic methods (HHIE-S and tonal threshold audiometry).

When comparing the HHIE-S overall results with the tonal threshold audiometry regardless of the intensity levels, i.e. considering the hearing impairment only as lacking or present, and the audiometric test as normal or abnormal, we calculated (Table 3) the sensitivity, specificity, as well as the positive and negative predictive values, and the accuracy of the HHIE-S questionnaire, if compared to the gold standard (tonal threshold audiometry).

When evaluating the sensitivity, the specificity, and the positive and negative predictive values, as well as their confidence interval, while viewing the two methods together, taking into account the gender, we observed that all results were higher for females.

The sensitivity rate in females, for instance, was 65% (28/43); the specificity rate was 62.5% (10/16); the positive predictive value rate was 82.4% (28/34), while the negative predictive value rate was 40% (10/25). As for males, we could observe a sensitivity rate of 45% (27/60); the specificity rate was 37.5% (3/8); the positive predictive value was at 64% (27/42), whereas the negative predictive value was at 11.5% (3/26).

While analyzing the HHIE-S questionnaire alone, we could see that 40.0% of the participants did not perceive hearing impairment, while 60.0% reported perception impairment of varying severity (from mild/moderate to severe); when comparing the result, we observed predominating perception problems in female patients (61.8%) in contrast to male patients (57.6%). At the moment, the available data on the prevalence of hearing disorders, unfortunately, are extremely scattered in terms of the population sample and the survey scenario. Our results are consistent with the data obtained through the Servidonietal study [14] regarding the total share of patients with hearing impairment based on self-report data (76.1%). As for respective Russian literature, we failed to find any items on the prevalence of hearing disorders as defined by HHIE-S only, which might allow any broader comparative analysis.

In view of the overall hearing thresholds result, as well as including all of its intensity degrees, following the WHO audiometric classification, we could observe a high prevalence of hearing loss — 81.0%. Less severe hearing loss was most common, with 30.0% of the participants suffering from mild hearing loss and 38.0% — from moderate hearing loss; more disabling hearing loss was less common, with 9.0% of the participants suffering from severe hearing loss and 4.0% featuring profound hearing loss. Despite the difficulties comparing the data on the prevalence rates, notable is a higher (if compared to the Servidonietal study) rate of patients belonging to the older group with hearing impairment [14] — 79.7%.

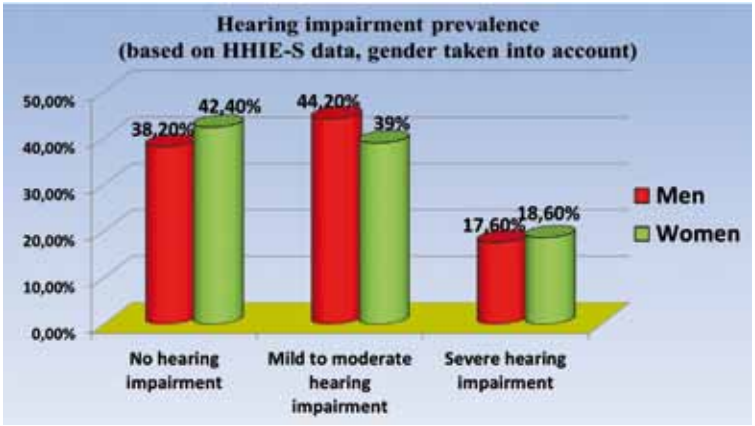

Fig. 5. *Hearing impairment prevalence (based on HHIE-S data, gender taken into account)*

The above-described study allowed identifying the average values in the accuracy (62.2%), the sensitivity (64.0%), the specificity (54.0%), as well as a high result of the positive predictive value (85.7%), while it was only the negative predictive value (26%) that demonstrated a lower rate. Given that, HHIE-S will not always allow independent detection of impaired auditory perception, whereas this screening method can be employed by medical services that are not specific to audiology, such as general geriatrics or primary care clinics [15].

CONCLUSION

1. Based on the HHIE-S outcomes, the prevalence of hearing impairment with or without its perception was 60% in our study.
2. The prevalence of self-reported hearing loss in male patients was by 4.2% higher than in female patients. Besides, mild and moderate hearing loss predominated in males (by 5.2%) if compared to women.
3. The prevalence of hearing impairment in audiometric testing, taking into account all degrees of severity, was 81% within our study.
4. Our findings confirm the feasibility of the HHIE-S questionnaire for evaluation of hearing loss screening in older age groups, especially by primary care physicians and for physical examination due to its reliable accuracy and ease of use (mean testing takes 10 minutes). The probability of a false positive result or overestimation of hearing impairment in older adults is not high. However, the survey should be accompanied by tonal threshold audiometry in all patients with detected hearing loss.

Table 1. *Hearing impairment prevalence based on audiometry and the intensity levels, by ears (right and left) and in general*

Hearing level	Right ear	Left ear	Total
	Quantity / Percentage	Quantity / Percentage	Quantity / Percentage
Norm	17/13,4%	16/12,6%	24/19%
Easy loss	36/28,3%	36/28,3%	39/30%
Moderate loss	50/39,4%	43/33,8%	48/38%
Heavy loss	10/7,9%	25/19,7%	11/9%
Profound loss	14/11%	7/5,6%	5/4%

Table 2. *Connection between HHIE-S outcomes and tonal threshold audiometry*

Audiometry	Norm	Mild hearing loss	Moderate hearing loss	Severe hearing loss	Deafness	General
HHIE-S	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)
No violations	13 (54,2%)	20 (51,2%)	17 (35,4%)	0 (0%)	0 (0%)	50 (39,4%)
Mild / moderate impairment	9 (37,5%)	15 (38,5%)	21 (43,8%)	7 (63,6%)	2 (40%)	54 (42,5%)
Severe impairment	2 (8,3%)	4 (10,3%)	10 (20,8%)	4 (36,4%)	3 (60%)	23 (18,1%)
Total	24 (100%)	39 (100%)	48 (100%)	11 (100%)	5 (100%)	127 (100%)

Table 3. *HHIE-S data matched against tonal threshold audiometry*

Index	Calculation	Results	95% CI
Accuracy	(13 + 66)/127	62,2%	46,4–80,0
Sensitivity	66/103	64,0%	44,7–82,2
Specificity	13/24	54,0%	34,1–92,3
Positive predictive value	66/77	85,7%	79,8–91,3
Negative predictive value	13/50	26,0%	19,1–74,6

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CHANGES IN ANTIGEN-PRESENTING (LANGERHANS) CELLS OF ORAL MUCOSA IN PATIENTS WITH HPV INFECTION

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ABSTRACT — Despite the fact that HPV infection is widespread among the population around the world, more than 150 strains of HPV viruses are known. At the present stage it is still unclear, why HPV-associated oral papillomas in dental patients either spontaneously undergo involution or become malignant. We investigated the quantitative dynamics of Langerhans cells depending on localization in the structure of such papillomas: in the peripapillary space, in the tissue of the oral mucosa in the presence of HPV infection, without a clinical picture of papillomas and in healthy tissue. It has been established that with long-term existing papillomas, antigen presentation is disturbed, and Langerhans cells can be an indicator of papilloma malignancy.

KEYWORDS — HPV; HPV-associated oral epithelial dysplasia; epithelial dysplasia, oral mucosa, Langerhans cells, malignancy.

RELEVANCE

According to static data obtained by the European Institute of Oncology (EIO) for the period 2000-2010, out of 675 patients with confirmed HPV-positive status, 48.1% of patients were diagnosed with cancer of the oral cavity, pharyngeal cavity and oropharyngial region (1.8 %, 2.2%, 40.4%, respectively) [6]. It is known that the barrier function of the epithelium is provided by constant interactions between various specific and nonspecific cellular and humoral defense mechanisms, however, their role in the conditions of viral HPV contamination at the present stage has not been studied, the causes of single formations and papillomatosis are unknown [2]. It should be noted that sometimes, for unknown reasons, the combination of drug therapy with the removal of all existing neoplasms can have a temporary effect with a high risk of reappearance of papillomas, which requires further deeper studies of this problem [1]. The danger of most HPV infections is that they can be latent, most clinical lesions are benign, with the possibility of transformation into malignant neoplasms [5]. Today HPV is recognized as the cause of cancer of the larynx, oral cavity and other organs [7]. Subtypes 6 and 11 are low-risk and usually present with genital warts and low-grade precancerous lesions [3]. HPV subtypes 16 and 18 are at high risk and are responsible for high-grade intraepithelial lesions that progress to malignant neoplasms [8].

Analysis of the literature revealed the absence of criteria for predicting the development of papillomatosis in ROS and pathogenic processes that cause the destruction and malignancy of periodontal tissues, which indicates the high relevance of research conducted in this direction [4]. Despite the successes achieved, the role of epithelial cells in the transmission of signals to the local immune system has not been sufficiently studied, as well as the importance of dendritic cells as carriers of periodontal pathogens to distant parts of the body, namely, their role in metastatic infection, which determined the direction of our research.

The aim of the research was to study changes in the system of local immunity of the oral mucosa (MO) in patients infected with HPV in order to improve the methods of diagnosis, prevention and treatment of complications in dental prosthetics.

MATERIAL AND RESEARCH METHODS

The subjects of the study were patients requiring dental prosthetics after trauma and adentia of infectious etiology, who had HPV infection with LIH MO of various localization, confirmed by PCR diagnostics aimed at determining the strain and viral load on the body. Langerhans cells were detected according to the protocol of Dako (Denmark) by a highly specific method of immune histochemistry using Anti-Human Monoclonal Mouse CD68 antigen EBM11, Y1 / 82A, Y2 / 131, Ki-M6, clone KP1, isotype IgG1, kappa.

In cases when conservative treatment and laser point methods for removal of large papillomas, accompanied by clinical complaints, produced no effect, surgical removal of neoplasms was used. In cases with suspicion of malignancy of the formation, histological studies were prescribed to determine the benign quality of the samples. This study was conducted in accordance with the fundamental ethical principles of the Declaration of Helsinki, the GCP (Good Clinical Practice, Good Clinical Practice) Rules and approved by the Interdisciplinary Ethics Committee of the Far Eastern Federal University (Vladivostok, Russia).

RESEARCH RESULTS AND THEIR DISCUSSION

The mechanisms of HPV infection, its clinical manifestations, histological features and differential diagnosis of pathologies of the oral cavity associated with HPV have not been fully disclosed. In our studies, the locally affected HPV RR was characterized by flattening of the papillae, local thickening of the epithelium and the appearance of the stratum corneum in atypical places, not on the chewing surfaces of the RR, but in the areas of localization of papillomas protruding above the RR surface (Fig. 1).

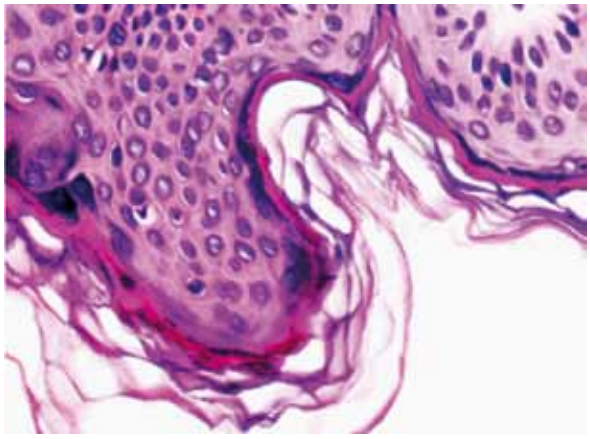

Fig. 1. *Papilloma tissue of HPV etiology in a 42-year-old patient. Staining with hematoxylin and eosin. Magnification ×100*

Langerhans cells (LC) are dendritic antigen-presenting cells present in the epithelium of the oral mucosa. Having studied quantitatively the density of Langerhans cells in the affected and intact epithelium using the method of immunohistochemical study, we did not find significant changes in the normal MO not affected by the virus, which indicated the absence of a primary defect in Langerhans cells. In contrast to the LIH MO data of the control group, the MO tissue in the structure of the papilloma in the layers of the epithelium contained an insignificant amount of Langerhans cells, and depending on the age of the presence of papillomas, Langerhans cells could be absent altogether, or single cells were identified (Fig. 2).

Studies of the number and localization of antigen-presenting cells in the HPV-infected oral mucosa (MO) epithelium showed that the percentage of Langerhans cells per 100 cells in the field of view in slices was significantly reduced in neoplasms, compared to the apparently clinically uninfected epithelium and surrounding papilloma tissue on the border with a healthy and unchanged oral mucosa (Table 1).

The morphological appearance of the identified Langerhans cells did not differ in the affected epithelial layers from intact samples of the oral mucosa. Langerhans cell activity is impaired in patients with papillomavirus dysplasia of oral mucosa, which can be partially explained by the interaction between viral-infected epithelial cells and inflammatory cells of the inflammatory infiltrate in the adjacent connective tissue lamina propria of loose connective tissue, which leads to inhibition of the response.

Migration, or death of Langerhans cells, their identification only in the connective tissue plate of the MO indicate a violation of antigen presentation in the COP structures, are evidence of a local defect of LIH MO and decrease in the barrier protective properties of the epithelium. For better informativeness of the dynamics of changes in the content of Langerhans cells in the MO of the control group and patients with HPV infection with clinical manifestations in the form of papillomas and without them, we presented the data in the form of a diagram in Fig. 3.

A noticeable decrease in the number of Langerhans cells per unit volume of the epithelium can be observed with HPV lesions of the epithelium, since it is possible that the virus is able to infect not only epithelial cells, but also Langerhans cells, like other mucosal cells. Thus, HPV infection may have both direct and indirect effects on LIH MO, affecting both cellular and humoral immunity.

CONCLUSION

The main elements of the classical LIH MO model in the age aspect, developed, supplemented and refined by V.E. Tolmachev. (2020) remain relevant today; however, our understanding of the dynamic interactions between various microbial and host factors has changed significantly. At the present stage, it has been established that the necessary conditions for the transition of chronic infection with human papillomavirus to carcinogenesis is the presence of high-risk HPV [7]. However, the distribution of genotypes

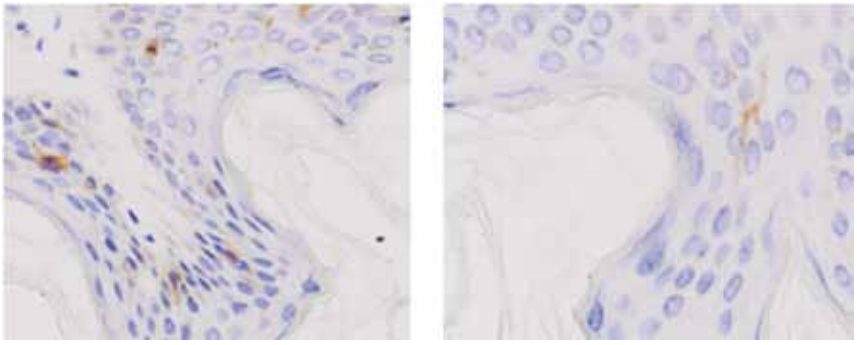

Fig. 2. Papilloma tissue of HPV etiology in a 42-year-old patient. Immunohistochemistry to identify the localization of Langerhans cells. a) an increase of 100; b) ×200

Table 1 Dynamics of the number of identified Langerhans cells depending on HPV infection in the oral mucosa В ТАБЛИЦЕ РУССКИЙ!!!!!!!!!!!!!!!!!!

Structures	Normal oral mucosa	СОР с ПВЧ		
		oral mucosa with HPV infection without papilloma	oral mucosa with HPV infection with papilloma	oral mucosa with HPV infection on the border with papilloma
Epithelium	4,10±0,023	1,1±0,07	0,52±	0,96±0,027
connective tissue plate of the oral mucosa	0	2,14±0,05	3,21±0,16	1,4±0,09

**P < 0,05*

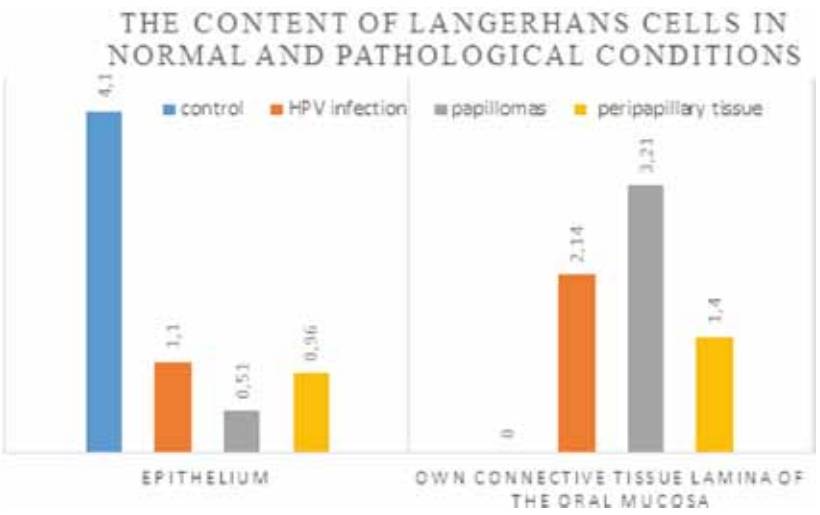

Fig. 3. Diagram of the dynamics of identification of Langerhans cells in health and disease with HPV etiology

shows that even low-risk HPV can cause MO cancer. The discrepancies in detection rates are likely due to the small sample size in the reviewed articles and different detection methods. Factors that may underestimate the prevalence of HPV include selectively searching for high-risk HPV, DNA destruction in fixed tissue, locally contaminated HPV, and possibly recovery from HPV infection before the time of biopsy. The dominant concept is that genetic and epigenetic changes in host cell genes are critical for the progression of precancerous lesions to invasive cancer. Although significant progress has been made in understanding the life cycle of HPV and its role in the development of malignant neoplasms, there is still an urgent need for precise surveillance strategies and targeted therapeutic options to eradicate this MO cancer in patients.

Given the prevalence of this viral infection and the strict type-specificity of currently available HPV vaccines, it is imperative to elucidate the molecular details of the natural course of HPV infection, as well as the biological activity of viral oncoproteins. To better understand the mechanisms involved in oncogenesis, it is necessary to deviate from dead-end ideas and develop new solutions and achieve an opportunity to justify effective therapeutic approaches to the prevention and treatment of malignant neoplasms associated with HPV. At malignancy, an increase in the activity of regulatory T cells leads to a decrease in the protective effect of the immune system against carcinogenesis. Under conditions of cancer, any increase in the activity of regulatory T

cells leads to a decrease in the damaging effect of the immune system on cancer cells.

FINDINGS

Systemic inflammatory processes and localized pathological processes mediated by the microbiome and LIH MO can be taken into account as diagnostic and prognostic biomonitors of malignancy of MO neoplasms.

An additional reduction in immunological surveillance at sites of potentially oncogenic human papillomavirus infection may increase the risk of malignant epithelial transformation.

LIH MO status can be identified based on histological characteristics and Langerhans cell count.

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ORAL HOMEOSTASIS STATUS IN MILD CHRONIC GENERALIZED PERIODONTITIS AND MILD DENTAL PERI-IMPLANTITIS

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ABSTRACT — The paper is focused on evaluating the oral cavity homeostasis in patients with mild chronic generalized periodontitis (CGP) (Group 1, 35 persons) and mild peri-implantitis (Group 2, 30 persons). The control group included healthy individuals (20 persons) with neither dental nor somatic issues. The material used for the study was oral fluid. The general metabolic processes in the periodontal and peri-implant area tissues were described based on analysis of the protein and mineral metabolism indicators, as well as on the hygiene and periodontal status indices. The paper presents the results of a comparative assessment involving Groups I and II with the control group and between Groups I and II. Our findings show changes in ion balance in both groups. Significant disturbances in the protein and mineral metabolism have been identified in the main groups, which contributes to the development of inflammation and reduced detoxification in periodontal and peri-implant tissues. A rise in Calcium and Magnesium indicates destructive processes in bone tissues. In case of mild CGP, these changes are more prominent. The oral hygiene and periodontal status indices in Group I proved to be significantly worse. Therefore, while performing implantation on the background of chronic generalized periodontitis, it is important to take into account its metabolic imbalance and implement preventive measures.

KEYWORDS — dental peri-implantitis, chronic generalized periodontitis, oral fluid, oral cavity homeostasis.

INTRODUCTION

Of all dental issues affecting different population groups, the recent years have witnessed an increase in various periodontal diseases [1, 2, 5, 7, 14]. Their overall prevalence remains high with no decrease trend to be observed practically anywhere in the world [3, 4]. The data available in the literature in Russia shows that 95% -100% of patients among different age groups have signs of inflammatory periodontal diseases [12, 15]. A special place here belongs to chronic generalized periodontitis (CGP), which is a serious social, economic and medical issue [6]. Periodontal diseases feature pathogenic microflora in the oral cavity. Accumulating bacterial plaque facilitates inflammation, which often results in removed teeth. Once lost, the teeth can be restored through various methods, including implants. In modern conditions, the indications for implantation in patients with periodontal diseases are expanding.

However, failure to follow oral hygiene requirements and periodontitis belong to the risk factors for peri-implantitis [8–11, 13]. The hypothesis here is that pathogenic microorganisms detected on periodontal teeth can develop colonies, so implants, similarly to cross-infection, develop a complication known as dental peri-implantitis. Despite the undeniable progressive value of implantation, dental peri-implantitis complicates osseointegration. Typical is the fact that inflammatory and destructive complications can be observed even in cases where the bone-to-implant connection is optimal and are to be regarded as osseointegration. In this regard, improving implants osseointegration and maintaining the area of the implant and the surrounding bone tissue, which is discussed in the literature, stands out as an urgent issue faced by implantology.

Currently, there is a need for newer data that would reveal the role and the nature of the effect that CGP has in modeling molecular processes responsible for physiological and reparative osteogenesis, search for individual criteria, and identification of predictors behind the development of inflammatory and destructive complications in dental implantation. Oral fluid (OF), in this context, is a universal medium that can be obtained noninvasively and it is widely available when it comes to studying various processes. To determine the most specific character of metabolic changes in dental peri-implantitis, as we see it, can be done through a comparative study of oral fluid in inflammatory diseases of periodontium and the peri-implant area tissues.

Aim of study:
to evaluate the oral homeostasis status in patients with mild chronic generalized periodontitis and mild dental peri-implantitis, in order to predict the development of inflammatory and destructive complications of dental implants.

MATERIALS AND METHODS

To evaluate oral homeostasis, 85 patients were examined, including 35 (41.2%) of them featuring mild chronic generalized periodontitis (Group 1) and another 30 (35.3%) with mild dental peri-implantitis (Group 2). In order to compare the OF studied indicators, 20 more persons (23.5%), comparable in gender and age, healthy in term of dental and somatic health, and referred to as the control group, were examined. The oral homeostasis status was evaluated through studying a number of indicators reflecting the destruction process, the mineralization and demineralization of the bone tissue. For this purpose, the biochemical composition of the unstimulated mixed oral fluid and the hygiene status of the oral cavity were studied. The study relevance relies on the need to establish pathological changes at the metabolic level, thus aiming to develop further treatment tactics. All the patients had their OF content of mineral components (Calcium, Magnesium, Ammonium Cation, Nitrate Anion), protein metabolism indicators (total protein, total albumin concentration, effective albumin concentration, albumin binding reserve and toxicity index) evaluated.

The dental status was evaluated through the following indexes: the Green-Vermillion index in the Cowell modification, the Russel index, the Loe & Silness index, and the Muhlemann index. Statistical data analysis was performed within the SPSS 25 package. Descriptive statistics were represented via the mean and standard deviation (M±SD). Group comparison implied single-factor analysis of variance (one-way ANOVA) followed with inter-group comparisons involving the Bonferroni criterion. The differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

Table 1 shows the results of protein metabolism.

The total protein concentrations in the oral fluid of all the three groups featured comparable values and did not differ statistically. There was no difference between the total albumin concentration in the control groups and in patients with chronic generalized periodontitis, yet it was lower in patients with dental peri-implantitis ($p<0.001$ compared to the control group and Group 1). Significantly lower values of effective albumin concentration, albumin-binding capacity and toxicity index were observed in both groups of patients, if compared to the control group ($p<0.001$). The effective albumin concentration and the toxicity index in Groups I and II, though, revealed no statistically significant difference, whereas the albumin-binding capacity was the lowest in patients with mild dental peri-implantitis ($p=0.003$ compared to patients with mild CGP).

Table 2 shows the results of mineral exchange.

Statistically significantly higher concentrations of oral fluid mineral components (Calcium, Magnesium, Ammonium Cation and Nitrate Anion) were identified in patients with mild chronic generalized periodontitis and mild dental peri-implantitis, if compared to the control group ($p<0.001$). When comparing the groups among themselves, higher concentrations of Calcium and Ammonium Cations were to be observed in Group 1 compared to Group 2 ($p<0.001$), while the Nitrate Anions level was higher ($p=0.007$). The Magnesium concentrations in the oral fluid obtained from patients with mild CGP and mild dental peri-implantitis did not differ statistically.

The Ammonium Cation and the Nitrate Anion contents were evaluated in order to detect the degree of microbial invasion as the ions in question are mainly products of microorganisms' metabolism. Their increase in Groups I and II, if matched against the control group, inspired the idea of identifying the reason behind microbial contamination. From this stance, of interest is studying the indices of oral hygiene, the periodontal tissues status, and the peri-implant area. The results are to be seen from Table 3.

Analysis of the data in the table shows that the hygiene indices, as well as the periodontal index and

Table 1. *Oral fluid protein metabolism indicators in Groups I and II compared with the control group*

Indicator	Control group M±SD n=20	Patients with mild chronic generalized periodontitis (Group I) M±SD n=35	Patients with mild dental peri-implantitis (Group II) M±SD n=30	p, Control group – Group I	p, Control group – Group II	p, Group I – Group II
Total protein, g/l	3.40±0.47	3.50±0.36	3.45±0.35	1.000	1.000	1.000
Total albumin concentration, g/l	0.33±0.01	0.33±0.04	0.29±0.03	1.000	<0.001	<0.001
Effective albumin concentration, g/l	0.26±0.05	0.13±0.05	0.10±0.06	<0.001	<0.001	0.095
Albumin-binding capacity	78.8±10.5	42.7±9.6	34.4±9.4	<0.001	<0.001	0.003
Toxicity index	0.27±0.15	2.01±0.82	1.91±0.95	<0.001	<0.001	1.000

Table 2. *Mineral components content in the oral fluid, Groups I and II vs. the control group*

Indicator	Control group M±SD n=20	Patients with mild chronic generalized periodontitis (Group I) M±SD n=35	Patients with mild dental peri-implantitis (Group II) M±SD n=30	p, Control group – Group I	p, Control group – Group II	p, Group I – Group II
Calcium (mmol/l)	0.55±0.07	1.13±0.21	0.92±0.20	<0.001	<0.001	<0.001
Magnesium (mmol/l)	0.29±0.08	1.23±0.24	1.10±0.65	<0.001	<0.001	0.826
Ammonium Cation (mmol/l)	3.10±0.29	7.12±0.76	6.22±0.72	<0.001	<0.001	<0.001
Nitrate Anion (mmol/l)	2.74±0.38	7.21±0.89	6.51±0.87	<0.001	<0.001	0.007

Table 3. *Indicators of index assessment of the state of periodontal and peri-implant zone tissues of Groups I and II*

Group	Green-Vermillion index	Russel index	Muhlemann index
Group I	3.24±0.23	2.53±0.21	1.96±0.21
Group II	2.57±0.22	1.51±0.13	1.75±0.15
Control group	1.3±0.01	1.2±0.09	1.1±0.10

the gum bleeding index are significantly higher in Groups I and II if compared to the control one. Comparing Groups I and II, we can see that the values are higher in Group I, which suggests that the increase in the Ammonium Cation and Nitrate Anion in the OF is due to poor oral hygiene.

The oral homeostasis evaluation in patients with mild CGP and mild dental peri-implantitis revealed an ionic imbalance with a certain correlation dependence. A decrease in the albumin effective concentration reflects a decrease in its free binding centers. Their number helped identify the protein protection status. The effective concentration of this transport protein serves to describe its ability to be involved in detoxification processes. The albumin-binding capacity decreased significantly in Groups I and II, which can be viewed as a pathogenetically important link within inflammation development in peri-implant and periodontal tissues. The decrease in the Calcium and Magnesium levels observed in Groups I and II demonstrates a unidirectional process of bone resorption in the dentoalveolar zone.

CONCLUSION

Thus, the analysis of oral fluid protein metabolism indicators showed a decrease in protein protection in Groups I and II if compared with the control group, which is evidence to the development of inflammation and a decrease in detoxification processes in periodontal and peri-implant tissues. In case of mild CGP, these changes are more pronounced. The evaluation of mineral metabolism showed a significant increase in the Calcium and Magnesium levels in the OF collected among patients of Groups I and II, compared with the control, which points at bone resorption, especially in Group I. Low levels of oral hygiene as well as the periodontal and peri-implant tissue condition indices correlate both with the control group, and among the groups. Mild CGP, though, features more significant disturbances in protein and mineral metabolism, if compared with mild dental peri-implantitis. Lack of periodontal ligaments in implants attached to them may cause peri-implantitis on the background of chronic generalized periodontitis, even in mild cases. This factor should be taken into account when carrying out dental implantation.

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IMPROVED DIAGNOSIS FOR ORAL MUCOSAL TUMORS IN THE DENTIST'S OFFICE

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ABSTRACT — Based on currently available literature, clinical examination remains the major method when handling cases of suspected malignancy. However, this method does not allow diagnosing cancer, due to which a large group of patients with possible oral mucosa cancer are referred to an oncologist. The search and use of affordable non-invasive methods for early diagnosis of oral mucosa tumors is an urgent issue facing the health system. The study involved analyzing 134 records of outpatients examined at the Samara Regional Oncological Clinic who were referred by dentists within 2014-2019 from the local polyclinic in Samara due to detection of tumors in oral mucosa and who underwent a biopsy. The patients were divided into two groups according to the examination methods. The inclusion criteria were: detection of various superficial oral mucosa neoplasms; referral from the dentist. The exclusion criteria were as follows: patients with submucosal oral cavity neoplasms referred to the oncologist by other medical specialists or self-referred patients. The control group included 63 patients who, after a conventional examination (including interview, examination, palpation), underwent an incisional biopsy followed by morphological examination at the oncologist's office. In the major group, in 71 patients at their respective initial dental appointments a special examination algorithm was applied. This algorithm entailed an assessment of the identified risk factors. Indications for biopsy were identified using the histological verification index (HVI). Apart from the conventional examination methods (interview, examination, palpation), autofluorescence stomatoscopy was used, this being done for the purpose of differential diagnostics of inflammation, precancerous and malignant issues, depending on the glow type. In the main group, the initial stages of oral mucosa cancer were detected in 17 patients after biopsy; in the control group – in 4 patients (p=0.004). The developed algorithm used for scoring the patient's clinical examination data combined with autofluorescence stomatoscopy allowed diagnosing accurately (90% of reliability) precancerous and cancerous diseases, as well as to use invasive research methods (biopsy) strictly following the indications.
Aim of study: to improve diagnosis of oral mucosa neoplasms through improvement of the examination algorithm.

KEYWORDS — oral mucosa (OM), precancer, cancer, histological verification index (HVI).

INTRODUCTION

High prevalence of dental diseases, their progressiveness, individual differences in anatomy, the variety of nosological forms — all this complicates the early diagnosis of pathology in the maxillofacial region [1-6]. The possibilities of additional examination methods allow us to differentiate the effects of etiological factors, clarify various aspects of pathogenesis, study the effect of the drugs used, conduct early diagnosis, and personalize the treatment of a particular patient [7, 8].

One of the priority areas in medicine is the use of non-invasive non-contact optical technologies. Optical research methods used in dentistry (stomatoscopy and photoscopy; capillaroscopy method; ultrasound Doppler sonography; laser fluorescence diagnostics; laser Doppler flowmetry; optical tissue oximetry), in terms of their information content, visualization are not inferior to radiation methods. Insufficient knowledge of the optical properties of pathological tissues in various organic and functional disorders requires additional medical and biological research [9, 10].

Statistics shows that over 355 new cases of oral mucosal cancer are registered annually globally [11]. In 2018, the total number of cases registered with OM cancer in Russia was 9518, while the Samara region accounted for 199 patients. OM cancer, which is ranked 18th in the overall cancer occurrence structure, the diagnosis of OM cancer was confirmed morphologically in 97% of Russians [12]. Even though OM tumors belong to external locations, the share of advanced stage cases is still quite high reaching 62% (in Russia). The major reasons behind OM cancer neglect involve lack of proper oncological awareness among dentists, general public education, screening programs [13, 14, 15]. The current literature witnesses that clinical examination still remains a major method employed in case of suspected malignancy [16, 17]. This method, however, does not allow delivering a final diagnosis, while most patients with suspected OM cancer are referred to an oncologist for a biopsy, which, in turn, may result in excessive diagnostics [18, 19]. OM neoplasms biopsy is an invasive method, which involves obtaining tissue samples for histological examination, thus trying to ensure differential diagnostics and establishing a reliable diagnosis [20, 27, 28]. The procedure in some cases leads to unfavorable events, so it should be carried out while sticking strictly to certain indications — first of

all, in case a malignant OM issue cannot be excluded. The resulting histological conclusion determines the correct diagnosis, further due and timely treatment as well as the disease outcomes forecast. The somatoscope autofluorescence method has been known for a long time as a tool for diagnosing OM tumors. There have been numerous respective research publications, nationally and internationally, yet they featured no relation to the available methods such as interview and clinical examination [21, 22, 23]. Given that, the authors developed (2017) an interview algorithm with an application (#2019133760 of 08/11/2019) submitted for an invention patent *A method to identify indications for the red lip border neoplasms and the oral mucosa histological verification in the dentist's office*.

MATERIALS AND METHODS

The study was based on the analysis of 134 records of patients who underwent examination at the Samara Regional Clinical Oncological Clinic (Samara, Russia) in the period of 2014–2019 due to referrals by dentists from the local clinics because of suspected OM neoplasms. All of them underwent respective biopsy procedures. The patients were divided into two groups depending on the examination methods used. The control group included 63 patients who were referred by dentists within 2014–2016 as diagnosed with OM neoplasms. After a conventional examination procedure, which included an interview with clarification of complaints, a visual examination and palpation, an incisional biopsy was performed followed by a morphological study at the oncological clinic. In the main group (71 patients) we applied a specially developed examination method conducted at an initial dental appointment (along with an interview and a visual examination). The newly introduced method included a point-based assessment of the detected risk factors thus determinating the indications for biopsy as well as the histological verification index (HVI). In addition to the conventional examination methods (an interview, a visual examination and palpation), autofluorescence stomatoscopy was used for the purpose of differential diagnostics of inflammatory and precancerous lesions and cancer. Incisional biopsy in both groups was performed under local anesthesia with the use of otorhinolaryngological conchotomes, followed by a morphological study. Incisional biopsy in the main group was applied only to patients with HVI exceeding 5 points. The inclusion criteria were: primary referral by a dentist with OM superficial neoplasms. The exclusion criteria included cases referred by other medical specialists, self-referred, as well as those who refused to be examined, as well as cases of oral submucosal neoplasms. The patients were comparable by sex M/F 3:1 (p=0.858); age — in the control group 63+2.8 yrs, in the main group — 71 = 2.8 yrs; localization (Pearson criterion — 2.7567; p=0.8386). The newly applied method used in the main group was presented as a protocol with anamnestic data identified, an examination performed, the palpation result evaluated, as well as an examination performed with an AFS400 autofluorescent lamp (manufacturer: *Polyronik*, Moscow).

Each method in the protocol is evaluated subject to a point-based system. To facilitate and fix the final score, the HVI was used. The index value is recorded in the column with a letter mark of the lesion topographic location. A separate protocol is prepared as per each identified focus, with a respective index calculated. In the event the index is below 5, then follow-up and treatment at the dentist are administered, followed by another examination; in case the value was 5 or above, a biopsy of OM neoplasms was recommended. The main criterion for evaluating the effectiveness of this examination algorithm was the confirmed diagnosis of precancerous issues or cancer after biopsies and morphological examination. The indicators that were evaluated included the type of the complaint presented, pathological processes noted through the examination, the rate of precancerous diseases, malignant tumors and the degree of cancer after a histological conclusion. The study employed multivariate models of logistic regression in patients with oral mucosa lesions. The significance criterion was $p<0.05$ (the p-value below 0.05 was considered statistically significant). All statistical analysis procedures were performed using Statistica 10.0.

RESULTS AND DISCUSSION

The evaluation of the complaints of the patients of the main and control groups enabled their differentiation. Patients in the main group mentioned tumors less often than those in the control group (0.54 and 1.17 times, respectively). Pain was reported in the main group (M1) in 23.9% of cases, while in the control group (M2) it was reported in 47.6% of cases. Discomfort, as a condition scored high in both groups. Symptoms like sensations of burning and itching were observed equally in both groups. Table 2 offers a comparative view at the symptoms identified through the clinical examination both in the main group (M1) and in the control group (M2). Changed oral mucosa color was 0.82 times more common in the main group (54.9% vs. 28.4%); plaque was an issue observed equally in the two groups (62.0% and 60.3%), while hyperkeratosis was observed in 45.1% and in 58.7% of cases, respectively. The control group featured significant prevalence of erosions (55.6%) if compared to

Table 1. *Distribution (%) of complaints reported at the clinical examination, the main group (M1) and the control group (M2)*

Complaint Group		Tumor	Pain	Discomfort	Burning sensation	Itching	Bleeding
M1	Identified	35.2%	23.9%	64.8%	40.8%	29.6%	7.04%
	Not identified	64.8%	76.1%	35.2%	59.2%	70.4%	92.96%
	Difference	->0.54	->3.17 times	+>1.84 times	->1.45 times	->0.98 times	->13.2 times
M2	Identified	53.9%	47.6%	80.9%	42.9%	39.7%	22.2%
	Not identified	46.1%	52.4%	19.1%	57.1%	60.3%	77.8%
	Difference	+>1.17 times	->1.1 times	+>4.25 times	->1.33 times	->1.52 times	->3.5 times

Table 2. *Comparative features (%) of the disease symptoms identified through the clinical examination, the main group (M1) and the control group (M2)*

Oral mucosa examination		Changed mucosa color	Mucosa moisture (glare)	Plaque			Pathological issues			
				Present	Removable	Non-removable	Hyper keratosis	Hyper plasia	Atrophy	Erosion / ulceration
M1	Identified	54.9%	43.7%	62.0%	31.0%	28.2%	45.1%	31.0%	12.7%	36.6%
	Not identified	45.1%	56.3%	38.0%	69.0%	71.8%	54.9%	69.0%	87.3%	63.4%
	Difference	+>0.82 times	->1.29 times	+>1.63 times	->2.23 times	->2.55 times	->1.22 times	->2.23 times	->6.9 times	->1.73 times
M2	Identified	28.4%	53.9%	60.3%	33.8%	36.5%	58.7%	17.5%	11.1%	55.6%
	Not identified	71.4%	46.1%	39.7%	66.2%	63.5%	41.3%	82.5%	88.9%	44.4%
	Difference	->2.5 times	+>1.17 times	+>1.52 times	->3.2 times	->1.7 times	+>1.42 times	->4.7 times	->8.0 times	+>1.25 times

the main group (36.6%). Hyperplasia and atrophy rate varied from 11.1% to 31.0% of cases.

Thus, complaints involving pain, burning sensation, discomfort, and erosions were more frequent in the control group, whereas in the main group, plaque and tissue hyperplasia were more often identified. Given our observations, the pathological conditions of the oral mucosa localized to a greater extent on the tongue, both in the control (46%) and in the main (47%) groups, which does not contradict the data available from the currently available studies [12, 15]. After the biopsies and the obtained histological conclusion in the control group, precancerous diseases as a diagnosis were confirmed in 18 patients in the main group as well as in 36 patients in the control group, whereas the difference was significant (p=0.016). In the main group, in turn, malignant OM issues were diagnosed in 28 cases, while in the comparison group — in 14 (p=0.051).

Inflammation was observed in 7 patients in the main group and in 31 patients — in the control group (p=0.001) (Fig. 1). In the main group, the initial stages of OM cancer were detected in 17 patients after biopsy, while in the control group — in 4 patients (p=0.004). There were no significant differences in diagnosing advanced stages in the comparison groups (11 patients in the control group and 10 — in the main one) (Fig. 2). Therefore, patients with OM inflammations appear as the greatest issue in terms of diagnosing, especially when talking of differential diagnosis, for primary care dentists, and these patients are most often referred unreasonably to undergo invasive examination. Speaking in general, this method, if employed for identifying indications for histological verification of the vermillion border and oral mucosa issues at the dentist's office, allowed confirming precancerous and malignant oral mucosa issues in 90 % of the cases within the main group, whereas in the comparison group, the traditional examination produced a similar result in 51% of cases only.

If comparing the rate of false-positive outcomes in diagnosing precancerous and malignant diseases in both groups, while using traditional examination methods vs. the new one, there were some significant

differences identified (p=0.001). From the stance of early diagnostics, or in terms of secondary prevention, to be exact, where primary-care doctors are employed mostly, the detection of precancerous and malignant tumors in the main group (using the new method) featured significant differences compared to the traditional method. A number of previous studies claim that visual examination cannot be viewed as a diagnostic test when it comes to differential diagnostics, so there are also additional fluorescent and a number of other tests used, which, given our observations, proved effective when combined with the available conventional traditional ones [22, 24, 25, 26].

CONCLUSION

Using an improved algorithm for examining patients with OM diseases combined with autofluorescence somatoscopy we have identified with a high precision (90%) precancerous and cancerous tumors. It enabled us more efficient detecting initial stages of OM tumors as compared with conventional examination methods (24% and 5%, respectively). Besides, it allowed avoiding invasive methods — biopsy — unless it was indicated.

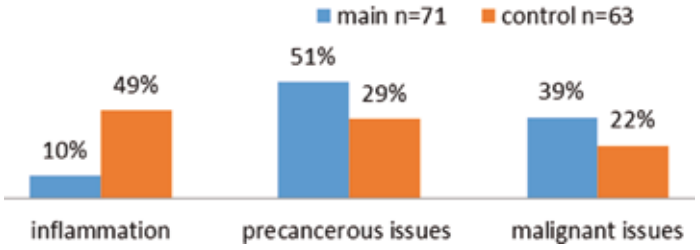

Fig. 1. Distribution within group by diagnosis

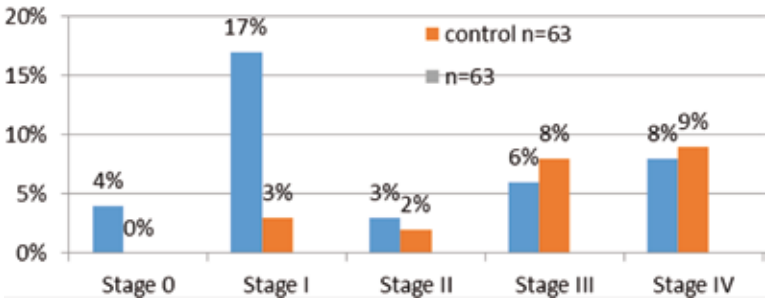

Fig. 2. Distribution within group by cancer advance

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A METHOD FOR MODELING ARTIFICIAL DENTURES IN PATIENTS WITH ADENTIA BASED ON INDIVIDUAL SIZES OF ALVEOLAR ARCHES AND CONSTITUTION TYPES

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ABSTRACT — 87 persons of older age groups with complete adentia underwent somatometric (anthropometric) as well as biometric measurements with cast models of the toothless jaws. The linear and index somatometric parameters, and linear and index parameters for the upper jaw alveolar arches, were calculated. Alveolar arches were classified in view of the total sum of the diagonal dimensions (macro-, micro- and normodiagonal type), the arch index (brachy-, dolicho- and mesoarch type). Modelling the projected shape of the dental arch was based on the parameters of length (the sum of the alveolar arches diagonals multiplied by the 1.06 coefficient), width (the product of the width of the alveolar arches by a coefficient of 1.16). The depth of the dental arch frontal segment was calculated as the product of the diagonal by the incisor-canine angle sine, which in case of mesotrusion arches is 0.42 (angle value — 25°), for protrusion arches — 0.5 (angle value — 30°), for retrusion arches — 0.34 (angle value — 20°).
Given the regularities of the circle geometry, the frontal segment dimensions served to determine the radius of the circle where the front teeth sat. The graphical method developed to construct the forecasted upper dental arch shape, based on the balance of the alveolar and dental arches major parameters, allows forecasting the optimal shape and size of the artificial dental arch, achieving a balanced relationship between the shapes of the teeth and the alveolar arches, as well as constructing a balanced articulatory relationship while achieving optimal functional and aesthetic results.

KEYWORDS — complete adentia, alveolar arches, dental arches, constitutional anatomy, somatometrics, biometrics, alveolar triangle, dental triangle.

INTRODUCTION

Currently, the issue of studying human constitution features, which provides the basis for clinical and anthropological areas, refers to the field of both theoretical and clinical medicine. However, classical anthropometric methods can be well complemented by modern innovative research methods, thus, increasing precision and effectiveness of the outcomes[2, 4, 16, 18, 22, 32, 38, 49, 52].

Personalized medicine is, currently, a rapidly emerging field of healthcare, aimed to improve treatment protocols considering patient's body constitution and typology features, determined by a complex set of phenotypic and genetic markers. It offers an objective reflection to morphological, functional and biochemical specificity, remain stable through ontogenesis, and have individual anatomical variability with insignificant intra-individual variability [1, 15, 20, 23, 33, 36, 39, 51, 54].

According to epidemiological studies, the average prevalence of complete secondary adentia in Russia is 8.4–18.0%, while in the age category of 50–59 this rate is 8.9-21.6%; among the populations aged 60–69 — 9.3–25.2%; 70–79 — 17.4–29.5%, and in the category over 80 — 27.8–46.7%. The surge in the number of patients with complete loss of teeth can be observed annually not only among older patients , yet also among those who fall within the group of the middle-aged [59].

Complete absence of teeth in the maxillofacial area entails the following functional and morphological changes: disturbed anatomical and topographic ratio of the facial skeleton and soft tissues; increased jaw bones osteoporosis; discoordinated neuro-reflex action; progressing in the toothless jaws and the covering mucosa atrophy; decrease in the masticatory muscles volume and tone; developing dysfunction of the temporomandibular joint (TMJ). In addition, there are psychoemotional tension, chewing and speech problems, which limit quality of life, communication and lead to social isolation [5, 27, 42, 48, 58].

The success of the diagnosis and the quality of the diagnosis are determined not only by the introduction of instrumental and technical methods for recognizing diseases in clinical medicine, but also by the ability of practicing physicians for analytical and logical thinking. With the increase in information on diseases, the

process of mental activity of the doctor becomes more complicated, the requirements for the logical validity, timeliness, completeness and accuracy of the diagnosis has been accelerated [7–12, 21, 26, 30, 40, 45, 55].

The effectiveness of prosthetic treatment for edentulous patients, which is performed in view of the pathogenetic maxillofacial changes, is determined by restoring oral function, delivering prosthesis stabilization through functional suction capacity and anatomical retention, improved aesthetics, as well as preserving the jaw hard tissues under the prosthesis base, and reducing the period of functional adaptation. Implementing these provisions will create conditions for proper social adjustment, systemic improvements in the patient's body and the quality of life [13, 29, 35, 50].

When designing tooth rows on toothless alveolar processes, the priority task is to restore a balanced occlusal and articulatory relationship, where the TMJ functional features are compensated by the shape of the artificial teeth chewing surface, while the angle of any slope of the tubercle corresponds to the movement trajectory of the articular mandibular head, thus ensuring equal loading of all tissues in the prosthetic bed. Besides, when shaping the dentition, it is important to reach an optimal balance between the impacts caused by the neuro-musculoskeletal system of the jaw bones and the physical and mechanical interactions occurring between the prosthesis and the prosthetic bed tissues, providing for multiple interdental contacts of the same power under equally distributed and slight pressure on the denture base supporting tissues [24, 28, 31, 46].

Of reasonable interest are studies focusing on the most variable part of the dental arch — the frontal area, while the biometric features of the anterior part serve the basis for the forecasted graphic reproductions of the dental arches. Here the authors present calculations of the circle radius, offer grounds for mathematical modeling methods of artificial and abnormal dental arches [3, 19, 25, 44, 47, 53, 56, 57].

The data suggest that the central (interincisal) point of the dental arch has an anterior location of the alveolar arch central point in people with protrusion, mesotrusion and retrusion arches at a distance of 3.5 mm, 2.5 mm and 1.5 mm, respectively [37, 43]. In this case, the angle between the anterior diagonal and the width of the arch depends on the front teeth location. In people with a normal tooth torque, the incisor-canine angle is about 25°. In case of incisors protrusion and retrusion, this angle is 30° and 20°, respectively [17, 41]. At the stages of identifying the teeth size, experts recommend focusing on the arches' diagonal dimensions. The diagonal of the upper dental arch has been noted to exceed the diagonal dimensions of the alveolar arch by 1.06 times, while the sum of the six anterior teeth crowns width is 2.45 times as low as the length of a dental arch comprising 14 permanent teeth [34]. The width of the upper dental arch has been proven to be 1.16 times the width of the alveolar arch, this fact being of practical value in clinical dentistry [6, 14].

Despite the algorithms described in the reference literature for treating patients with dental arches anomalies and defects, the data on making forecasts regarding the parameters of artificial dental arches based on the alveolar arch major dimensions in people with complete adentia is neither systematic nor complete, which underlies a rationale for a morphometric study.

Aim of the study:
to develop a method for constructing an upper dental arch of a forecasted shape based on the alveolar process size of a toothless jaw in patients with complete adentia.

MATERIALS AND METHODS

The study used cast models obtained from 87 persons (38 males and 49 females; median age — 74.1±3.2), elderly and old, with complete absence of teeth. All the patients gave their written informed consent in compliance with the guidelines for the Ethics Committee.

When studying the cast models of jaws, measurements were made between the designated points. The central point of the upper alveolar arch corresponded to the location of the alveolar process anterior point in the incisor papilla (in_{al}). The reference points were the upper frenulum and the median palatal suture line. The retromolar points were placed on both sides on the maxillary tubercles tops in the center of the alveolar process (m_{al}). The alveolar arches width was measured between the m_{al} points, whereas the diagonal dimensions were measured between the central and the retromolar points ($in_{al} - m_{al}$). The total size of the diagonals of the upper normodiagonal arches varied from 103 to 112 mm. Micro- and macrodiagonal arches included types where the total diagonal size indicator was below or above the value of the considered range.

The ratio of the arch width to the total sum value of the diagonals determined the arch index, which varied from 0.46 to 0.5 for meso-arch types. An increase in the index indicated belonging to the brachy-arch type, whereas a decrease pointed at the dolicho-arch type of the alveolar arches.

The dental arch length was calculated as the product of the total value of the alveolar arches diagonals to a factor of 1.06. At the same time, calculating the

size of the six upper front teeth implied dividing the calculated value of the dental arch length by a factor of 2.45. The resulting value allowed identifying the approximate width of each tooth. The medial-distal diameter of the upper canine, therefore, corresponded to 1/6 of the arch anterior segment length. The width of the medial and lateral incisors was calculated relying on the size of the canine (key tooth), employing the factors of 1.1 and 0.9, respectively.

The product of the alveolar arch width by a factor of 1.16 allowed identifying the calculated width of the upper dental arch. The arch depth was calculated based on the Pythagorean theorem.

The length and width of the dental arch anterior segment was determined between the tearing tubercles (cd points). The length of the anterior segment corresponds to the sum of width of 4 incisors crowns and the half-sum of the mesial-distal diameters of the canines. Half the length of the anterior segment was close to the size of the anterior (incisor-canine) diagonal. The depth of the anterior segment was calculated as the product of the diagonal by the sine of the incisor-canine angle, which for mesotrusion arch type was 0.42 (an angle of 25°), for protrusion type — 0.5 (angle of 30°), and in case of retrusion of incisors – 0.34 (angle 20°).

Meso-arch normo-diagonal, brachy-arch macrodiagonal and dolicho-arch macrodiagonal arches were attributed to the mesotrusion type of arches. Anterior teeth protrusion was typical of dolich-arch types with macro- and normodiagonal dimensions, and was to be observed in case of meso-arch macrodiagonal types of dental arches. Retrusion was typical of brachy-arches with normo- and microdiagonal, as well as of meso-arch macrodiagonal types (Fig. 1).

In view of the circle geometry patterns, the anterior segment determined the radius of the circle where the front teeth sat. The radius was calculated as the ratio of the sum of the segment half-width square and the segment depth square to the segment double-depth.

For the quantitative distribution of constitution types, somatometric measurements were performed relying on a basic set of anthropometric tools, which had undergone metrological verification subject to generally accepted methods. The obtained outcomes were recorded in individual protocols. In order to ensure objective description of the physical constitution type and the physique proportions, the constitutional morphology index was employed (L. Rees – H. J. Eisenk). The L. Rees-H. J. Eisenk index = L × 100 / transverse chest diameter × 6; where L is body length (cm). Interpretation: picnical constitution — males (under 96.2), females (under 95.9); normosthenic constitution — males (96.2–104.8), females (95.9–104.3); asthenic constitution — males (beyond 104.8), females (beyond 104.3). The data processing was performed using the Microsoft Excel 2013 software as well as the SPSS Statistics statistical software package (Version 22). The critical level of the possible zero statistical hypothesis was set at 0.05.

RESULTS AND DISCUSSION

The results of the quantitative distribution of somatotypes by proportion and body constitution (L. Rees-H. J. Eisenk index) reveal that the picnical constitution was observed in 9 males and 6 females (23.7% and 12.2%, respectively), normosthenic constitution — in 21 males and 16 females (55.3% and 32.6%, respectively), whereas another for 8 males and

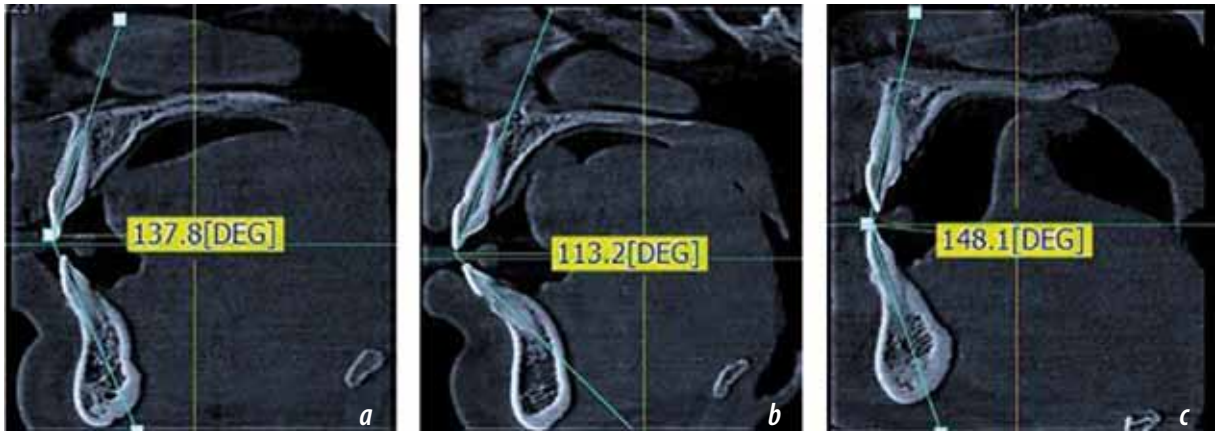

Fig. 1. *Variants of the location of the medial incisors on the CBCT images: a — mesotrusion type of dental arches; b — protrusion type of dental arches; c — retrusion type of dental arches*

27 females featured the asthenic constitution — 21.0% and 55.2%, respectively).

The alveolar arch measurements laid the basis for constructing the alveolar triangle, whose sides are the arch diagonal, while the base is the alveolar arch width. The mental triangle construction was based on detecting the location of the central interincisal point, which depends on the dental arch type. The distance between the ind – inal points for the retrusion type made up 1.5 mm, for the mesotrusion type — 2.5 mm, and for the protrusion type — 3.5 mm (Fig. 2).

apart from the interincisal point at a distance equal to the calculated depth of the anterior dental arch, while the position of the canines tearing tubercles is determined by the diagonal size, which is set with a compass from interincisal point to the junction with the base of the triangle on both sides, and is marked as cd. The alveolar and dental triangles are joined for further construction of the artificial dental arch template (Fig. 4).

The circle passes through the points that correspond to the location of the canines tearing tubercles and the interincisal point.

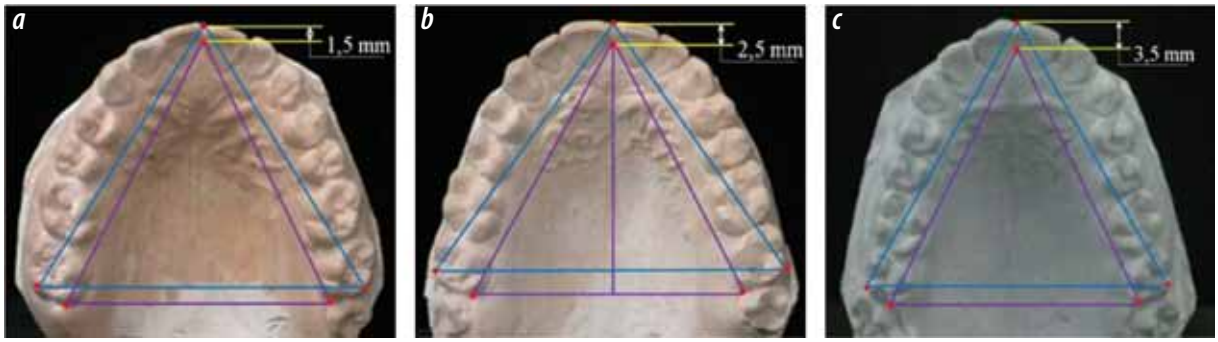

Fig. 2. *Mutual position of dental and alveolar triangles for retrusion (a), mesotrusion (b) and protrusion arches (c)*

The dental triangle base, which is the width of the dental arch, is separated from interincisal point at a distance equal to the calculated depth of the dental arch, whereas the position of the vestibular distal tubercles of the second molars is determined by the size of the diagonal, which is to be set with a compass from the interincisal point to the junction with the triangle base on both sides and is marked as md. The procedure above serves to identify the location of the second molars, which are the key teeth within the designed dental arch (Fig. 3).

The anterior triangle determines the position of the canines, which are the key teeth for the anterior segment of the artificial dental arch. The front triangle base, which is the width of the dental arch anterior segment, stands

When systematized, the obtained data reveal that when treating patients with compete adentia, it is reasonable to use the size of the alveolar arches thus to identify the key reference points, in order to forecast the size and shape of the artificial dental arch, which should be taken into consideration at the stage of designing the artificial dental arch through prosthetic treatment.

CONCLUSIONS

1. Clinical and morphometric grounds for the proportion of the main parameters of the upper jaw alveolar and dental arches allowed developing, explaining and testing a method for constructing an upper

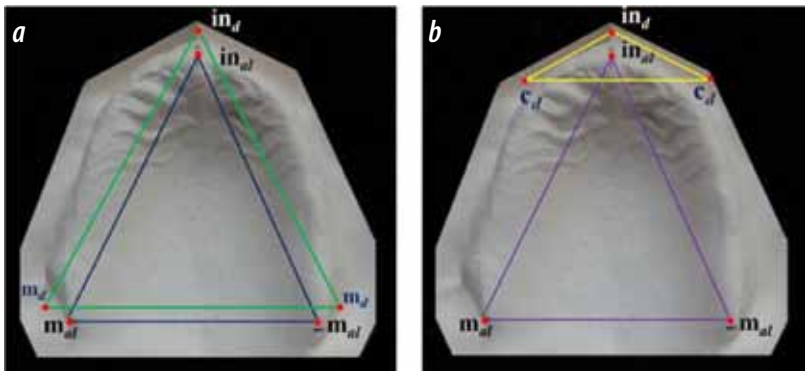

Fig. 3. *Cast model of the upper jaw with applied reference points and the construction of the alveolar and dental triangles (a) and the alveolar and anterior dental triangles (b)*

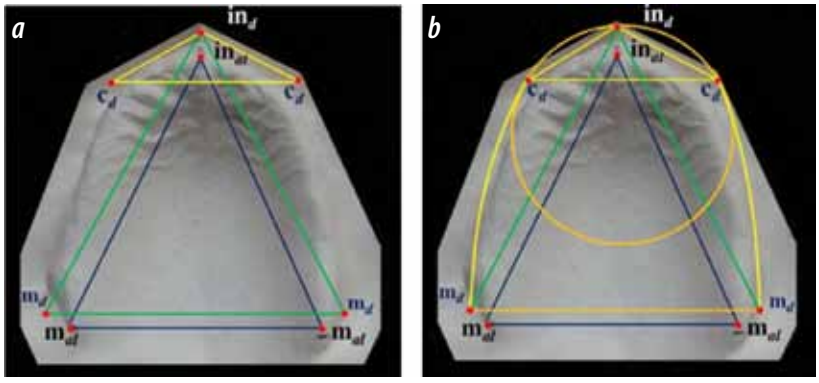

Fig. 4. Cast model of the upper jaw with applied reference points showing the key teeth location (a) and the construction of an artificial dental arch template (b)

dental arch of a forecasted shape based on the size of the toothless jaws alveolar processes in people with complete adentia and featuring various types of the body constitution. The following points were used as stable anatomical references that are most resistant to atrophy: retromolar points (m_{al}) located in the mucous mandibular tubercles of the retromolar triangles and maxillary alveolar tubercles; central points (in_{al}) located in the middle of the incisor papilla on the upper jaw hard palate.

2. The total index of the diagonal dimensions between the central (in_{al}) and the retromolar (m_{al}) points on the right and left sides in people with complete adentia, which falls within the reference intervals of 103–112 mm, points at the normodiagonal type of the alveolar arch. The total diagonal value of in_{al}–m_{al} below 103 mm indicates the microdiagonal type, while more than 112 mm means we are dealing with a macrodiagonal alveolar arch.

3. The arch index value taken as the ratio of the arch width to the sum of the diagonals in case of meso-arch, ranges between 0,46 and 0,5. The dimensional features of the arch index exceeding 0.5 are indicative of the brachi-arch type, whereas the same index below 0.46 points at the dolicho-arch type of the alveolar arches.

4. The value of the incisor-canine angle sine of the front segment for mesotrusion normodiagonal arches is 0.42 (angle — 25°), for protrusion arch — 0.5 (angle — 30°), for retrusion arch — 0.4 (angle — 20°).

5. The mesotrophic type of the dental arches includes meso-arch normodiagonal, brachy-arch macrodiagonal, and dolicho-arch macrodiagonal ones. The protrusion type of dental arches is diagnosed in dolicho-arch cases with macro- and normodiagonal dimensions, as well as in meso-arch macrodiagonal cases. The retrusion type of the dental arches features brachy-arch types with normo- and microdiagonal size as well as in case of meso-arch macrodiagonal types.

6. Due to complete loss of teeth, atrophy of the alveolar process and jaw bone tissue affects the shape and the size of the alveolar arches. Applying the limits of the alveolar arches reference intervals as reference points, when designing the dentition, may allow reproducing the volume and the nature of the structure available prior to the teeth loss and bone atrophy of the alveolar processes and jaws, which will finally allow designing a prosthesis to meet both the functional and the aesthetic requirements.

7. The individual-centered approach employed for the quantitative identification of the constitution types reveals that the normosthenic constitution prevails among elderly and old males, while the asthenic constitution prevails among females belonging to the same age group.

8. Rational prosthetic treatment can be improved through expanding the aesthetic aspects of modeling artificial teeth (Nelson's triad) with the size values and ratios identified for the alveolar arches of the upper jaw. Graphical identification of the key reference topography would not only allow forecasting the optimal shape and size of the artificial dental arch as well as arriving at a proper balance between the shapes of the teeth and the alveolar arches, yet would also help designing a well-balanced articulatory relationship, thus ensuring optimal functional and aesthetic outcomes.

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OCCLUSAL PLANE ORIENTATION IN PATIENTS WITH DENTOFACIAL ANOMALIES BASED ON MORPHOMETRIC CRANIO-FACIAL MEASUREMENTS

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ABSTRACT — Based on 79 lateral projection head teleroentgenograms obtained from relatively young patients (median age, 37.4±4.3), we have developed a method for the occlusal plane orientation in view of cranio-facial anatomical reference points. As stable anthropometric reference points, we employed the gnathic angle shaped by the spinal and mandibular planes, as well as the interalveolar angle, where the subspinal Downs point and the supramental point were employed as retention elements. When reconstructing the occlusal plane in patients with dentoalveolar anomalies, the construction of the bisector of the interalveolar angle was explained as a key reference point, which allows diagnosing occlusion anomalies in the vertical direction (symmetrical and asymmetric) not only in the lateral, yet also in the frontal segment of the dental arches. The method developed for constructing the occlusal plane does not depend on the position of the incisors and the second permanent molars, which can be used to identify the vertical deformation of the dental arches.

KEYWORDS — teleroentgenogram research methods, occlusal plane, Camper's plane, pathological occlusion, physiological occlusion, dental arch defects, cranio-facial complex.

INTRODUCTION

In order to carry out morphometric studies of the craniofacial structure, modern dentistry relies on precision methods of X-ray diagnostics as well as on computer analysis [1, 6, 9, 13, 18, 20, 23, 30, 34].

Dental references and horizontal planes of the skull are of value for orthopedic and orthodontic analysis of the upper jaw spatial location, which means it is their stability that ensures potential for a clear transfer of its true spatial position to the articulator [2, 8, 22, 32, 37, 44, 48, 58].

Treating patients with abnormal dentition is a complex issue associated with the need to restore the individual occlusal plane, which is an average plane determined by the incisors cutting edges as well as by the lateral teeth occlusal surfaces. There is every reason to expand this concept by defining it as a planar total image of the curvature formed by these surfaces [10, 14, 17, 28, 53, 59].

If restored the right way, the dentition shape (occlusal plane) will maintain not only the biomechanic features of the masticatory system, but also the facial aesthetics, the temporomandibular joint function, and that of the maxillofacial area muscles [4, 7, 12, 16, 24, 3 1, 35, 40, 43, 45, 49].

Deformed dentition, which is due to early removal of temporary teeth, disturbed teething, cause lower jaw functional displacements, as well as altered interalveolar height. The functional changes get fixed morphologically over time [3, 15, 19, 29, 39, 50, 55].

According to A. Jacobson (1985), the occlusal plane is a line connecting the lowest point of the maxillary central incisor cutting edge with the lowest point of the palatal tubercle of the left maxillary first molar. Korkhaus (1939) claims that the occlusal plane runs through the middle of the incisor overlap to the middle of the overlap of the second molars mesial buccal tubercles of the upper and the lower jaws. Ujumetskene I.I. (1970) noted that the line passing through the middle of the molars and fangs vertical overlap, located slightly below the Xi point, basically being the bisector of the face lower third height angle, makes the occlusal plane. R. Slavicek (2004) divides the occlusal plane to the front (from the cutting edge of the central incisor to the first premolar buccal tubercle) and the distal one, which connects the molars and premolars [5, 27, 51].

The study includes a comparison of occlusal planes built relative to the hinge-orbital, facial and dental axes; Camper's and Frankfort's horizontals; the skull base plane drawn both through the lower point of the Turkish saddle and through its middle; the lower incisors plane; as well as a plane built along the inter-jaw angle, dividing it in the 27/73 ratio [47]. In orthodontic practice, the occlusal plane position

is determined by the occlusal plane angle shaped by Frankfort horizontal and the line located tangentially to the lower premolars' tubercles and the recesses between the second lower molars buccal tubercles. Normally, the angle value is 8±4° [26, 42].

Improving the occlusion is aimed at restoring the individual anatomical dentition relationship within all the three planes in view of the central position of the lower jaw heads. This requires an integrated approach implying clinical examination, X-ray examination to identify the position of the mandible head and the occlusal plane inclination, cephalometric analysis, as well as an axiographical examination in order to explore the lower jaw articulation [21, 25, 33, 38, 46, 52, 54].

In case of occlusion issues, especially affecting the vertical direction, when there is a tooth-alveolar extension of the second molars to be observed, identifying the distal point of the occlusal plane falling within the normal range would be complicated. Besides, vertical or deep incisor disocclusion would make it difficult to determine the interincisal point, since this pathology can be caused by an anomaly either on one of the jaws or on both dental arches [11, 36, 41, 56, 57, 60].

Despite a significant number of published research items touching upon methods for constructing the occlusal plane in orthodontic and orthopedic patients employing various anatomical structures and cephalometric parameters as reference points, there are no methods available for constructing the occlusal plane for abnormal vertical occlusion and lengthier dental arch issues. This serves an explanation for carrying out our own X-ray morphological study.

Aim of study:

to develop of a method for identifying the occlusal plane orientation via cranio-facial morphometric parameters in case of vertical occlusion issues as well as lengthier dental arches.

MATERIALS AND METHODS

The study involved 79 head lateral teleroentgenograms obtained from people of the first and second mature age (median age, 37.4±4.3), who came to a dental clinic with various dental complains. In compliance with the Ethics Committee requirements, informed consent was obtained for the X-ray examination from all the patients. The study employed points and lines that are conventionally used in clinical dentistry, in orthodontics in particular.

Subject to the study objectives, the gnathic part of the craniofacial area was separated by a spinal plane connecting the anterior nasal spine (the SNA point) with the SNP point located on the posterior nasal spine. This plane is the upper jaw base plane. The other line was the mandibular plane (MP) passing along the lower convex points of the lower jaw body. This is the lower jaw base plane. These planes intersected at the C point shaping the so-called gnathic angle, which was used in our further study to draw radial lines to the points of the jaw apical bases, in particular to the Downs subspinal point of the (A) and the supramental B point, thus shaping the interalveolar angle.

Camper's horizontal (CH) connected the anterior nasal spine (SNA) point to the point of the external auditory canal base (lower edge).

The occlusal plane was drawn following the standard procedure by connecting the incisal point (the middle of the medial incisors overlap) with the point located at the top of the vestibular distal odontomer of the second upper molar. Besides, we suggested drawing the said plane from the C point as the bisector of the interalveolar ACB angle (Fig. 1).

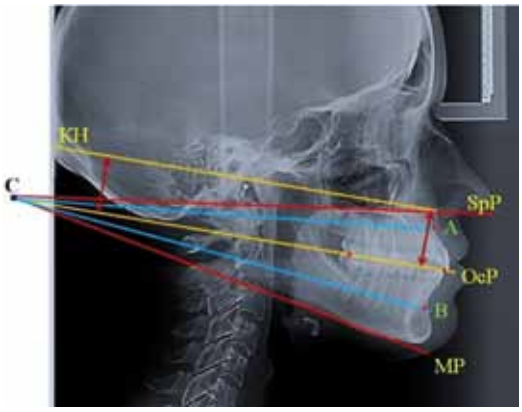

Fig. 1. *Specific features of the facial gnathic horizontal lines location in case of permanent teeth physiological occlusion*

The method proposed for constructing the occlusal plane allowed detecting vertical occlusion issues (symmetric and asymmetric) both in the lateral and anterior segment of the dental arches.

To identify the parallelism of the occlusal and Camper's horizontals, vertical measurements were taken between the lines in the anterior and posterior head parts. The conformity was assessed based on two meets / does not meet criteria, which required no extra statistical analysis methods.

RESULTS AND DISCUSSION

In people with physiological occlusion, the occlusal plane location corresponds to its construction according following the generally accepted method. In addition, the occlusal plane is parallel to Camper's horizontal, whereas the distance between the lines in

the anterior part of the head matches the size in the distal area for all types of the face gnathic part (Fig. 2).

People with vertical occlusion issues, however, had significantly different values, depending on the research methods employed. The construction of the occlusal plane, for instance, following the generally accepted method, namely, through the interincisal point and the distal vestibular tubercle of the second molar, differed from the proposed construction method (i.e. the gnathic angle bisector) (Fig. 3).

When dealing with dental arch issues combined with vertical deformations (Popov-Hodon phenomenon, dentoalveolar extension of antagonists), constructing the occlusal plane based on the method in question proved to offer an advantage, too (Fig. 4).

In case the traditional construction method was employed, too, the distal point of the occlusal plane did not coincide with the gnathic angle top. The distance between the Camper's horizontal and occlusal

Fig. 2. *A — the vertical growth of the jaws (mandibular angle, 128°); B — the neutral growth type of the jaws (mandibular angle, 119°); C — the horizontal type of growth (mandibular angle, 113°)*

Fig. 3. *Specific features of the facial gnathic horizontal lines location according to the generally accepted research methods (a) and following the proposed method (b) for abnormal vertical occlusion in the chewing teeth area*

In case of employing the traditional construction method, the distal point of the occlusal plane failed to coincide with the gnathic angle top (C point), while the distance between Camper's horizontal lines and the occlusion line in the anterior area did not match the distance in the distal part (in the figure, the scale of the mismatch indicated with a yellow arrow). The construction of the occlusal plane following the proposed method, fell within the physiological occlusion values and revealed the malocclusion in the vertical direction, which allows claiming this method can be employed to construct the occlusal plane in case of abnormal occlusal ratio.

line in the anterior part did not correspond to the distal part distance (yellow arrow).

The construction of the occlusal plane following the method we proposed matched the physiological occlusion parameters and showed the vertical occlusion anomaly, which allows this method to be recommended for constructing the occlusal plane for lengthier dental arch defects combined with vertical occlusion issues.

When systematized, the obtained data is a sufficiently convincing proof to support the idea that the proposed method can be used when dealing with various maxillofacial pathologies, as well as it can

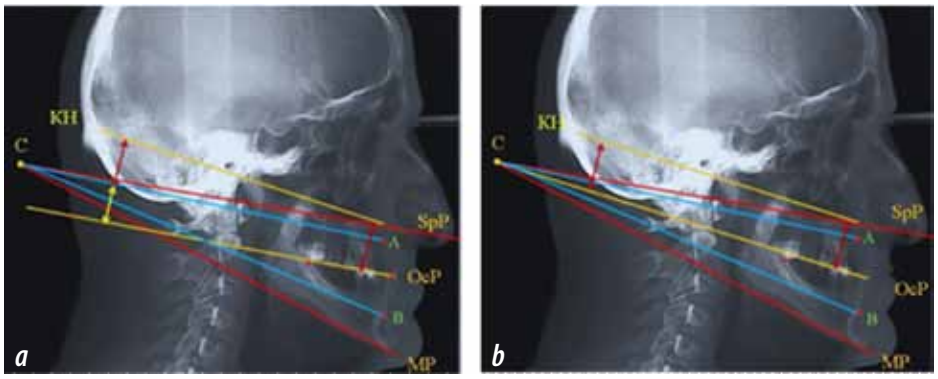

Fig. 4. Specific features of the facial gnathic horizontal lines location according to the generally accepted methods (a) and following the proposed method (b) for dental arch issues complicated by dentoalveolar extension of antagonists

prove useful when trying to develop the right tactics for comprehensive treatment.

CONCLUSIONS

1. Identifying the correct location of the occlusal plane is a task of prime importance in clinical dentistry when planning prosthetic and orthodontic treatment for patients with vertical occlusion issues, both in the lateral and in the anterior segments.
2. Improving the diagnostic reliability of various vertical occlusal anomalies, as well as forecasting acceptable functional and aesthetic outcomes for orthodontic and prosthetic treatment requires a comprehensive cephalo-, gnathic- and profilemetric examination.
3. The method developed for constructing the occlusal plane does not depend on the incisors' or the second permanent molars' position, while this fact can be used to identify the scale of the vertical deformation in the dental arches.
4. It is reasonable to employ the proposed method when determining the prosthetic plane in people with extended dental arch forms, as well as in case of complete absence of teeth.
5. Clinical and X-ray explanation for the orientation of the occlusal plane subject to the bisector of the gnathic angle allows programmed changing of the teeth position when recreating the occlusal plane through orthodontic and prosthetic treatment, i.e., its individualization. If recreated properly, the occlusal plane will allow constructing a balanced articulatory relationship and preventing functional disorders affecting the TMJ.

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DEVELOPMENT OF THE PRECISION DEVICE FOR TARGETED DELIVERY OF MEDICATION AND CREATION OF ISOLATED RESERVOIRS IN THE WEDGE-SHAPED LESION

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ABSTRACT — This study proves the necessity of using new minimum intervention tooth-preserving technologies and their implementation methods in hard dental tissue pathology treatment, in particular, wedge-shaped defects within enamel. Personalized approach to choosing the treatment method for this type of pathology is updated. The study prioritizes the pathogenetic mechanisms of this process, taking into account morphofunctional changes in enamel. Changes in architectonics of tooth enamel and its elemental composition are studied and discussed. A method of delivering the medication directly into the lesion is suggested.
The objective of this study was to develop a precision device for targeted delivery of medication and creation of isolated reservoirs in the wedge-shaped lesion. Materials: slices of teeth removed due to orthodontic indications. Methods: experimental, analytical, statistical, sociological, electron microscopy.
The scientific basis and principles of the research concept are based on the data on microstructural transformations, changes in the elemental composition of the tooth with a wedge-shaped defect. It is proved that oxygenation increases in a wedge-shaped lesion while the amount of fluorine and carbon compounds decreases, leading to the presence of such non-specific microelements as sulfur. The results obtained are the basis for the application of a targeted and personalized algorithm for treating this pathology, using additive technologies and 3D printing.

INTRODUCTION

The global scientific community has proved in theory, and dentists have confirmed it in practice that the incidence of hard dental tissue disease, both before and after tooth eruption, tends to increase [1, 3]. Based on the data from foreign scientists, carious lesions of hard dental tissue are diagnosed in 98% of the world population [2], while the incidence of non-carious lesions forming after tooth eruption has increased significantly and has reached 60% in some of the Russian regions and 82% in the world [3, 4, 5]. At the same time, this pathology is becoming more prevalent in younger people [3, 6, 7], with 53.6% of people being diagnosed with this pathology at the age of 21 to 35 years old [3] which makes it not only a medical, but also a socio-economic issue [1, 2, 4].

The diagnostic difficulty and the low efficiency of treatment at earlier stages are caused by the lack of consensus regarding the etiology, pathogenic mechanisms [4] and the treatment strategy, and depend on the intensity of destructive changes in the enamel structure, as well as the oral cavity conditions [5]. Most of the existing treatment methods do not provide the necessary long-term effect and require follow-up visits and additional treatment courses, as the disease state worsens and complications appear [3, 4,5, 6]. Moreover, the application of such methods leads to discomfort in the oral cavity of patients, as well as aesthetic defects on the enamel surface [3, 5, 7]. In order to solve this problem, it is necessary to find new minimum intervention tooth-preserving technologies and methods, and to develop a personalized approach to choosing the treatment method in each specific clinical situation [4, 5].

OBJECTIVE

Development of the precision device for targeted delivery of medication and creation of isolated reservoirs in the wedge-shaped lesion at initial stages.

MATERIALS AND METHODS

We have carried out a controlled, guided, experimental in vitro study, aimed at studying enamel architectonics, and its elemental composition in a wedge-shaped lesion, and subsequently analyzing e-copies of the enamel structure. We focused on the initial symptoms of a wedge-shaped defect because it determines the choice of non-invasive technologies. The study was conducted at a laboratory for electron microscopy and small-angle X-ray diffractometry using a Quanta 200i

3D FEI scanning electron microscope (USA) with a energy dispersive spectroscopy system (Fig. 1).

Fig. 1. *A Quanta 200i 3D FEI scanning electron microscope*

The study materials were slices of teeth removed in vitro due to orthodontic indications with a HM 450 microtome and having a wedge-shaped defect on their surface. We analyzed the results of e-copies of teeth slices, registered changes in enamel architectonics (represented by fissures along the enamel columns) and pores in the lesions (Fig. 2), and visualized the enamel lesion demineralization area (Fig. 3)

The enamel elemental composition in a wedge-shaped lesion (Fig. 4) showed an increase in oxygenation, decrease in the amount of fluorine, presence of sulfur (which most likely proves a change in the crystal structure of hydroxyapatite) as well as decrease in the amount of carbon compounds. The calcium-phosphorus ratio was 1:0.7 which indicates a demineralization process.

The obtained results were subjected to statistical processing which showed statistical confidence ($p < 0.05$, confidence coefficient — 95%).

The obtained results were used to develop a method for mathematical modelling-based transfer of lesion parameters to a 3D model using mathematical formulas, to determine the amount of damaged tissues, to calculate the optimal amount and size of cavities required to deposit the medication in the hard dental tissue lesion, to develop a technology for computer modelling of a personalized 3D tooth lesion model, to develop a method for creating pores of any complexity, shape and size on the 3D model prototype of a personalized mouth guard for high-precision delivery and deposition of medication, and to develop a technology for SLA 3D printing of a jaw model with a medication reservoir prototype.

The following equipment was used for the study:

An SLA 3D printer — Formlabs Form 2 (USA) (Fig. 5), a 3D scanner — Shining 3D (Fig. 6)

Fig. 2. *Enamel surface in the wedge-shaped lesion area, fissures and pores in the lesion area; SEM, 3000x magnification*

Fig. 3. *Enamel demineralization in the wedge-shaped lesion, SEM, 3000x magnification*

Element	Wt%	At%
CK	22.27	32.57
NK	07.92	09.94
OK	38.22	41.96
NaK	00.62	00.47
MgK	00.52	00.37
SiK	00.10	00.06
PK	10.09	05.72
SK	00.11	00.06
ClK	00.26	00.13
CaK	19.88	08.71
Matrix	Correction	ZAF

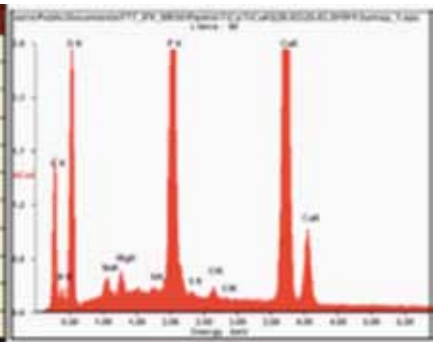

Fig. 4. *Enamel elemental composition of a tooth with a wedge-shaped defect*

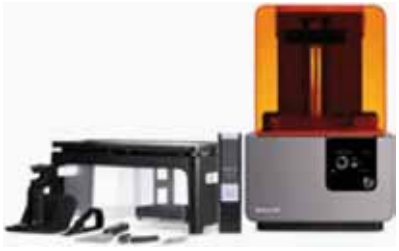

Fig. 5. *An SLA 3D Printer – Formlabs Form 2 (USA)*

Fig. 6. *A 3D Scanner – Shining 3D*

The technological process consists of the following stages:

Stage 1: taking the impressions of the upper and lower jaw, using silicone material on plastic impression trays, and model casting (Fig. 7). ***Stage 2:*** 3D scanning of the stone jaw model and obtaining a virtual 3D prototype of such model (Fig. 8). ***Stage 3:*** loading the virtual prototype into the Autodesk Meshmixer software (USA) and hybrid parametric modelling of the pathological lesion on the 3D model of a patient's damaged tooth (Fig. 9). ***Stage 4:*** modelling the microspheres for local retention of the medication. Performing a boolean operation, in order to combine the area of the pathological lesion and the reservoir precisely filled with one layer of microspheres (Fig. 10). ***Stage 5:*** exporting the jaw models created using the software in .stl format so that they could be printed using photopolymer material on a SLA 3D printer (Fig. 11). ***Stage 6:*** using the vacuum forming method, in order to produce an individual device using elastomeric thermoplastic polyurethane (Fig. 12), which is then grinded, polished and treated with an antiseptic solution. In order to assess the precision of jaw models produced using the newly developed technology, a study was conducted which included 38 patients. A randomization method (random number generator) was used to divide them into 2 groups: 1 — models made using the newly-developed algorithm (n=19), 2 — models made using the traditional method (n=19). The study provided statistically significant proof ($p < 0.05$) that the localization parameters of reference points for targeted medication delivery on jaw models were most precise in group 1. Thus, the developed technology allows to ensure precise planned parameters of non-invasive treatment of a tooth with a wedge-shaped defect within enamel.

CONCLUSION

The personalized non-invasive approach to choosing the treatment method for a wedge-shaped defect within enamel will allow to use an individual device for minimum intervention tooth-preserving treatment, designed for targeted delivery of medication to the lesion.

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Fig. 7. An impression of the lower jaw and a cast stone model

Fig. 8. 3D scanning of a jaw stone model using a Shining 3D scanner

Fig. 9. Hybrid parametric modelling of the pathological lesion, "Autodesk Meshmixer" (USA)

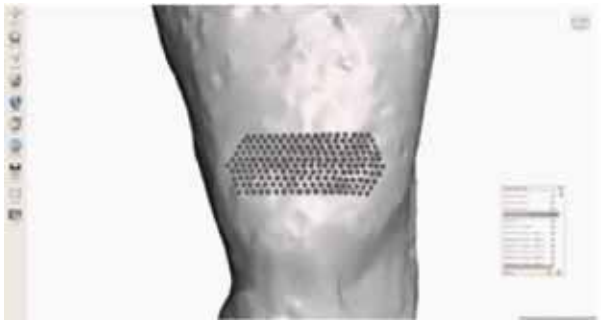

Fig. 10. Modelling the microspheres in the pathological lesion area

Fig. 11. Printed models of the upper and lower jaws, made using the newly developed technology

Fig. 12. A ready individual device made of elastomeric thermoplastic polyurethane (DURAN®, Scheu Dental, Germany)

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CLINICAL EFFECTIVENESS OF OCCLUSAL SPLINTS IN PATIENTS WITH FUNCTIONAL OCCLUSAL PROBLEMS

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ABSTRACT — Occlusal disorders caused by missing teeth and without timely and proper treatment, lead to poorly diagnosed pathology of the masticatory muscles and the temporomandibular joint. Our study included 31 patients with dental defects, impaired canine guidance, and TMJ pathology. With a specifically developed computer program we accomplished the differentiation of various degrees of muscle and joint dysfunction in the temporomandibular joint. The results obtained by examining the patients prior to, and after the treatment, provide evidence to the effect that the modified occlusal splint has on the upper jaw.

KEYWORDS — muscle and joint dysfunction, temporomandibular joint, canine guidance.

INTRODUCTION

A common dental pathology affecting adult population involves functional occlusal disorders, the prevalence of which reaches 40–70% in Russia. Most often, it is the first lower permanent molars that are removed, and their share in the entire pool of all removed teeth is 9.38% [4, 13]. Occlusal disorders affect the lower jaw biomechanics, while the front teeth – given the loss of the lateral ones — have to compensate for a function that is not conventional in this case, namely, a masticatory function. Long-term occlusion defects lead to change in the functional and static occlusion, which comes along with disturbed canine guidance or the teeth group contact on the working side [5, 11, 12, 17–19, 22].

Occlusal interferences caused by missing teeth is accompanied by an increase in the number of chewing movements and the time that a single act of chewing takes, the result of that, in turn, being compensatory contraction and hyperactivity of the chewing muscles, followed by poor metabolism and the muscle pain syndrome [1, 6, 7, 10, 21, 23].

Comprehensive treatment offered duly to patients with occlusal defects helps relieve the symptoms of the TMJ muscle-and-joint dysfunction, which has already been proven through numerous studies, held both nationally and internationally [2, 3, 8, 9, 14–16, 20].

Aim of study: to improve the treatment effectiveness in patients with lateral occlusion interferences complicated by the temporomandibular joint dysfunction, as well as by disturbed canine guidance.

MATERIALS AND METHODS

To achieve the goal set for the study, 31 patients suffering from lateral occlusion defects, disturbed canine guidance and symptoms of the temporomandibular joint dysfunction were examined at the Department of Orthopedic Dentistry of the Saratov State Medical University. The main group included 16 (51.61%) females and 15 (48.39%) males. The control group consisted of 30 patients (19 females and 11 males) featuring orthognathic occlusion, intact dentition, and no symptoms of muscle-and-joint dysfunction. A written voluntary consent to participate in the study was obtained from each of the patients.

The planning and selection of rational treatment methods were carried out based on the data obtained from the outcomes of the basic and special examination methods. The severity of the temporomandibular joint dysfunction was identified using specifically developed software — Program for Identifying the Degree of Muscle-and-Joint Dysfunction (Certificate of Official Registration for Software, #2016614212 from 04/18/2016). The functional status of the masticatory and temporal muscles was evaluated using the surface electromyography method.

While aiming at restoring the occlusal contact and canine guidance, the comprehensive treatment relied on an occlusal splint was fixed on the upper jaw, whereas the splint was modified following some specific features proposed by the authors (Utility Model Patent #175428).

The statistical analysis was performed using the Statistica 6.0 and Microsoft Office Excel 2016

software, whereas the Student's parametric t-test was employed to determine the significance of the difference between the two averages.

RESULTS AND DISCUSSION

All the patients in the main group had uni- and bilateral occlusal interferences as well as terminal defects of the lateral guidance, including disturbed canine guidance and symptoms of the muscle-and-joint dysfunction in the temporomandibular joint.

External examination of the patients belonging to the main group with their teeth closed in the conventional occlusion, allowed identifying facial asymmetry in 61.29 % of the cases. Restricted vertical movements in the lower jaw were observed in 77.42% of the patients, while lateral and anterior movements accounted for 74.19% of the patients. Premature contacts in the static and dynamic occlusion were observed in 70.97% of the patients. Besides, all the patients featured disturbed canine guidance.

Painless palpation of the masticatory muscles was observed in 64.52%, and the temporomandibular joint — in 61.29% of the patients. The TMJ palpation resulted in unpleasant sensations in 25.81% of the patients, causing pain in 12.90% of the cases. Painful palpation of the masticatory muscles was observed in 35.48% of the patients involved in the study. Following the auscultation results, joint noise was detected in 61.29% of the patients.

The software used to detect the degree of the muscle-and-joint dysfunction reported mild dysfunction symptoms in 35.48% of the patients of the main group; moderate symptoms in 38.71% of the patients and severe symptoms in 25.81%.

The occlusiogram index determined subject to the method by N. Khamitova (1986) in patients with mild muscle-and-joint dysfunction was 76.89%; with an average degree of the dysfunction it was 68.28%, and in cases of a severe degree of the dysfunction the index value was 54.86%.

Spontaneous activity of the masticatory muscles remaining in a state of relative physiological rest, according to the electromyographic study (EMG), was observed in 6.45% of the patients, and reached 85 μV; in 9.68% of the patients — 170 μV. All the patients revealed a significant ($p < 0.001$) decrease in the bioelectric activity of the masticatory and temporal muscles if compared with the control group (see Table 1).

The treatment of patients with lateral occlusion defects, disturbed canine guidance and symptoms of the muscle-and-joint dysfunction included two stages. At Stage 1 (preparatory), a modified splint for the upper jaw was used to restore occlusal relationship and canine guidance. After the masticatory muscles and the temporomandibular joint adjustment (based on the electromyography data), all patients underwent rational prosthetics using removable and non-removable dentures.

Upon analyzing the data on the time of the occlusal splint being used by the patient, a conclusion was made that the time of getting adjusted to the restored occlusal dentition relationship in patients with a mild muscle-and-joint dysfunction was significantly shorter compared to patients with moderate and severe degrees, and averaged 27.27 ± 4.29 days. In patients with a moderate degree of the TMJ dysfunction, adjustment took an average of 35.50 ± 8.23 days; in cases of a severe degree — 81.75 ± 14.12 days.

Following the treatment, the TMJ muscle-and-joint dysfunction symptoms disappeared in 48.39% of the patients. The number of patients with mild dysfunction went down by 3.22%, which could be explained by the shifting from a moderate to a severe degree. During that, the number of patients with a moderate TMJ dysfunction decreased by 22.58%, with a severe degree — by 22.59% of the cases observed.

After the treatment, a reliably significant ($p < 0.001$) increase in the average action potential amplitude of the masticatory and temporal muscles was detected subject to the electromyographic data (see Table 1). The obtained data had normal indicators and revealed no significant differences when matched against the same indicators for the patients in the comparison group.

Following the rational comprehensive treatment, the occlusiogram index rose from 67.87 ± 2.09% to 86.15 ± 1.51% ($p < 0.001$).

Matching the data from the respective literature focusing on this pathology treatment terms, while using occlusal splint, against the results of our own research as described above, allows concluding that the proposed modification of the occlusal splint is more effective if compared to its counterparts.

CONCLUSION

When examining patients with occlusion defects, it is not enough to identify signs of the TMJ muscle-and-joint dysfunction alone, yet special attention should be paid to the severity of these symptoms, as well as they are to be taken into account when designing a comprehensive treatment plan. The degree of the TMJ dysfunction symptoms severity can be identified employing the software that has been developed specifically for this purpose.

The study outcomes provide the evidence of the efficacy of the modified occlusal splint installed on the upper jaw thus to restore the canine guidance and treat the TMJ muscle-and-joint dysfunction in patients

Table 1. *Functional specifics of masticatory and temporal muscles, before and after the treatment, EMG data, μV*

Muscle functional status	EMG period	Masticatory muscle		Temporal muscle	
		right	left	right	left
Contraction	Before treatment	248.93 ± 13.17	244.96 ± 12.49	277.96 ± 14.28	296.54 ± 14.05
	After treatment	325.61 ± 13.74	325.96 ± 13.86	359.83 ± 12.26	359.80 ± 11.92
Chewing	Before treatment	425.25 ± 14.98	423.45 ± 14.51	344.45 ± 14.44	342.38 ± 14.18
	After treatment	499.61 ± 13.61	504.77 ± 13.59	406.64 ± 12.28	405.67 ± 12.26

with disturbed lateral occlusal surfaces. The adjustment of the masticatory muscles to the new functional context has been proven through a changed action potential amplitude of the masticatory, temporal, and supra-lingual muscles on the electromyograms. During that, the masticatory muscles adjustment occurred within a shorter time in patients with a mild degree of the temporomandibular joint dysfunction rather than in patients suffering from moderate and severe degrees of the issue.

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PERSONIFIED APPROACH TO SELECTING A METHOD FOR BRACKET POSITIONING WITH 3D TECHNOLOGY

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ABSTRACT — The concept of creating the so-called esthetic smile is still subject to debate. While there is no optimal way to achieve the smile esthetics, this fact drove the idea of improving the available algorithms employed for the treatment of dentofacial anomalies. Smile reconstruction in orthodontic treatment is a complex process, which is subject to certain rules and laws, and takes an interdisciplinary approach from dental specialists. When dealing with dental anomalies, one of the most important practical components is the correct method of the bracket positioning. Based on the analysis of the options offered currently by digital technologies, and the negative outcomes of orthodontic treatment, the following aim was set for the current study – to improve the algorithms employed to select individual methods of bracket personalized placement as per each clinical situation in particular. The methods used through the study included: clinical, digital, statistical, and analytical one. Following the criteria of the esthetic smile, the location, the shape and the structure of the teeth of a particular patient, an individual method for bracket positioning was developed, the final outcomes of that being a smile with individual parameters. This method allows achieving a maximum esthetic result. The proposed technique is the method of choice in each specific clinical situation and can be used depending on the indications.

KEYWORDS — brace, 3d-technology, positioning, dentofacial anomalies.

INTRODUCTION

High prevalence of malocclusion, related complications through treatment [1-6], improperly fixed brackets [7], imperfect equipment [8], as well as inefficient conventional methods used to position brackets — all these explain the search for newer ways to treat dentofacial anomalies. The core of orthodontic treatment is the tooth movement caused by various forces. The magnitude and direction of the force depends on the device design and on the mode it uses, which is opted for by the doctor. Employing the Edgewise technique for treating patients with abnormal shape and size of dental arches, the orthodontist determines the treatment methods, the brackets specification as well as the size of the metal arch [9–12].

Nowadays, apart from solving problems of function, Orthodontics pays great attention to esthetics [13], whereas an esthetically appropriate outcome is not always achievable in this area. Offering a rational set of treatment to patients with occlusive disorders associated with dentition defects is an important problem within interdisciplinary dentistry [14, 15]. The basic role for an effective treatment outcome lies in a personalized approach and an individualized choice of the braces positioning method, thus aiming at reconstructing the smile [16–19]. The final outcome visualization done through virtual positioning of braces will allow evaluating its effectiveness as well as making sure that the method selected for the brace positioning in a specific clinical situation was the right one, even prior to fixing the brace system.

Aim of study:

to improve the algorithms for selecting individual methods of personalized bracket positioning in each clinical situation.

MATERIALS AND METHODS

The dental anomalies were studied at the Dentistry Department, Faculty of Postgraduate Training of the Privolzhsky Research Medical University (Nizhny Novgorod, Russia). The study involved 15 patients of both sexes aged 11 to 20 with dental anomalies. A signed consent was obtained from each patient agreeing voluntarily to join the study as well as to follow the proposed treatment plan.

Materials

1. Digital models of jaws.
2. Maestro 3D Ortho Studio software.
3. Bracket positioning methodology by MBT, Pitts, Alexander.
4. Esthetic smile evaluation criteria.

Methods

1. Clinical.
2. Digital.

3. Analytical.
4. Statistical.

RESULTS

Here below we are offering a clinical case presentation in order to disclose the algorithm developed for arriving at an effective esthetic outcome.

Patient K., 11 y.o.; diagnosis: distal bite (07.20)

1. Clinical stage

Visual examination: the face configuration — not changed; skin — clean, with no visible pathological changes; mouth opening — unobstructed; TMJ — normal.

Oral cavity examination: the lateral part features closure of the molars on the right and left (Class II by Angle); V-shaped upper dental arch; trapezoidal lower dental arch; the sagittal gap within 4 mm; the upper central incisors overlap the lower ones by more than 2/3; diastema observed; oral mucosa — pale pink, moderately wet.

Photoprotocol (Fig. 1).

Model analysis (Fig. 2).

X-ray examination (Fig. 3)

McLaughlin telerentgenogram calculation (using the Onix Ceph software) (Fig. 4).

Diagnosis set based on the clinical examination data: distal bite (K07.20).

The conventional treatment method implies the installation of a bracket system subject to one of the three standard methods, each of them being failing to prove perfect and, therefore, featuring both its own advantages and disadvantages.

2. Digital stag

3D scans of the patient's jaw models were obtained with a 3D-scanner, the entire procedure performed in the Laboratory for Additive Technologies of Privolzhsky Research Medical University (Fig. 5).

To select the optimal treatment method and improve the previously approved algorithms, virtual positioning of brackets was done according to the three standard methods (MBT, Pitts, Alexander) with the Maestro 3D Ortho Studio software (Fig. 6).

Each of the positioning techniques featured its own height of the brackets on the teeth. Depending on the bracket location, the teeth could move to differ-

Fig. 1. *Photoprotocol of the oral cavity, patient K. 11 years old*

Fig. 2. *Models of the patient's jaws*

Table. 1. *Biometric study of jaws diagnostic models*

Index before treatment:	Result before treatment:	Norm:
Pont	upper jaw: premolar – 33.5 molar – 46 lower jaw: premolar – 32 molar – 41.5	premolar – 35 molar – 43.75
Tonn	1,55	1,33
Bolton	For 12 teeth: 87.6% For 6 teeth: 74.4%	For 12 teeth: 91.3% For 6 teeth: 77.2%
Deficiency of space in the dentition	Upper jaw: 4mm Lower jaw: 4mm	Upper jaw: 0 Lower jaw: 0

Fig. 3 *Orthopantomogram and teleroentgenogram of patient K., 11 years old*

variable	description	norm value	value	difference	deviation	verbal
SNA	SNA angle	82,0±3,5°	82,4°	0,0		
SNB	SNB angle	80,0±3°	75,5°	-1,5		
ANB	ANB angle	2,0±2,4°	6,9°	+2,5		
A / NP	distance of A-point to Nasion perpendicular	0,0±3,1mm	0,4mm	0,0		
Po / NP	distance of Pogonion to Nasion perpendicular	-4,0±5,3mm	-14,8mm	-5,5		
WITS	distance of A and B on occlusal plane	0,0±1mm	13,0mm	+12,0		
SN / MP	angle between S-N and mandibular plane	32,0±5°	35,7°	0,0		
FH / MP	angle between FH and mandibular plane	26,0±5°	27,9°	0,0		
PP / MP	angle between palatal and mandibular plane	28,0±5°	30,9°	0,0		
PP / OP	angle between palatal and occlusal plane	10,0±4°	9,8°	0,0		
MP / OP	angle between mandibular and occlusal plane	17,4±5°	21,1°	0,0		
U1 / A Po	angle between axis of U1 and A-Po	6,0±2,2mm	17,0mm	+8,8		
L1 / A Po	angle between axis of L1 and A-Po	2,0±2,3mm	-6,1mm	-5,8		
U1 / PP	angle between axis of U1 and palatal plane	110,0±5°	118,1°	+3,1		
L1 / MP	angle between axis of L1 and mandibular plane	95,0±7°	87,9°	-0,1		
U1 / OP	angle between axis of U1 and occlusal plane	57,3±7°	52,1°	0,0		
L1 / OP	angle between axis of L1 and occlusal plane	72,0±5°	71,0°	0,0		

Fig. 4. *Calculation of McLaughlin teleroentgenogram using Onix Ceph software*

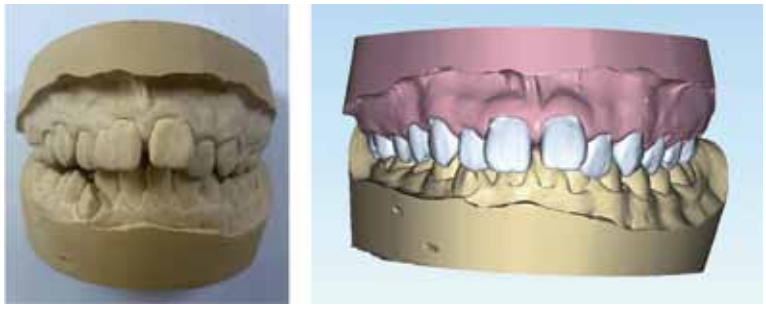

Fig. 5. *Plaster (a) and virtual (b) diagnostic models of the patient's jaws*

ent positions. Further, the teeth virtual movement based on specified parameters was performed automatically, whereas the final result of the planned treatment was visualized on the PC (Fig. 7).

The results obtained were evaluated in terms of meeting the aesthetic smile criteria (Table 2). None of the methods met the esthetic smile criteria, so, based on those, virtual positioning of the brackets was performed according to the individually developed method (Fig.8), following the analysis of standardized methods for bracket placement.

Next, the teeth virtual movement with the specified parameters was also carried out automatically, with the final result visualized (Fig. 9).

3. Analytical stage — matching the obtained smile against the esthetic smile criteria (Table 3).

Apart from the esthetic parameters, the individual method for bracket positioning was employed to model the orthognathic bite for the patients, which facilitates complete functions of speech, swallowing and chewing. No supercontact was observed in any of the occlusions.

CONCLUSION

Based on the study outcomes, we may conclude that creating the esthetic smile and improving the function requires planning the treatment outcome through building a 3D-model as well as selecting optimal bracket positioning following an individual method. The final outcome is the best-balanced smile and orthognathic bite.

Therefore, the treatment algorithm with individual bracket positioning has accomplished the smile maximally matching the criteria of an esthetic smile.

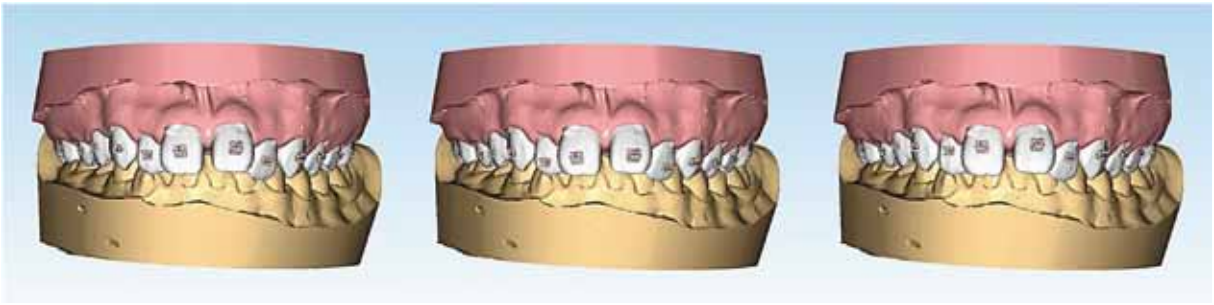

Fig. 6. Virtual positioning of brackets using three standard techniques MBT, Pitts, Alexander

Fig. 7. Virtual movement of teeth with specified parameters when positioning brackets according to standard techniques

Table. 2. Comparative characteristics of the criteria for esthetic smile and the parameters of the received smile options with standard methods of bracket positioning

Criteria	Positioning by MBT	Positioning by Alexander	Pitts positioning
Length of central and lateral incisors	-	+	-
Location of zeniths	-	-	-
Condition of the gums and interdental spaces	+	+	+
Axes of teeth	+	+	+
Interdental contact areas and points	+	+	+
Gaps between cutting edges	+	+	+
Individual and total sizes of teeth	+	+	+
Teeth proportions	+	+	+
Shape, color and micro-relief of teeth	+	+	+
Teeth position	+	-	-
Smile line	+	-	-
Upper and lower lip lines	+	-	-

The proposed method offers the following advantages:

1. Virtual bracket placement at the stage of treatment planning aimed at a predictable outcome.
2. Lower level of error due to the teeth movement 3D modeling.
3. Evaluation of the expected smile prior to the treatment and fixing the brackets.
4. Possible development of a key for bracket placement in the patient's mouth.

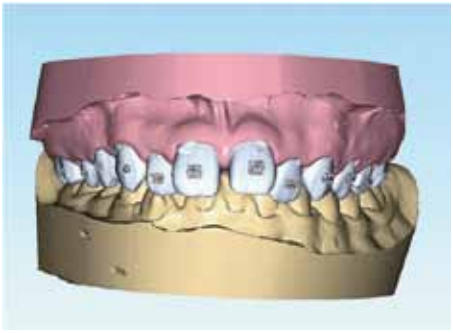

Fig. 8. Virtual positioning of braces according to an individual technique

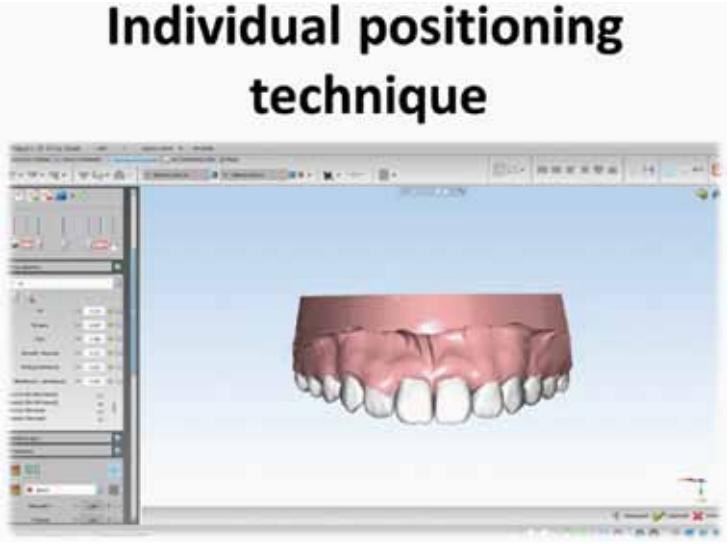

Fig. 9. Virtual movement of teeth with preset parameters when positioning brackets according to an individual technique

Table 3. Comparative characteristics of the criteria for an aesthetic smile and the parameters of the received variants of a smile with an individual technique for installing brackets

Criteria	Individual positioning
Length of central and lateral incisors	+
Location of zeniths	+
Condition of the gums and interdental spaces	+
Axes of teeth	+
Interdental contact areas and points	+
Gaps between cutting edges	+
Individual and total sizes of teeth	+
Teeth proportions	+
Shape, color and micro-relief of teeth	+
Teeth position	+
Smile line	+
Upper and lower lip lines	+

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CLINICAL EVALUATION OF ORAL CAVITY STATUS IN PATIENTS WITH KERATINIZATION DISORDERS

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ABSTRACT — Pathological processes associated with disturbed keratinization and risks of cancer tend to become more common and affect younger people. However, the currently available diagnostic methods are not always reliable, which explains the need to further study this. The aim of the study was to improve the efficiency of early diagnosis of keratoses of the oral cavity under autofluorescence spectroscopy incorporated into the proposed screening algorithm. The examination methods involved clinical, luminescent, analytical, statistical evaluation. The study allowed obtaining optical images through autofluorescence stomatoscopy in patients with keratinization disorders, identifying their color range within affected and healthy tissues, as well as confirming their reliability employing the Color Spatioplotter ver 2.46 software. The tested autofluorescent stomatoscopy method featured sufficient sensitivity (98%) against relative specificity (75%), with prediction of a positive outcome (100%).

KEYWORDS — keratoses, autofluorescence spectroscopy, optical images.

INTRODUCTION

Pathological processes associated with keratinization disorders occur in 13.5±1.67% of all patients affected with diseases of oral mucosa (OM) [2, 6, 8, 9, 12]. According to the WHO data, OM leukoplakia ranks first (80%) among keratoses. Besides, it tends to affect a growing number of people, and is diagnosed most often in middle aged male adults. Per 100% of leukoplakia cases, OM issues account for 5.6% of precancerous conditions and 4.8% of early cancer, these being patients with verrucous and erosive-ulcerative leukoplakias, where the precancerous condition can transform into invasive squamous cell carcinoma [10, 14, 17, 21, 23]. Epidemiological studies show that oral lichen planus (OLP) accounts for 30–35% of all oral mucosa diseases, affecting 0.1–2% of the population, more often in women aged 40 to 65 [18, 20]. The hyperkeratotic form of OLP also belongs to facultative precancerous diseases [11, 22].

The etiology of these diseases has not been investigated fully yet [15]. These conditions display no notable pain syndrome in the early stages. In this very period patients have a low motivation for undergoing dental treatment, which, in turn, contributes to the disease progression as well as adds to the risk of developing malignancy [19]. However, currently there are no universal methods for early diagnosis of these pathologies at the clinical examination and the screening techniques have not been commonly applied yet [3, 5, 24–29]. Therefore, search for tools that would help detect the first symptoms of pathological processes at the preclinical stage is a feasible task [1, 4, 7, 13, 16]. In this study we attempted to objectivize the capabilities of autofluorescence stomatoscopy as a method, which could be universally applied for early diagnosis and screening.

MATERIALS AND METHODS

To achieve the goal stated above, a clinical study was carried out involving 162 patients of both sexes aged 20 to 50 diagnosed with keratoses (OLP — 83; leukoplakia — 29), who, depending on the clinical status of the oral cavity, were divided into two groups:

Group 1 — patients with healthy oral cavity mucosa (control group) — 50 persons.

Group 2 — patients with oral cavity mucosa diseases — 112 persons.

The study implied a comprehensive dental examination of patients with OM issues, identifying increased risk areas, and evaluating the diagnostic capacity of autofluorescence stomatoscopy.

The patients underwent clinical examination subject to the following algorithm:

1. Interrogation: complaints; duration of the process; previously prescribed treatment and its result; bad habits; general somatic status.

2. Visual examination in natural and artificial light.

3. Manual examination of the lymph nodes, salivary glands, OM lesion foci — all done to identify the density, to detect infiltrate, as well as to assess the degree of the pain and its boundaries.

4. Instrumental research and index evaluation:

4.1. Oral hygiene index OHI-S (Greene J. C., Vermillion J. R., 1964);

4.2. Papillary-marginal-alveolar index (PMA);

4.3. Dentoalveolar sulcus bleeding evaluation by H. P. Miihlemann, S. Son (1971);

4.4. Community periodontal index of treatment needs index (CPITN);

4.5. K. Kojima et al. index (1985) to evaluate the degree of the tongue plaque;

4.6. Permanent teeth caries intensity index DMF.

5. The oral cavity mucosa was studied using an autofluorescent somatoscope (Manufacturer: OOO Polironik, Russia). The diode wavelength of the device employed was 400 nm, which is within the blue light spectrum that stays in the OM surface layers at a depth of 4–19 mm. The data was introduced in a dental medical record card developed specifically at the Department of Dentistry (Fig. 1).

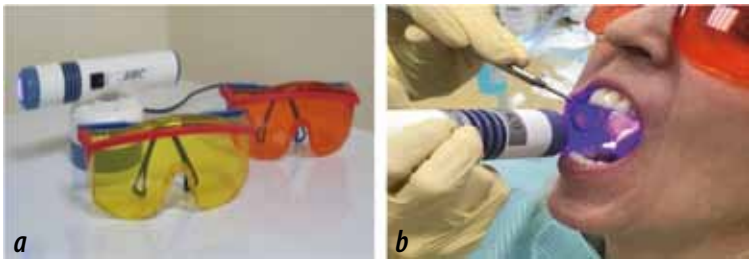

Fig. 1. *AFS: a — AFS kit; b — oral mucosa examination*

Table 1. *Index-based evaluation of oral cavity hygiene, M±m*

Investigated indices	First group	Second group
OHI-S (J.C. Green, J.R. Vermillion, 1964), (p=0,0212)	0,9±0,3	3,6±0,55
PMA (Schour, Massler, 1948) modified by Parma (C. Parma, 1960), (p=0,0392)	11±0,55	28±0,5
Groove Bleeding Index (SBI Muhlemann and Son, 1971) modified by Cowell (1975), (p=0,0412)	0,2±0,15	1,3±0,65
CPITN (WHO index), (p=0,0421)	1,3±0,09	2,9±0,12
KPU index - component "Carious teeth" (p=0,0021) - component «Filled teeth» (p=0,0354) - component «Extracted teeth» (p=0,0034)	10,5±1,5 1,9±0,2 7,3±1 1,3±0,3	14,5±2,3 4,3±0,55 6,3±0,2 3,9±1,55
Index K. Kojima	Distribution of index 0 and 1 (34 and 16 patients)	Index distribution 1-4 (41,48,52,59 patients)

Topography and coding of the OM lesion elements were performed using the Roed-Petersen and Renstrup topogram-scheme modified by O. S. Gileva et al., 2008.

6. The obtained optical images were investigated using the Color Spatioplotter ver 2.46 software in order to obtain and analyze the color code of the selected OM segment, using the LAB format, the results to be further introduced in the data bank.

RESULTS

The analysis of the complaints reported by the patients, as well as their further ranking, allowed identifying the most common ones, including a feeling of discomfort and roughness on the oral cavity mucosa (14.8%); burning sensation on the oral mucosa and tongue (7.4%), with another 10.5% of patients reporting a combined manifestation of symptoms. The timing of their occurrence and the fact the respective patients were seeking dental care much later point at a low motivation activity among the patients. Of all those patients, only 7% had turned for help to dentists previously.

Identification of exogenous and endogenous risk factors allows placing patients in outpatient observation groups at the stage of dental rehabilitation. There was a correlation detected between smoking and the occurrence of hyperkeratosis in 85.2% of cases.

On average, the age of oral cavity mucosa diseases was 1.6±1.1 months. 13% of the patients were observed to have an increase in the lymph nodes falling within the submandibular and chin groups.

The dental status in the control group differed significantly from that in the study group. Patients of Group 2, for instance, while featuring a high intensity of the carious process (14.5±2.3), the D and M elements dominance (4.3±0.55 and 3.9±1.55) ($p<0.01$), poor oral hygiene (3.6±0.55) and severe periodontal diseases, also revealed a tendency to growing hyperkeratosis.

The dental patient map we created specifically based on the modified topogram-scheme by O. S. Gileva (Roed-Petersen and Renstrup, modification by O. S. Gileva et al., 2008) enabled to detect the most common localization zones for hyperkeratoses. Leukoplakia, for instance, is typically located at the region buccal mucosa (29 patients / 41.43%), on the tongue lateral surface (17 patients

/ 24.29%), at the upper and lower jaws transitional fold (15 patients / 21.43%), and at the mandible alveolar process mucosa (9 patients / 12.85%).

Oral cavity mucosa OLP was diagnosed in 83 patients, while in 31 patients the lesion elements were observed in the retromolar area (37.39%); in 33 patients pathological changes were observed on the buccal mucosa (39.76%), in 12 (14.45%) — in the transitional fold, with another 7 patients (8.4%) having the said issues on the lower jaw alveolar process.

The oral cavity mucosa examination was performed with the autofluorescent somatoscope. Pathological processes of different nature feature different optical images, since the affected areas, even at the preclinical stage, reveal zones of dimmed fluorescence whose intensity depends on the nature of the pathology. The para- and hyperkeratosis foci act as lightening agents, which have clear boundaries.

To enhance the diagnostic reliability of this method, all the obtained optical images were processed with the standardized Color Spatioplotter ver 2.46 software with the lesion color code identified (the average value detected in 12 measurement areas, based on the patient's 5 photos).

All the studies implied identifying the color code boundaries. A healthy oral cavity mucosa, for instance, is pale pink with its average values at L=63, a=54, b=39, x=130, y=191, which corresponds to pink shades within the coordinate system. Analyzing the results obtained from patients with OM keratosis allows saying that the x values increase, while y values decrease (corresponding to the light pink spectrum).

DISCUSSION

The study outcomes serve proof to the high efficiency of the AFS-diagnostics (98% sensitivity and 75% specificity of the method).

Examining the groups of patients with healthy oral cavity mucosa and those with keratoses provided the evidence for exploiting fluorescence, which adds to the potential and diagnostic capacity of this system. Fluorescent stomatoscopy involving an AFS device allowed differentiating the pathological process at the preclinical stage, as well as to identify its true boundaries.

The study has helped identify the clinical effectiveness of using the AFS screening system developed nationally; detect OM pathological processes in the preclinical stage; evaluate the system while defining the diagnostic reliability parameters.

The AFS device used for oral cavity mucosa diagnostic purposes revealed a different spectrum of its luminescence both in case of the oral mucosa normal status and with pathological changes, which is of high diagnostic importance in terms of their differentiation.

Besides, notable is that the fluorescence stomatoscopy can be described as a method, which features non-invasiveness, a possibility to obtain diagnostic results directly at the time of the study, high accuracy and data reliability, as well as economic affordability, which could be observed through this current study.

CONCLUSION

Fluorescence stomatoscopy is an advanced technology with a high degree of sensitivity, specificity and diagnostic accuracy. Decoding the optical images using the Color Spatioplotter 2.46 software helps reduce diagnostic errors, perform early diagnosis of oral cancers and differentiate the exact boundaries of the lesion, which is crucial for further treatment.

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Table 2. *AFS diagnostic capacity evaluation*

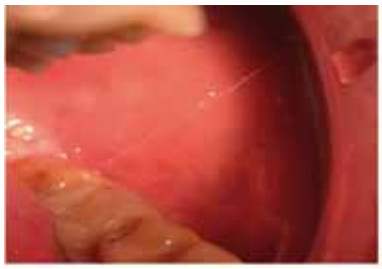
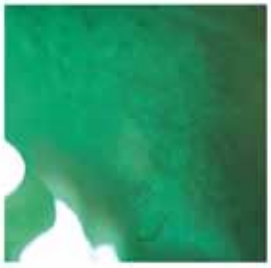
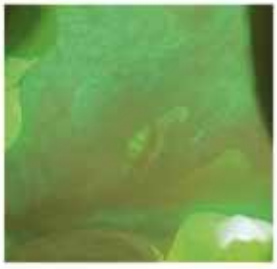
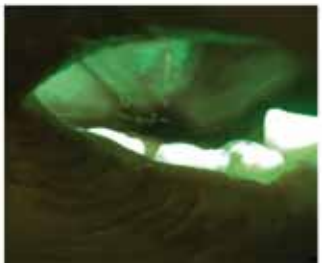
Glow	Artificial lighting	Autofluorescence
The glow of a healthy oral mucosa is registered as different shades of green light		
The foci of hyperkeratosis are determined when glowing in the form of white foci		
A focus of hyperkeratosis on the mucous membrane of the hard palate (Tuppainer's leukoplakia)		
A focus of hyperkeratosis on the buccal mucosa		
Cancer of the mucous membrane of the floor of the oral cavity is recorded as a focus of fluorescence quenching with a black and burgundy tint		

Table 3. *Color code identification in Color Spatioplotter 2.46 software*

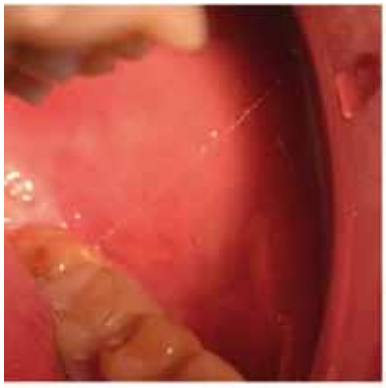
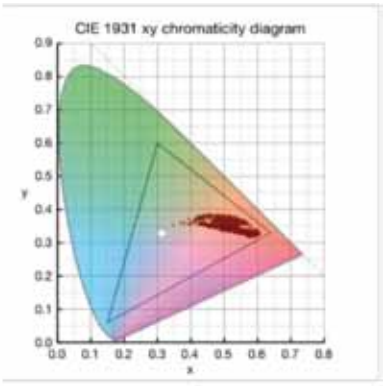
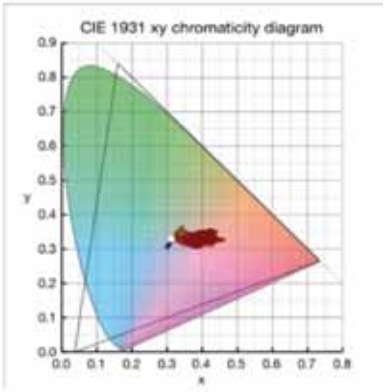
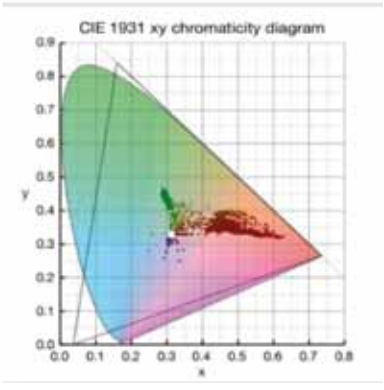
Artificial lighting	Photo in LAB format	Color code
		Healthy oral mucosa L = 63 A = 54 B = 39 X = 130, y = 191
		Site of hyperkeratosis L = 78 A = 21 B = -3 X = 194, y = 268
		Oral floor cancer L = 83 A = 135 B = 8 X = 101, y = 393

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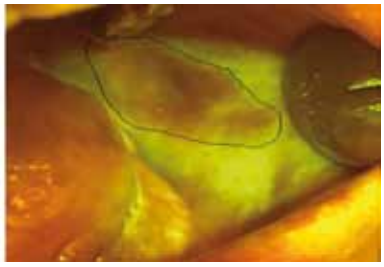
Table 4. *Identifying lesion true boundaries not visible at examination*

Artificial lighting	Autofluorescence
	

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http://dx.doi.org/10.35630/2199-885X/2021/11/1.31

THE EFFICIENCY OF ORTHODONTIC TREATMENT OF CLASS II MALOCCLUSION IN CHILDREN WITH B -THALASSEMIA MAJOR

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ABSTRACT — Aims: Evaluation of the effectiveness of orthodontic treatment of Class II malocclusion with the Twin-block appliance in children withβ-thalassemia major. Methods: The study was conducted with 49 patients with Class II malocclusion aged 10-14 years. The control group included 23 healthy patients. The main group included 26 patients with β-thalassemia major. Patients had received orthodontic treatment with a Twin-block appliance. The duration of orthodontic treatment was 1.5–2 years. Results: In both groups, a statistically significant increase in the SNB angle was observed. Subsequently, the ANB angle was normalized. The effective length of the maxilla growing and mandibular length increasing was observed. Overjet distance is decreased due to favorable torque changes. Pre-treatment assessment revealed that overbite was smaller in children with β-thalassemia major. As the effect of orthodontic treatment, statistically, significant changes were observed on both overjet and overbite distances ($p < 0.001$). Conclusions: Orthodontic treatment of β-thalassemia major of patients with Twin-block appliance in mixed dentition stage is effective in improving inter arch relationships and the orofacial functions.

KEYWORDS — β –thalassemia, orthodontic treatment, distal occlusion, twin-block.

INTRODUCTION

β-thalassemia major, which is based on the defect in the synthesis of the β-chain of hemoglobin, caused by a mutation in 11 pairs of chromosomes, is one of the life-threatening hereditary blood diseases. Severe anemia underlying β-thalassemia major causes intense but ineffective erythropoiesis and extramodular hematopoiesis [1]. The main treatment for the disease is regular blood transfusions, which reduces the degree of bone marrow activity. Untimely blood transfusion regimen causes hyperplasia and bone marrow proliferation. This leads to pronounced changes in the development of the bones of the face and skull and forms the characteristic appearance of patients: an increase in the parietal regions (*tower* skull), zygomatic bones, flattening of the bridge of the nose, a wide distance between the orbits of the eyes (Fig. 1). The strongly protruding upper jaw creates the typical pathognomic appearance of a thalassemic patient — the face of a *chipmunk*. The lateral skull radiograph shows a widening of marrow cavities.

Fig. 1. *Photo of β-thalassemia major patient (13-year-old)with Class II malocclusion*

According to the literature, the main facial changes in patients with β-thalassemia major who are on permanent blood transfusion include the distal position of the lower jaw in combination with the underdevelopment of its body, which creates conditions for the formation of a skeletal Class II dentoalveolar anomaly (distal occlusion) [2, 3].

Class II anomaly is one of the most common dentoalveolar anomalies among children [4, 5]. Class II is distinguished by the anterior position of the maxilla relative to the mandibula, dental arch discrepancies, masticatory muscle hyperactivity, etc. Distal occlusion also leads to functional and aesthetic defects [6, 7].

Since dentists have little awareness of the essence of β-thalassemia major, there is no algorithm for the

provision of orthodontic care for patients with this pathology. Treatment of craniofacial disorders in the appropriate age period is of great practical importance for the prevention of the following changes in the stomatognathic system and social adaptation of patients with β-thalassemia [3, 8].

Aim

Evaluation of the effectiveness of orthodontic treatment of Class II malocclusion with the Twin-block appliance in children withβ-thalassemia major.

MATERIAL AND METHODS

The work was carried out in the dental clinic of the Azerbaijan Medical University from 2015 to 2017. Observations were performed on data from 49 patients with distal occlusion at the age of 10–14 years. The surveyed patient population was divided into 2 groups. The control group (group 1) consisted of 23 patients with Class II skeletal due to underdevelopment of the lower jaw, without any syndromic and systemic diseases (mean age 11.8 ± 2.4 years). The main group (group 2) included 26 patients with β-thalassemia major (mean age 12.2 ± 1.9 years). All patients of group 2 underwent regular transfusion of erythrocyte mass, due to which the level of hemoglobin in the blood was normalized. All patients had not previously received orthodontic treatment. Since the type of growth and development of the upper and lower jaws is of decisive importance for the harmonious shaping of the face during growth, in our treatment, we used a functional Twin-block orthodontic appliance, which is used to modify the growth of the lower jaw and to completely correct the ratio of the jaws in the sagittal plane. In each group, the duration of orthodontic treatment was 1.5–2 years. All patients underwent complex clinical and radiological examinations before and after treatment. Changes in the parameters of the jaws, dentition, and soft tissues were studied on lateral cephalograms. To determine the effectiveness of orthodontic treatment, comparative cephalometric analyzes were carried out before and after treatment between the study groups. For statistical analysis, analysis of variance and Student's t-test was used.

RESEARCH RESULTS

In patients with β-thalassemia major, an enlargement of the maxilla and zygomatic bones, a change in the configuration of the midface due to flattening of the bridge of the nose, was observed. Also, a lag in the growth of the body of the lower jaw and vertical rotation of the lower jaw was observed. In most cases, the upper lip was shortened and protruded, as a result of which the frontal teeth of the upper jaw were significantly exposed. As a result of abnormal perioral muscle tone, nasal breathing disorders were observed.

Healthy children with distal occlusion demonstrated a slightly prominent maxilla and the middle third of the face, but the incomponent lips, changes in the labiomental angle, and retropositon of the chin attract the attention (Fig. 2). As can be seen in figure 2, the profile is corrected by the forward displacement of the mandibula induced by the Twin-block appliance.

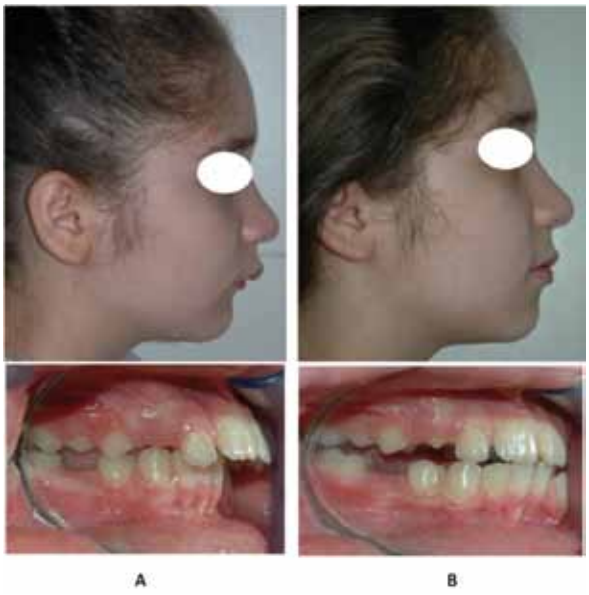

Fig.2. *11-year-old patient with Class II. A-before treatment, B-after treatment*

In group 1, parameter SN, which represents the length of the anterior cranial base, increased to 1.15 m (p <0.001). There was also a decrease in the SNA angle at 0.29° (p <0.001). Under the treatment effect of the Twin-block appliance, the SNB angle, which characterizes the position of the mandibular basal arch towards the anterior cranial base, increased at 1.25° (p <0,01). In the main group, the SNB angle increased at 2.78° (p <0.001). The SNA angle, which characterizes the position of the mandibular basal arch towards the anterior cranial base, was somewhat reduced in both groups. The angle of sagittal inter jaw relationship ANB decreased at 1.46° (p <0.001) in group I and 2.36° in group 2(p <0.001). The length of maxilla PNS-ANS (ANS-PNS) and the length of the mandibular (Co-Gn) increased in both groups. A relatively stable angle Go-Gn/SN indicates that the mandibula is not rotated downwards and backward towards the cranium base. There was a statistically significant increase in the parameters of N-ANS, ANS-Me, and N-Me, which

determine the anterior face height. The change in the N-S-Ar and S-Ar-Go angles during the observation period was statistically significant. The value of overjet in group 1 before treatment was 8.36 mm, and after treatment decreased to 3.78 mm (p <0.001), which is within the limits of the norm. In group 2, the value of the overjet was not greatly increased due to the rotation of the lower and upper incisors (3.68 ± 1.63 mm) (p <0.01). The overbite distance was 4.46 ± 1.98 mm in group 1 and 1.56 ± 0.98 mm in group 2. In group 1, as the result of treatment, there was a statistically significant reduction in the value of the overjet and overbite (p <0.001).

DISCUSSION

The increase in cranial base length was consistent with normal growth-development processes in both groups, where we believe that the main factor is the opposition of the Nasion area. The reason for the small decrease in the SNA angle is the prevention of maxillary growth caused by Twin-block treatment. Also, the change in torque values due to the effect vestibular arch of the appliance on the upper incisors, in turn, affects the point A region. Guilherme et al., Hagg et al. obtained similar results in their studies [9, 10]

Jena et al., Candir et al. observed anterior displacement in the mandible in their study of patients

Table 1. *Cephalometric parameters in groups*

Cephalometric parameters	Groups	Before treatment	After treatment	Difference	P
		M1±σ	M2±σ	M3±σ	
S-N	1	70,49±3,09	71,64±3,09	1,15±0,56	***
	2	67,78±3,83	69,04±2,76	1,26±0,43	***
SNA	1	82,43±3,19	82,14±3,23	-0,29±1,02	
	2	78,14±4,04	78,36±3,28	0,22±1,18	
SNB	1	75,54±3,15	76,79±3,24	1,25±1,39	**
	2	71,48±2,94	74,26±2,45	2,78±1,24	***
ANB	1	6,45±2,13	4,99±2,30	-1,46±1,01	***
	2	6,59±3,01	4,23±2,16	-2,36±1,14	***
ANS-PNS	1	58,41±3,64	59,34±4,70	0,93±1,94	*
	2	47,42±3.84	48,58±3.53	1,16±1,72	*
Co-Gn	1	110,00±8,40	113,70±9,33	3,70±2,49	***
	2	108,92±4,51	112,48±3,57	3,56±1,92	***
SN/GoGn	1	33,66±3,93	33,79±3,77	0,13±1,59	
	2	28,61±4,21	28,36±3,17	-0,25±1,12	
N-S-Ar	1	128,13±6,09	127,36±6,32	-0,77±3,17	
	2	127,22±5,62	128,36±5,62	1,14±2,36	
S-Ar-Go	1	137,21±5,80	138,46±4,53	1,25±4,25	
	2	139,72±7,35	141,84±5,46	2,12±3,88	*
Overjet	1	8,36±1,63	3,78±0,75	-4,58±1,59	***
	2	3,68±1,53	1,44±1,28	-2,28±1,45	**
Overbite	1	4,46±1,98	2,31±1,41	-2,15±1,72	**
	2	1,56±0,98	1,12±0,85	0,44±0,35	
N-ANS	1	55,33±4,16	55,75±3,84	1,39±1,35	**
	2	46,11±3,74	48,25±3,21	2,14±2,85	***
ANS-Me	1	64,41±6,28	67,46±7,21	3,05±1,41	***
	2	63,01±4,06	66,12±3,78	3,11±2,89	***
N-Me	1	115,26±8,97	119,76±9,48	4,5±1,66	***
	2	106,67±6,56	109,76±5,34	3,08±1,45	***

*Statistical significance of p p-value - p<0,05 ** — p<0,01 *** — p<0,001*

with distal occlusion [11,12]. In our groups, as a result of orthodontic treatment, the mandible moved forward. This is an expected result of the effect of Twin-block therapy. Correction of the sagittal inter-jaw relationship is ensured by the forward displacement of the mandible.

The effective length of the maxilla has increased according to the dynamics of normal growth. We think that the length of the mandible increases during the treatment with functional appliances. This is evidenced by the increase in both the SNB angle and the Co-Gn parameter. A bigger mandibular growth is a desirable outcome in the treatment of distal occlusion. Kanuru at all., in his study, highlighted the effect of activators on mandibular growth [13].

Against the background of the relatively stable Go-Gn/SN angle in the results of our study, the increase in vertical face size may seem contradictory. We think that this is due to the parallel downward movement of the mandibular bone. In this case, the angle does not change, but the anterior height of the face increases. The presence of statistically significant increases in N-ANS, ANS-Me, and N-Me parameters can be considered normal because patients are in the growth period. Overjet distance decreased by 4.58 mm in group 1. The reduction of the overjet was caused by mandibular displacement and, to a lesser extent, the torque movement of the incisors.

We observed a large amount of displacement in the incisors, especially in patients with β-thalassemia major. We think this is related to bone structures. Also in thalassemic patients, before treatment, the overjet distance is latent due to the lower-back rotation of the upper incisors. The overbite distance is smaller in main group patients before treatment due to protrusion of the lower incisors.

CONCLUSION

Analysis of the cephalometric data of patients with β-thalassemia major and healthy children with Class II revealed a significant difference of the parameters, which indicate anteroposterior jaw relationships. Orthodontic treatment β-thalassemia major patients with Twin-block appliance in mixed dentition stage is effective in improving interarch relationships and the functioning of the orofacial appliances.

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RECONSTRUCTION OF MANDIBULAR DEFECTS USING INDIVIDUAL VASCULARIZED AUTOGRAFTS COMBINED WITH MACROPOROUS TITANIUM FIBER MATERIAL

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ABSTRACT — The choice of donor material poses a problem for surgeons handling reconstruction of large combined bone defects or limited maxillofacial bone defects. Restoration methods, applicable in reconstructive microsurgery are based on materials of non-biological origin and musculoskeletal autogenous transplants which have complications and may inhibit the processes of osseointegration. Our study aimed to improve the efficiency of surgical treatment and rehabilitation of patients with mandibular defects using vascularized autograft in combination with macroporous titanium fiber material. The reconstruction of the defective mandible caused by chronic osteomyelitis, trauma, benign tumors was performed in 107 patients either by means of conventional methods (titanium plates, free and vascularized bone autografts), or by a novel engineered bone substitute. Our novel vascularized bone autotransplant combines a macroporous fiber titanium material and spiral bone autochips. For its fabrication we applied digital 3D technologies and methods of rapid prototyping, whereas its vascularization was harvested in iliac crest. Unlike the standard methods of reconstruction, the use of the engineered vascularized implant showed a significant reduction in stages, volume and invasiveness of surgical procedures and an improvement of esthetic and functional outcomes in patients with mandibular defects.

KEYWORDS — bone tissue engineering, 3D modeling, rapid prototyping, porous titanium fiber mesh (TFM), bone autotransplant.

INTRODUCTION

The conditions following cancer treatment, such as severe maxillofacial traumas, post-traumatic deformities of the facial skeleton with a bone defect are common in maxillofacial surgery [1, 7, 15].

Accelerating mobility and speed of modern society, the spread of weapons and military conflicts, there is a growing incidence of post-traumatic deformities of various origin affecting bones. The corresponding surgical reconstruction requires a more sofisticated and comprehensive approach [2, 5, 10, 13, 16].

As reported by various authors, the number of patients with maxillofacial traumas ranges from 11 to 25% (Bernadsky Yu. I., 2016; Kulakov A. A., 2017; Drobyshev A. Yu., 2017; Bayrikov I. M., 2018), whereas some other researchers, both national and interantional ones, claim the rate to be at 30–38% (Balin V. N., 2015; Wong K. H., 2016; Guerrissi J. O., 2018).

The rate of post-traumatic complications varies, according to the references, from 7 to 36% (Zuev V. P., 2015; Erokhina I. L., 2016; Eshiev A. M., 2018; Andra A., et al., 2018). Specialized hospitals sometimes fail to offer timely and high-quality care, which leads to repeated surgical interventions and the emerging mandibular defects of disturbed continuity [9, 14].

At the current stage, reconstructive maxillofacial surgery progress utilizes widely reconstructive surgery methods capable of improving defects while relying on materials of non-biological origin (titanium, teflon, polyethylene, etc.) or on multicomponent musculoskeletal autografts involving microvascular technology. These methods have advantages and disadvantages and universally applicable to the fullest extent, which inevitably leads to traumatization of both the donor and the recipient areas [3, 4, 6, 8, 11, 12].

Furthermore, despite numerous fundamental studies, a number of issues still require more detailed consideration, namely, the change patterns involving the status of bone and soft tissue structures after resection of various jaw parts, depending on the causes behind it, and the timing of the removal.

MATERIALS AND METHODS

In our work, we rely on a combined method, which implies using vascularized autografts and a

unique macroporous titanium fiber material. The reliability of the study can be confirmed a sufficient number of clinical observations (107) and numerous X-ray data, processing of the outcomes obtained through advanced statistical analysis methods. The hypotheses were tested relying on the methods of parametric statistics. The description of the quantitative parameters was performed using the mean and the error of the mean. The observations frequency was expressed as a percentage. The level of statistical significance through the study was set at 0.05. The obtained data of aesthetic indicators, both prior to, and after the surgery were processed statistically using the MS Excel 2010 software package.

Through our project, we used a combined treatment method to replace mandibular defects based on using vascularized autografts and a macroporous titanium fiber material.

The surgical treatment planning, the pre-surgery preparation, the surgical stages of the treatment were carried out following the clinical recommendations offered by the Chief Freelance Maxillofacial Surgeon of the Russian Ministry of Health *Protocol for treating patients with facial skeleton bones defects*.

Written voluntary informed consent (approved by the Samara State Medical University Ethics Committee of 22/11/2015, Protocol #147) was obtained from each of the patients treated for mandibular defects, the signed papers allowing clinical trials, taking photos and videos, as well as using the outcomes in research work.

We had 107 patients under our observation, all of them divided into 2 groups. Group I (76 persons), standard and widely used methods were employed to reconstruct mandibular defects — titanium reconstructive plates in 32 people; free bone autografts — in 22 people, and vascularized bone autografts used in other 22 people.

The study group included patients of Group II, who were treated using vascularized bone autografts in combination with a through-porous non-woven titanium material. The group in question included a total of 31 patients. Vascularized autografts were used to treat the patients of the study group. Their maturation was carried out in the anterior abdominal wall subject to the method developed at the Maxillofacial Surgery and Dentistry Department of the Samara State Medical University.

The patients were selected from those seeking medical assistance in the Maxillofacial Surgery and Dentistry Clinic of the Samara State Medical University (Samara, Russia) and in the Department of Maxillofacial Surgery of the Research Institute — Regional Clinical Hospital # 1 (Krasnodar, Russia).

The patients' general and local status regarding the issue of the potential reconstruction of mandibular defects was evaluated following the traditional plan. First of all, the clinical section of the examination was carried out, which included an interview survey; the patient's general status evaluation; an examination; evaluation with extra diagnostic methods (ultrasound, CT, MRI), and evaluation involving rapid prototyping methods (Fig. 1, 2).

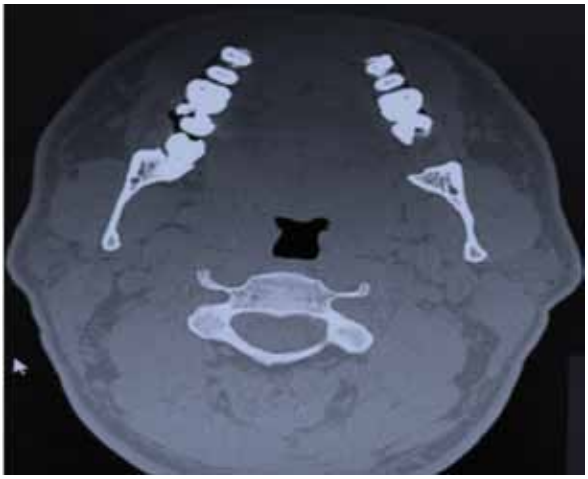


Fig. 1. *Defect of the chin of the lower jaw in 3D format*

The clinical data of 107 patients, revealed that 30% of the cases had deformities that developed after surgical treatment for chronic osteomyelitis of various etiologies; 30% more (30 patients) had lower jaw defects associated with maxillofacial injuries; another 30% of the patients (30 persons) had mandibular defects originating from the removal of benign neoplasms, while 10% (10 patients) featured mandibular issues following complications of reconstructive surgeries (rejection of previously transplanted autografts and titanium plates) and oncological surgeries (Fig. 3).

The through-porous non-woven titanium material is an elastic-porous homogeneous mass fabricated by cold pressing of titanium chips stacked in a certain way. The production of the said chips involved using a titanium rod of various diameters, which depended on the required diameter of the spiral and the distance between the turns.

The desired parameters were set on the computer and within 17±6 minutes the number of spirals were obtained required for producing an implant of any size to be further used for replacing the lower jaw defect. The spirals in their length exceeded the defect length by 10±1 mm. The excess length was needed to bend the spiral ends inside the structure. This helped avoid

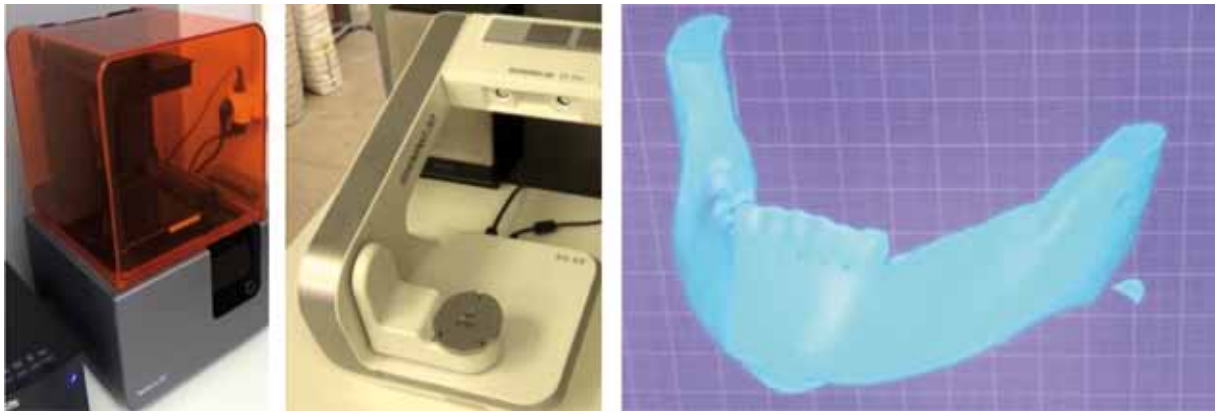


Fig. 2. Device for obtaining stereolithographic lower jaw: a — 3D printer; b — 3D scanner; c — 3D model of the lower jaw

Fig. 3. Orthopantomogram (a) and computed tomogram (b) with the possibility of 3D reconstruction of the lower jaw defect. Patient A., years old. D.S: large follicular cyst of the mandibular body on the left

any sharp edges of the implant and allowed hermetic insulation of the autobone chips through the first stage of developing the bioengineered composition. The technology for obtaining a medical implant is protected by a patent (Patent # 2733687).

To fabricate implants replacing the jaw defect, chips with a thickness of 0.05-0.015 mm were used. The spiral coil diameter was 0.8±0.2 mm, the distance between the coils thus making 0.8±0.2 mm. The chips were made on a numerically controlled machine (Fig. 4).

The engineered bone substitute is a combination of a non-woven titanium material with through porosity fabricated from titanium chips and a spiral-shaped autobone. In order to obtain a spiral-shaped autobone, a spiral-shaped milling cutter was designed and manufactured jointly with the KASKAD Machine-Engineering Plant (Krasnodar, Russia, with a respective patent obtained (Patent # 2733687).

The technology for producing engineered bone substitutes from macroporous titanium fiber material is based on the titanium chips cold pressing method. Jaw implants are supposed to augment bone defects, which means they are to have a respectively designed shape and size. To achieve these, a specially manufactured mold was used. The individual mold was based on a dental flask used to produce plastic prostheses.

In order to obtain an individual mold for a mandibular defect with no disturbed continuity, the neoplasm was removed within healthy tissues using a milling cutter and a drill, on a stereolithographic model. The resulting defect was filled with molten dental wax. Once cooled, the resulting wax model of the potential jaw implant was removed with the mold to be made further (Fig. 7–9).

Following a standard procedure, creamy die stone was made, which was then poured into the flask up to the middle of the side height. The wax composition

Fig. 4. Titanium shavings for the production of non-woven titanium through-porosity fabric

Fig. 5. General view of the manufactured cutter: a — shank; b — working part; c — cutter edge

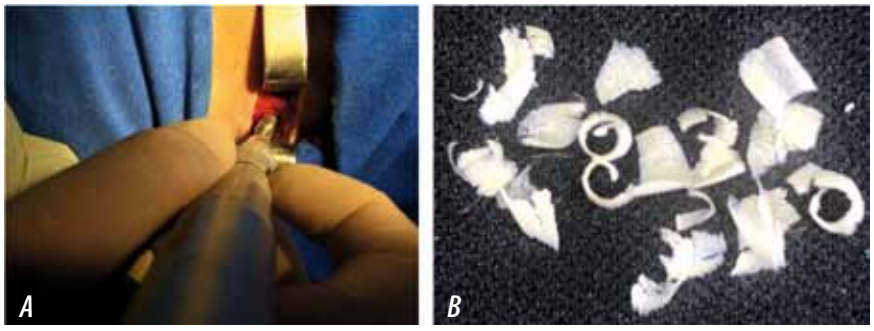


Fig. 6. A — The stage of sampling of bone autochips from the iliac crest; B — View of bone chips following cut with the original cutter

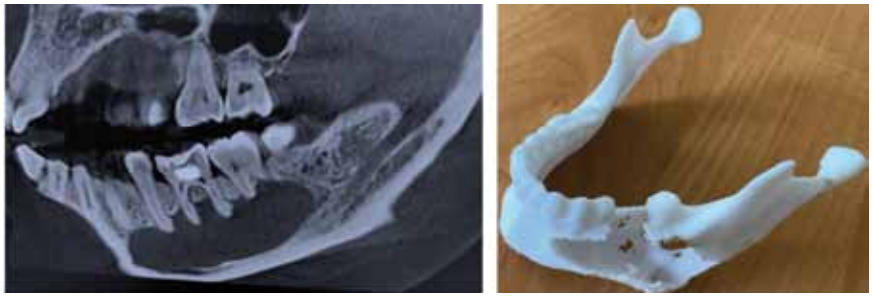


Fig. 7. X-ray and lithographic model of the lower jaw of the affected tumor

Fig. 8. Removal of a neoplasm and formation of a bone cavity on a stereolithographic model

was placed in the die stone in the center to the middle of its depth. Once the die stone was hard, a brush was used to cover its entire surface with a layer of paper glue, and then, once the glue dried, another portion of die stone was prepared, yet in salt water that time. When the die stone was completely dissolved to make a creamy substance, it was poured into the flask up to the upper edge. The flask was then covered with a lid and pressed down. When the die stone was completely solid, the flask was opened in the reverse order. A jet

Fig. 9. Individual wax composition of the jaw implant

of hot water helped melt the wax blank, and a mold for an individual implant was obtained. Knowing the volume of the implant and the porosity to be obtained, we used a special formula to calculate the amount of titanium chips required. In 85% of the implants, the porosity was 75±5% of the total implant volume. After weighing the required amount of chips, we got to laying them in the mold. Bone chips were obtained from the retromolar area or from the ilium. The result was a pyramidal stack of titanium chips with layers of autobone chips. The mold was assembled the right way based on the flask grooves. The cuvette flask placed under a mechanical press to be further squeezed until both halves were completely closed (Fig. 10).

removed part of the lithographic model, the teeth were cut off along with the tumor-altered part of the lower jaw.

The obtained lithographic model was used to bend a titanium reconstructive dynamic plate, in view of an additional section to be used for fixing the plate to the healthy stump of the lower jaw. On the upper part of the plate replacing the lower jaw branch, a titanium condylar process with a joint head was attached using special screws.

Having completely covered the resulting lithographic model with wax, we set to producing a plaster mold following the method described above. A titanium reconstructive plate was placed in the center

Fig. 10. Mold for the stage of cold pressing: a — finished mold; b — the stage of laying the components of the bioengineering composition; c — stage of cold pressing

a *b* *c*

In cases where a bioengineered design was required to replace the half of the lower jaw after its resection, a slightly different technology was employed.

For this purpose, a large flask was made (115 mm long, 35 mm wide and 70 mm high), while its components and the disassembly specifics were similar to the previous one.

A lower jaw lithographic model was made based on the CT data. Subject to the rules of oncology, retreating 2–2.5 cm from the tumor, resection of the affected area on the lower jaw was performed with its continuity disturbed. In the event that the condylar process was affected, resection was performed with the branch and the condylar process removed. On the

of the substitute depth. On all sides, the reconstructive plate was covered with a macroporous titanium fiber material combined with autobone. Given its shape, it matched the resected part of the lower jaw (Fig. 11, 12).

The first (control) group included 76 patients who were operated on following the standard conventional methods. After sequestration and cystectomy, the bone cavities were filled with blood clots or osteoplastic material. 37 patients had lower jaw tumors, of which 7 had true defects not only in the lower jaw yet also in the soft tissues. Patients with soft and bone tissue defects were operated on in two stages. Through the first stage, soft tissues were repleted. Microsurgical

Fig. 11. An intermediate stage in the fabrication of an engineered biomaterial

Fig. 12. Bioengineering design

techniques were used in 4 patients, while Filatov-Gillies tubed pedicle was used in the rest of the patients (Fig. 13).

In the second stage, the bone defect, which developed following the surgery, was filled with a split rib autograft or an ilium segment (Fig. 14).

The remaining 30 patients who had bone defects only were operated on using reconstructive titanium plates combined with autobone.

In the main group, in 31 patients with mandibular defects were augmented with the engineered bone autograft fabricated by us.

Of them, 9 persons were diagnosed with odontogenic cysts, another 3 — with the lower jaw osteomyelitis. These patients developed the defects after sur-

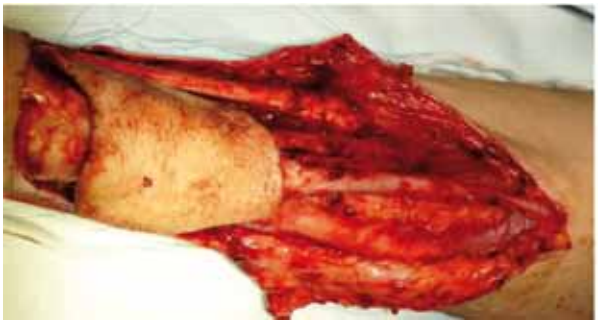


Fig. 13. Transplant-ready radial flap

A

B

Fig. 14. A — the stage of the collection of the parietal bone site; B — formed free bone autograft, ready for transplantation

gical interventions that did not lead to any disturbance in the jaw continuity. Once the major focus removed, the resulting bone cavity was profoundly washed with an antiseptic solution. A visual examination of the resulting bone defect revealed altered bone tissue areas, which were removed with a milling cutter down to healthy tissues. The causative teeth were removed. Following respective indications, the root resection was performed. Any sharp edges and resected roots were smoothed down with a cutter. The resulting bone cavity was filled with a specially prepared bioengineered structure made of the NWTMTP based on the lithographic model produced subject to the specifically designed method.

In 5 patients with true bone and soft tissue defects, a full-layer muscle-skin grafting was used, which contained inside a mature bioengineered structure of the NWTMTP in combination with bone autochips.

Of these patients with true bone and soft tissue defects, 3 had half-resected lower jaw with the condylar process exarticulation.

All other patients of the main group were treated for mandibular defects using an autotransplantant made by our method and harvested in the anterior abdominal wall. No skin was used there.

Harvesting and autotransplantation of engineered vascularized autotransplantant

The stage of the harvesting the autotransplantant in all cases was performed in the anterior abdominal wall. Prior to placing the autotransplantant in the anterior abdominal wall, surgical marking was performed on the abdomen skin; the course of the perforant vessels was outlined with a surgical marker, the entire process controlled by ultrasound (Fig. 15).

Fig. 15. *Surgical marking of axial vessels on the skin of the abdomen*

The incision line was applied strictly in the iliac crest projection. The crest was detected by palpation. The incision length of the was 9±3 cm. Once the iliac crest was skeletonized, autobone chips or bone fragments were collected (Fig. 16).

For this purpose, a physiodispenser and the specifically designed milling cutter were used to get a spiral-like autobone. Following our method, the titanium and bone chips were stacked in a sterile plaster mold in layers so as to make a pyramid. A dynamic reconstructive perforated plate was placed in the chip thickness, after which a manual press (pre-autoclaved and additionally wrapped with a sterile sheet) was used to compress both halves of the mold until they were completely in contact. Further on, the bioengineered structure was extracted. To ensure its maturation, it was to be placed in the anterior abdominal wall. During that, the perforant vessels markings on the abdomen skin were used as the reference points. The superficial abdominal muscle was dissected horizontally from the existing incision while the dissection went from the anterior vaginal wall of the rectus abdominis muscle up to the volume so as to ensure a smooth passage through it and the desired positioning of the bioengineered structure. The latter was fixed to the surrounding soft tissues with 2–3 sutures of absorbable material (Fig. 17).

X-ray examination was performed on a monthly basis in order to monitor the biocomposition location (Fig. 18).

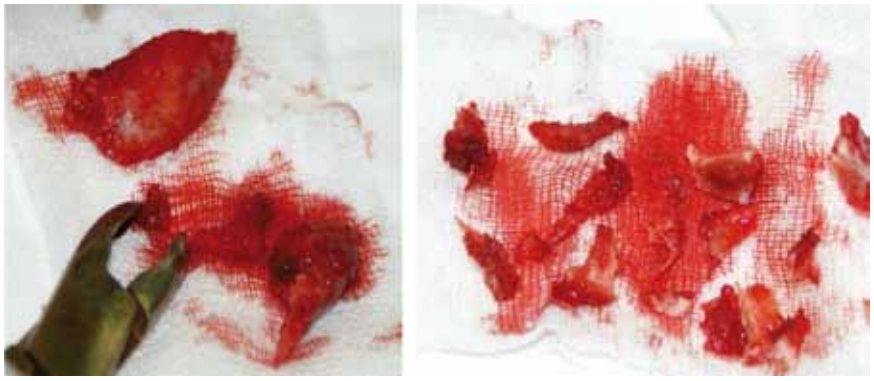
We performed intraoperative ultrasound scanning in order to identify the location of axial blood vessels.

3.5 ± 0.5 months later, the next stage was launched. Isolating the bioengineered structure from the surrounding tissues without a vascular pedicle presented no serious issue. The end sections of the dynamic plate with holes for the intraosseous screws were separated with gauze swabs. The sprouted part of the non-woven titanium material had to be isolated with a sharp tool (Fig. 19).

Following the generally accepted method, the tumor-affected area of the jaw was skeletonized, which was resected retreating 2 cm from the tumor into the healthy jaw. 10 patients had the lower resection jaw with their condylar processes exarticulation. In 13 patients, the joint was preserved (Fig. 20).

Prior to installing the bioengineered structure, the remaining part of the jaw was placed in the central occlusion position while controlled by the splint (Fig. 21).

A reconstructive dynamic titanium plate, along with the bioengineered structure, was attached to the jaw stump with 3-4 standard bicortical intraosseous Stryker system screws (Fig. 22).



A B

Fig. 16. A — Bone fragments from the iliac crest; B — Bone chips taken from the iliac crest

Fig. 17. The engineered biomaterial is fixed in the thickness of the rectus abdominis muscle (the wound is ready for suturing)

Fig. 18. X-ray of the pelvic bones. The arrow indicates a bioengineering structure

In 5 patients with soft tissue and jaw defects, the bioengineered structure – taken as a single conglomerate – was transferred to the affected area together with the surrounding skin and soft tissues (Fig. 23).

When working on a plastic surgery for a soft tissue defect, a reasonable idea is to have two teams of surgeons, for one of them to be responsible for preparing the recipient zone, the other team modeling the grafting. For all cases within our study, a team of duly certified microsurgeons were involved. In each clinical case, a mandatory ultrasound Doppler examination of the perforant and axial vessels was done (Fig. 24).

While controlling the bite, a dynamic reconstructive titanium plate was attached to the exposed lower jaw stumps, which was ran, as reinforcement, into the bioengineered structure depth (Fig. 25).

After that, microsurgeons used microscopes to stitch the facial vessels with vessels feeding the complex soft-tissue grafting with the bioengineered structure inside, applying traditional vascular sutures. The facial soft tissues and the transplanted grafting were stitched in layers (Fig. 26).

15 patients of the main group had their bone defects replaced with a bioengineered structure simultaneously with the lower jaw resection. All patients were treated for ameloblastomas, often recurrent tumors of the lower jaw. During that, no true soft tissue defects were observed. Before the lower jaw resection, individual molds were made based on our method, which were sterilized and delivered to the operating room.

During the surgery, bone chips were taken from the ilium using the specially designed cutter as mentioned earlier (Fig. 27).

As we started manufacturing a bioengineered structure, layers of titanium and bone chips were placed in layers into the earlier prepared mold, to make a pyramid and compressed. In the center of that the reconstructive plate was to be found (Fig. 28).

The resulting bioengineered structure was placed in the lower jaw defect area that developed following the tumor resection, to be fixed afterwards, and then the structure was covered with surrounding soft

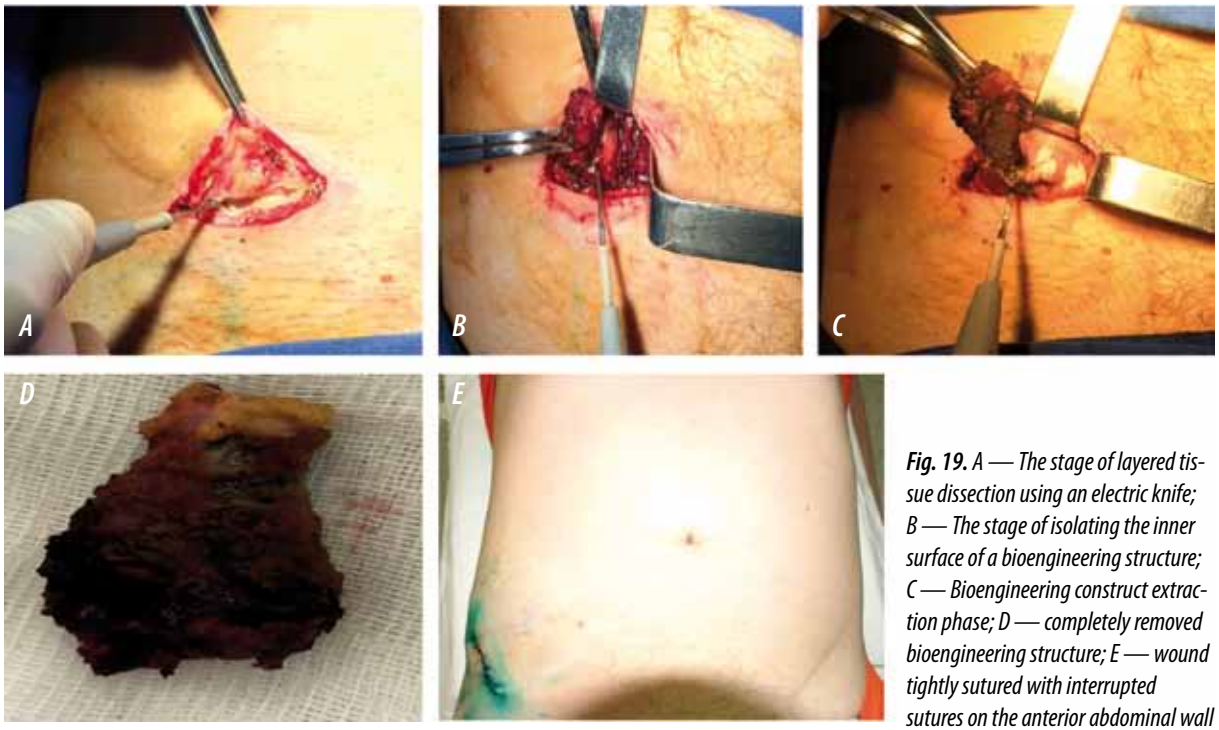


Fig. 19. *A — The stage of layered tissue dissection using an electric knife; B — The stage of isolating the inner surface of a bioengineering structure; C — Bioengineering construct extraction phase; D — completely removed bioengineering structure; E — wound tightly sutured with interrupted sutures on the anterior abdominal wall*

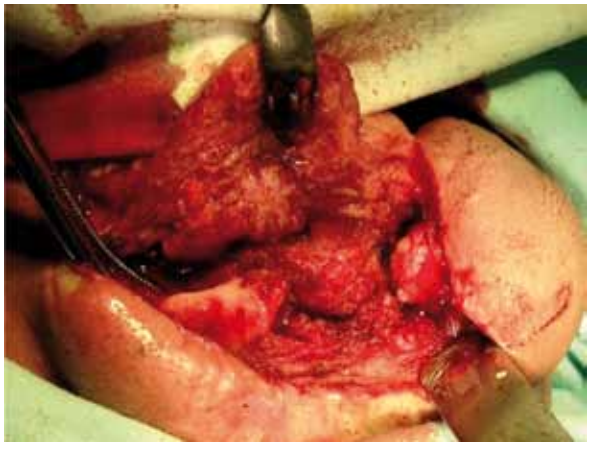


Fig. 20. *Patient K., 34 years old. D.S. Ameloblastoma of the lower jaw on the left. Resection of the affected area of the lower jaw performed*

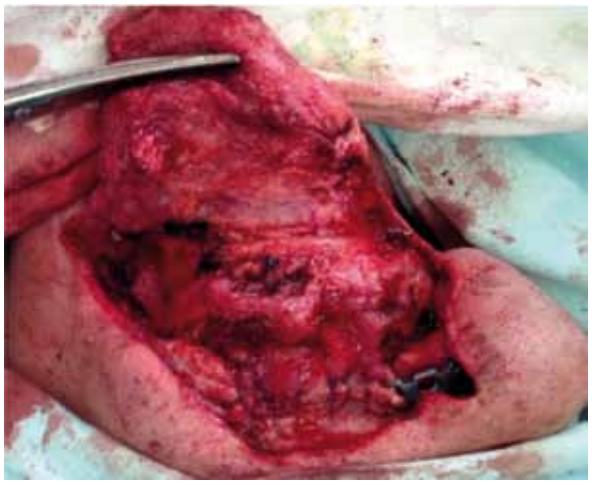


Fig. 22. *The graft is fixed in the wound; the wound is ready for suturing*

Fig. 21. *The stage of adjusting the bioengineering structure: a — matured bioengineering structure; b — titanium head of the condylar process; c — keys for bending*

tissues. The wound on the side of the mouth and skin was sutured tightly. Drainage was ensured with rubber drains (Fig. 29).

RESULTS AND DISCUSSION

The data from evidence-based medicine research projects revealed a 47% reduction in absolute risk with a confidence interval of 3–59%. The number of patients who need to be treated with our method (number needed to treat / NNT) was 2 (CI — 2–3).

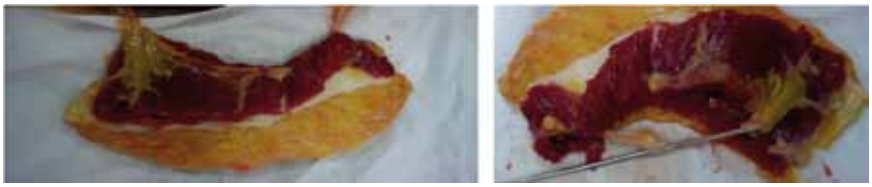


Fig. 23. General view of an autograft with a bioengineering structure inside

Fig. 24. Ultrasound examination of intraoperatively perforated vessels

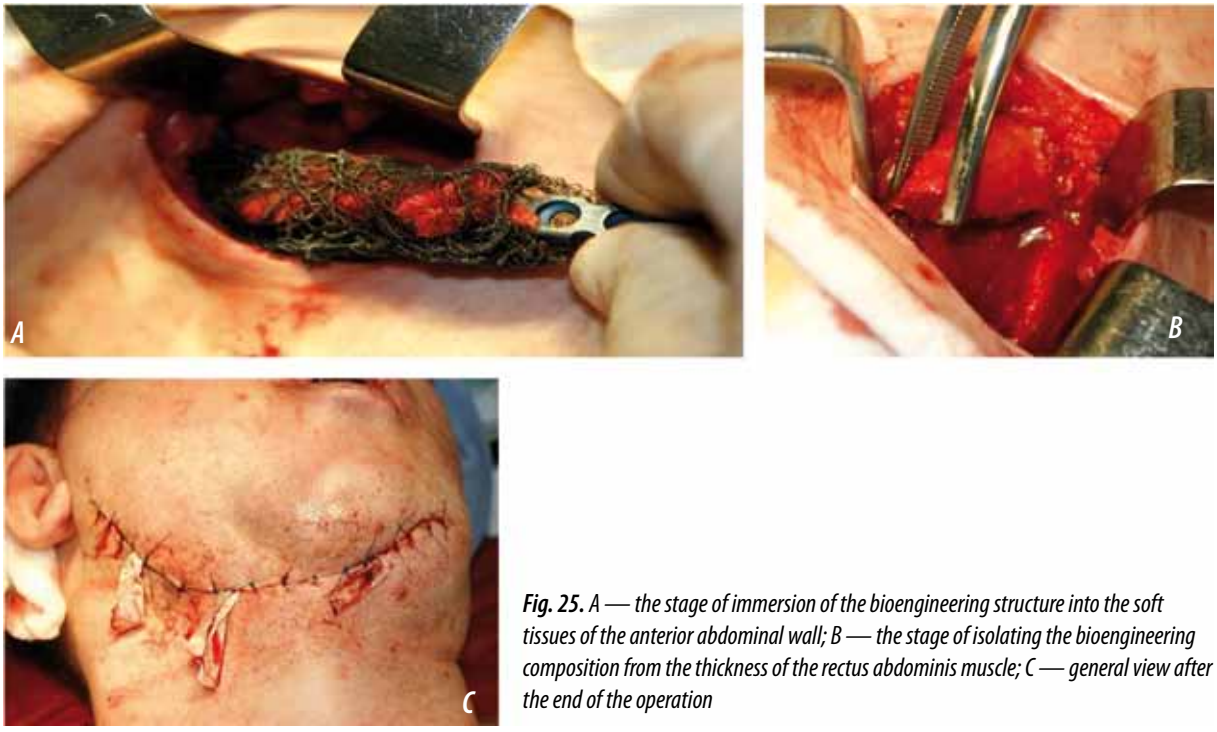


Fig. 25. A — the stage of immersion of the bioengineering structure into the soft tissues of the anterior abdominal wall; B — the stage of isolating the bioengineering composition from the thickness of the rectus abdominis muscle; C — general view after the end of the operation

The relative risk reduction was at 94% with a CI of 59–116%, which stands for a very high clinically significant effect. The odds ratio was 0.03 with a CI of 0.01–0.26, whereas the risk of adverse outcomes proved very low (χ^2 — 18.83; p = 0.0001).

These results here reveal a fairly high rate of insufficient aesthetic effectiveness in the control group if compared to the group treated using the specially developed method — 24 VS. 3%, respectively (χ^2 — 4.99; p = 0.026). The relative risk reduction was 84% with a

Fig. 26. General view of sutured vessels (magnification ×6)

confidence interval ranging from 2 to 133%. The absolute risk reduction was 21% with a CI of 5 to 32%. The number of patients who need to be treated in order to prevent one adverse outcome (poor aesthetic effect) is 5 with a CI of 3 to 19. The odds ratio of 0.11 with a CI of 0.02–0.85 means that, when using the newly developed method, the risk of an unfavorable outcome was 5 times as low compared to the generally accepted one ($p = 0.026$), this implying that the effectiveness of the proposed technology in terms of ensuring aesthetic effect is to be viewed significant both statistically and clinically.

An unfavorable outcome (poor functional result) was observed in many fewer cases — 3% and 42%,

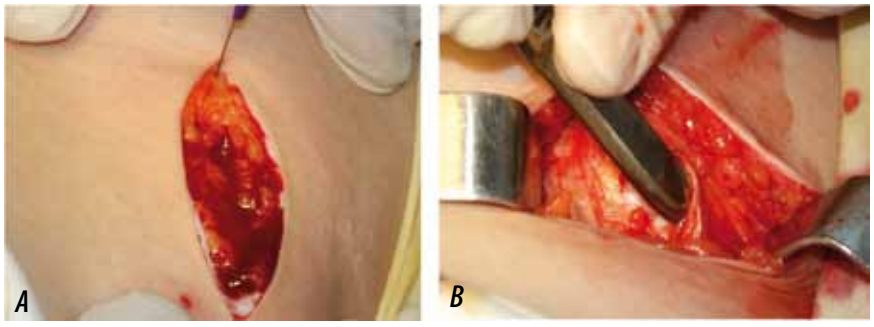


Fig. 27. A — Skin incision with an electric knife; B — Skeleton stage of the iliac crest

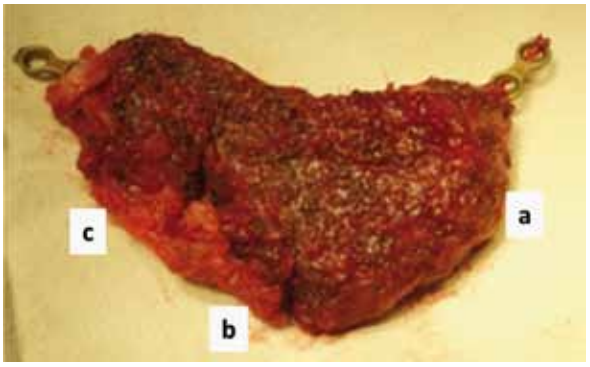


Fig. 28. Bioengineered composition ready for transplantation into the area of the lower jaw after removal of the ameloblastoma: a — the body of the lower jaw; b — the angle of the lower jaw; c — the branch of the lower jaw

respectively. The absolute risk reduction was 39% with a confidence interval of 22–50%. The number of patients to be treated with the proposed intervention was 3 (CI — 2–5). The relative risk reduction was 92% with a CI of 53–120%. Values exceeding 50% correspond to a clinically significant effect. The odds ratio was 0.05 with a CI of 0.01–0.36, i.e., the risk of an adverse outcome in terms of failure to arrive at a positive functional effect while employing the proposed method was very low.

The method was also associated with a high statistically and clinically significant positive result in terms of assessing the intervention effectiveness subject to factor like the patient's psychoemotional satisfaction following the surgical and orthopedic rehabilita-

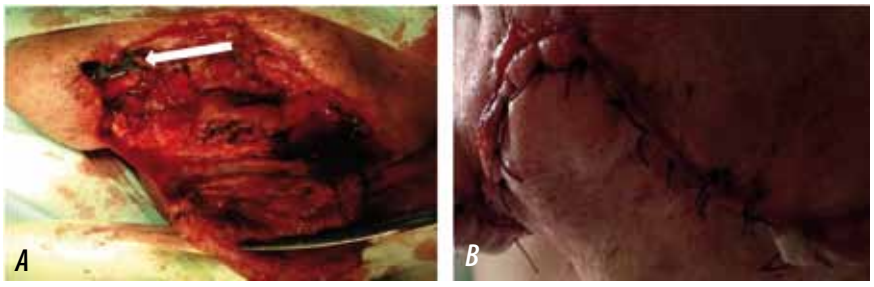


Fig. 29. A — Surgical wound after resection of a part of the lower jaw body on the right and replaced with a bioengineering composition; B — View of a sutured and drained wound

Table 1. *Key indicators of the intervention effect following the treatment of defects based on the specially developed method (Group I), compared to the defect reconstruction based on conventional methods (Group II)*

Comparison groups	Indicators							
	Event Rate in Treated Group %	Event Rate in Control Group %	Relative Risk Reduction % 95% CI	Absolute Risk Reduction % 95% CI	NNT 95% CI	Odds Ratio 95% CI	x2	P
Poor aesthetic effect								
Groups I and II	3	24	84 2-133	21 5-32	5 3-19	0.11 0.020.85	4.9 9	P = 0.026
Poor functional effect								
Groups I and II	3	42	92 53-120	39 22-50	3 2-5	0.05 0.01 0.36	13. 84	P =0.00 01
Poor psychoemotional status following the final stage of the surgical and orthopedic rehabilitation								
Groups I and II	3	50	94 59 -116	47 3 - 59	2 2 - 3	0.03 0.01 0.26	18. 83	P = 0.00 01

tion stage. Unsatisfactory psychoemotional status after surgical and orthopedic rehabilitation based on the proposed method, if matched against the conventional treatment, was much lower — 3% and 50%, respectively.

The absolute risk reduction was 47% with a confidence interval of 3–59%, whereas the number of patients in need of treatment (NNT) was 2 (CI 2–3). The relative risk reduction was 94% at a CI of 59–116%, which stands proof to a very high clinically significant effect. The odds ratio was 0.03 at a CI of 0.01-0.26, while the risk of adverse outcome proved very low (χ^2 — 18.83; = 0.0001).

In view of the above, the key indicators used to evaluate the intervention effectiveness in patients operated on using the proposed method, if compared to conventional methods, reveal a high clinical statistical significance of the obtained outcomes as well as point at the feasibility of employing the proposed treatment methods in practical healthcare.

The obtained outcomes allow recommending these technologies to be scaled up thus embracing a wider clinical practice.

CONCLUSIONS

1. Improved treatment effectiveness for patients with mandibular defects, which was due to employing a vascularized individual bioengineered composition based on non-woven titanium material with through porosity. The risk of an unfavorable treatment outcome while using the proposed method was 5 times as low compared to the generally accepted ones.

2. Analysis of the treatment results in patients with lower jaw defects, based on the data reported by specialized maxillofacial hospitals of the Samara and the Krasnodar Regions of Russia revealed the following: 32% of patients were not satisfied with the treatment outcomes, of which aesthetic dissatisfaction accounted for 18%, whereas another 14% of patients were not satisfied with the orthopedic structures.

3. The study helped obtain experimental proof, protect by a patent, manufacture and implement into clinical practice a special cutter to be used for spiral-shaped bone sampling (Patent # 2733687).

4. A 3D prototyping-based method of sampling and shaping a vascularized autograft combined with a non-woven titanium material with through-porosity has been offered its theoretical explanation as well as implemented in clinical practice. If using the proposed method, the risk of adverse outcomes with no positive functional result achieved remains very low, the odds ratio being at 0.05 with a CI of 0.01–0.36.

5. A new method of mandibular defects individual replacement has been improved relying on digital technologies, as well as the method has been protected by a patent and introduced into clinical practice. In case of using the proposed method, the rate of the patient's unsatisfactory psychoemotional status following the surgical and orthopedic rehabilitation stage was much lower, if compared to the conventional treatment — 3% and 50%, respectively.

6. The specifically designed individual vascularized autografts, while combined with a non-woven titanium material with through porosity allowed increasing the aesthetic and the functional outcomes as well as bring up the rate of the psychoemotional satisfaction following the treatment. Insufficient functional results were observed in 3% of the cases; the absolute risk reduction reached 47% with a confidence interval of 3–59%. The number of patients that needed

treatment (CNNT) was 2 (CI 2–3). The relative risk reduction was 94% with a CI of 59–116%, which corresponds to a very high clinically significant effect. The odds ratio was 0.03 with a CI of 0.01–0.26, while the risk of arriving at an adverse outcome proved very low (χ^2 — 18.83; p = 0.0001).

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SALIVA CRYSTALLIZATION IN PATIENTS WITH COMBINED GASTROENTEROLOGICAL AND CARDIOVASCULAR PATHOLOGY

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ABSTRACT — The purpose of this study was to estimate the specifity of saliva crystallization in comorbid pathology of digestive and cardiovascular systems. We collected saliva from 35 patients with coronary artery disease, 48 patients - with ulcer disease and 112 patients - with their combination. The features of self and initiated crystallization in the patients of all groups were evaluated using a specialized system of semi-quantitative parameters. It was stated that the crystallograms of comorbid patients are characterized by a clearly visible predominance of single-crystal elements over dendritic ones. The total density of structures in the facias is significantly reduced in comparison with both healthy people and patients of other groups.

KEYWORDS — saliva, crystallization, coronary artery disease, ulcer disease.

INTRODUCTION

Diseases of the digestive system and cardiovascular system occupy an important place in the structure of general morbidity, representing an important economic, social and medical problem [1, 2, 6–9]. It should be emphasized that the pathogenesis of isolated coronary artery disease (CAD) and peptic ulcer disease (PUD) has been studied in sufficient detail, but mechanisms of their formation and development of its combination are debatable [1–4, 6–9]. From these positions, the disclosure of the metabolic shifts accompanying this combined pathology is relevant [1, 3, 4, 6, 9]. Taking into account the above mentioned, the ***purpose of this study*** was to investigate the characteristics of saliva crystallization in comorbid pathology of digestive and cardiovascular systems.

MATERIAL AND METHODS

We collected saliva from 30 healthy people, 35 patients with isolated CAD, 48 — with UD, and 112 — with their combination. The features of self-and initiated crystal formation of these biological substrates were evaluated using a specialized system of semi-quantitative parameters [5].

The diagnosis of CAD was established by the clinical examination, as well as by instrumental methods (ECG registration at rest and during exercise, daily monitoring of the ECG by Holter, echocardiography). Angina pectoris of I FC was diagnosed in 45 examined patients (40.2%), angina pectoris of II FC — in 67 (59.8%). The duration of the history of CAD ranged from 2 to 8 years. In the anamnesis of 29 patients (25.8%), there was a history of myocardial infarction more than 2 years ago. During the study, 94 patients (83.9%) had peptic ulcer disease in remission, 18 — in the acute stage (16.1%). The diagnosis of peptic ulcer disease was verified by gastroduodenoscopy. In 83 patients (74.1%), duodenal ulcer was confirmed, in 29 (25.9%) — gastric ulcer. For the diagnosis of helicobacteriosis, a biopsy method and a serological blood test were used.

Statistical processing of the results was performed using variation statistics algorithms using Microsoft Excel 2007 and Statistica 6.1 for Windows.

RESULTS

The study of the free crystal formation of saliva in patients with combined ischemic heart disease and gastric ulcer disease allowed us to establish the following patterns. The discrete part of all samples is represented by amorphous bodies and single-crystal elements, and the extremely high density of crystallization centers in the samples is noteworthy. Numerous destroyed and altered structures are noted. The marginal zone is expressed along the entire perimeter of dried specimens.

The visuametric analysis of saliva crystalloscopic facias also demonstrated the formation of a new pathological *pattern*, a combined pathology, which is different from the symptoms of the single diseases and is not their algebraic mean (Fig. 1). It was found that for patients with only gastric ulcer disease, the transformation of the crystalloscopic picture of saliva includes a moderate inhibition of structure formation, manifested in an increase in the proportion of single-crystal elements in the facias.

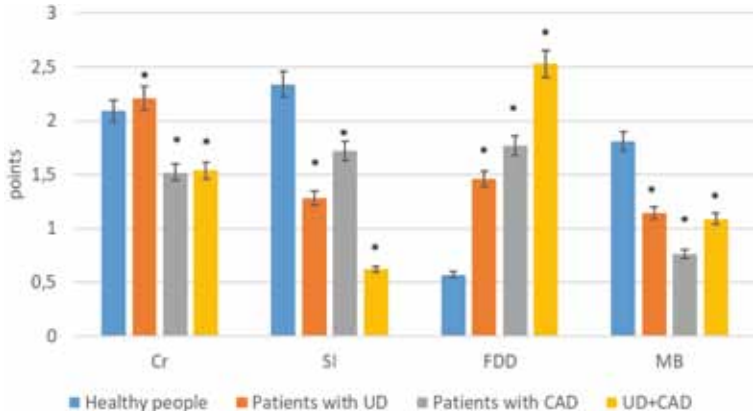

*Fig. 1. Visuametry of oral fluid facias in healthy people and patients with ulcer disease (UD), coronary artery disease (CAD) and combined pathology (UD+CAD) Cr — crystallizability, SI — structure index, FDD — facia destruction degree, MB — clearity of margina l belt; * — statistical value of differences to healthy people is p<0.05*

This is indicated by a pronounced drop in the level of the structural index combined with a minimal increase in crystallizability. In the presence of only ischemic heart disease, a moderate drop in saliva crystallizability was observed in combination with a similar, but smaller modulating change in the index of the structure of the biological environment relative to patients with isolated gastric ulcer. It should be noted that in the dried samples of oral fluid of this contingent of patients, the destruction of elements was more pronounced than only in gastroduodenal ulcerogenesis. In addition, the representatives of this group were found to have the minimum diameter of the marginal zone of the facia.

CONCLUSION

Based on the performed studies, it was shown that the most significant shifts in the crystal formation of oral fluid were detected in patients with a combination of coronary artery disease and gastric ulcer. Thus, the crystallograms of these patients are characterized by a clearly visible predominance of single-crystal elements over dendritic ones. The total density of structures in the facias is significantly reduced in comparison with both healthy people and patients of other groups. The severity and depth of metabolic disorders occurring in the oral fluid of patients with combined pathology is additionally indicated by the subtotal destruction of the structural elements of the facias.

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ORTHODONTIC TREATMENT FOR CONGENITAL CLEFT LIP AND PALATE IN CHILDREN

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ABSTRACT — One in 1,000 newborns appears with a congenital maxillofacial anomaly, which accounts for about 0.04% of the world's entire population of the planet. Patients with cleft lip and palate have a significantly lower quality of life. Early orthodontic treatment (EOT) offered to children from the first days of life is a preparatory link in the preoperative period, laying favorable grounds for surgical intervention. EOT is a reasonable option to separate the oral cavity from the nasal cavity, to prevent consequent issues as well as to bring feeding back to the normal. This study involved clinical examinations and early orthodontic treatment of 84 children with congenital bilateral cleft upper lip and palate (CBCULP) from the first days of life and infants based on their referrals coming from all regions of the Republic of Tajikistan embracing the period of 2015 to 2019. Newborns with bilateral CULP within 5 days following birth, and infants who were referred for early orthodontic treatment, had their upper jaw cast model prepared using specially designed and modified spoons for taking impressions in case of cleft lip and palate. Within the study, unrelated marriages prevailed 3.4 times over related ones, which accounted for 22.6% of the cases examined. There were 1.58 times more boys than girls. Close relatives featured congenital maxillofacial abnormalities in 16.1% of the cases. The share of related marriages was 12.9%. Follow-up period — 2016–2017; the patients' age — from the birth period to 1 year. The children were divided into two groups. In the main group, EOT was performed using a dental obturator for orthodontic treatment of children with CBCULP prior to the surgery (n=43). In the comparison group, treatment was carried out in the conventional way (n=41). Before the surgery, all the children were examined through clinical, anthropometric and photometric methods. The statistical processing of the obtained data revealed that before the start of treatment, the studied groups were comparable with no statistically significant differences identified. After the treatment, the age, the weight, as well as the height of the children expectably changed in both groups ($p<0.001$).

KEYWORDS — congenital bilateral cleft upper lip and palate, orthodontic treatment, standardized spoon, dental obturator.

INTRODUCTION

Dentofacial issues and deformities are ranked the third most popular among dental diseases giving way to dental caries and periodontal diseases [1–14]. Congenital bilateral cleft upper lip and palate (CBCULP) accounts for 12–25% of cases out of other types of cleft face and belongs to severe maxillofacial pathologies [15, 16]. One in 1,000 children is born with the pathology in question, which is about 0.04% of the globe's population. Patients with cleft lip and palate suffer from significantly lower quality of life [17, 18]. Early orthodontic treatment (EOT) for children from the first days of life is an element that serves a preparatory link within the preoperative period, which is a factor favorable for surgical intervention [19, 26–31]. EOT is a good option to treat cases implying separating the oral cavity and the nasal cavity, as well as to prevent secondary deformities and improve feeding [20–22].

Aim of the study

is to increase the effectiveness of orthodontic treatment offered to young children with CBCULP using specifically designed devices.

MATERIALS AND METHODS

A clinical examination and early orthodontic treatment were offered to 84 children with CBCULP, subject to their self-reports (age group — the birth time through infant age) embracing all regions of the Republic of Tajikistan within the period of 2015–2019. Newborns with CBCULP aged up to 5 days after birth and infants, who came seeking early orthodontic treatment, had their upper jaw models taken using alginate mass and spoons modified specifically to take impressions of cleft lips and palates (Certificate for innovation proposal # 3297/R 512 of November 9, 2012) (Fig. 1) [23–25].

RESULTS AND DISCUSSION

Generalized archival data of 2,630 children with CBCULP who were brought to the clinic seeking respective help in the Republic of Tajikistan show that the total number of patients went up 1.79 times within in the period of 2009–2019. Boys accounted for 55.1% of the patients. The studied pathologies included:

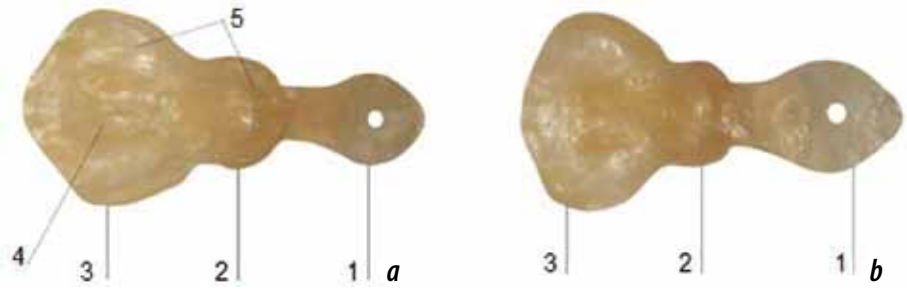

Fig. 1. Spoons modified to take impressions of cleft lips and palates (intermaxillary bone position in the middle of the upper jaw) (a — view from inside, b — view from outside): 1 — handle, 2 — intermaxillary plate, 3 — side board, 4 — middle protrusion, 5 — alveolar and intermaxillary parts tray

CUCULP (90.3%) and CBCULP (9.7%). The occurrence rate for the first pathology went up by 1.66 times, while for the other one the same increase index was 3.27 times (Fig. 2, 3).

An analysis of the outcomes obtained through surveying mothers/parents of children with CBCULP revealed that 100% of the children were born in due time, while the social status of families and the development forecast for the newborns were good. The parents' age at the time their respective child was born with CBCULP ranged from 20 to 43, the average age of the mothers was 27.8, the fathers' median age being 28.9. Unrelated marriages prevailed 3.4 times over related ones, which accounted for 22.6% of the case body. There were 1.58 times as many boys compared to girls. Closely related individuals were observed to have congenital maxillofacial issues in 16.1% of the cases. Related marriages accounted for 12.9%.

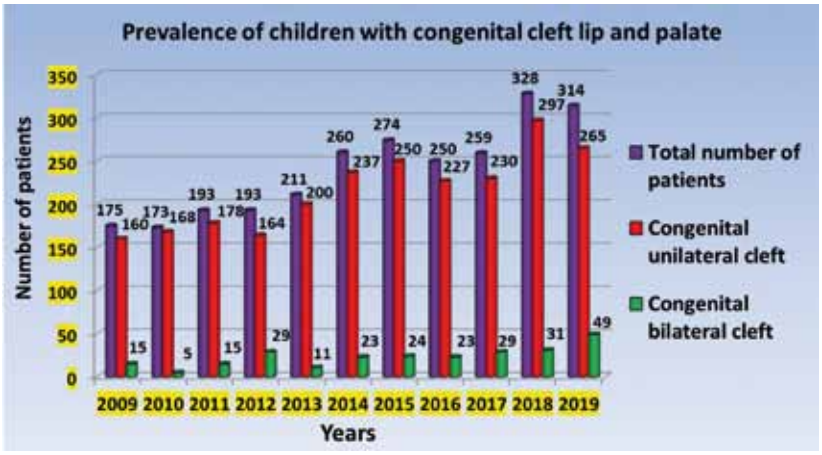

Fig. 2. Prevalence of children with congenital cleft of the upper lip and palate in the Republic of Tajikistan (City of Dushanbe) according to the data of appealability from 2009 to 2019

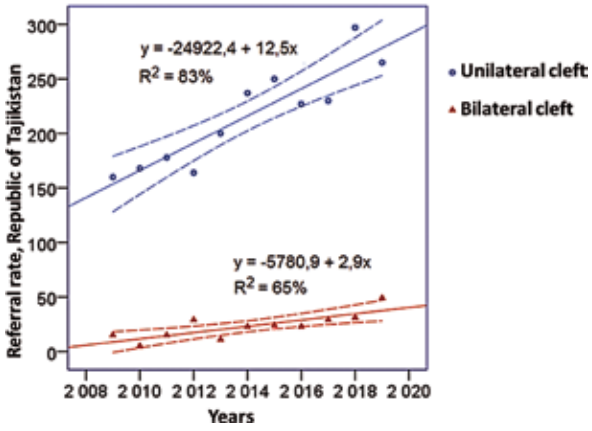

Fig. 3. Graphic representation of general data by the type of pathology in children with CULP based on referral in the Republic of Tajikistan (City of Dushanbe): a — smoothing by a linear filter, b — approximation by linear regression: regression lines and their 95% CI, the resulting equations and their determination coefficients (R2)

Feeding of newborns was mostly artificial (93.5%). Within their respective families, according to the order of birth, 32.3% of the newborns with CBCULP were first babies, of which 9.7% of the parents were related. The rates of the babies born second, third and fourth were 16.1%, 19.4%, and 16.1%, respectively. The seventh (3.2%) and eighth (3.2%) children in the family were born to parents aged 38 (mother) and 43 (father). The survey revealed that during pregnancy,

expectant mothers were healthy in 51.6% of the cases; 25.8% were diagnosed with anemia; 19.4% of all the cases had acute respiratory viral infection (ARVI), another 3.2% of the cases suffering from herpes.

84 children with CBCULP underwent examination and treatment at the Shifobakhsh medical consulting office of the Department of Child and Adolescent Maxillofacial Surgery, Research Center, Republic of Tajikistan, with a follow-up period of 2016–2017. The patients' gender distribution was as follows: boys — 55%, girls — 45%. The patients' age ranged from the birth day to 1 year. The patients were divided into two groups. In the main group, The EOT was performed using a dental obturator for orthodontic treatment of children with CBCULP before surgery (n=43). In the comparison group, the treatment relied on the non-conventional method (n=41). Prior to the surgery, all the children were examined using clinical, anthropometric and photometric methods. All the newborns in the main group, while remaining in a horizontal position only, had their upper jaw impression taken using an alginate mass, whereas the impression covered the intermaxillary bone. At the time the cast was made, the baby had to be hungry and crying, the cry testifying to its safety. Further, an analysis of the upper jaw cast model was performed followed with production of the obturator for dental orthodontic treatment of CBCULP in children, which can be fixed securely to the upper jaw due to the nasal part with no extra fixing elements involved (Fig. 4).

weight, and height changed naturally in both groups ($p<0.001$). The jaw cast model parameters in the main group changed significantly, whereas in the comparison group, the treatment was carried out using a rubber elastic bandage. The treatment duration was 6–8 months and depended on the baby's somatic status; there were certain issues observed during feeding — injured skin on the upper lip middle at the nostril area. In view of that, there were some corrective measures taken with a new elastic rubber bandage produced. While the conventional method was employed, there was some convergence identified of the maxillary bone with the upper lip middle at the anterior part of upper jaw the alveolar process, as well as a flattening in the upper lip middle. During that, the vomer retained its position with the deformation getting worse. As for the cast model parameters in cases where the conventional treatment method was employed, the observed changes were slight. The only statistically significant change was an 11.7% decrease in the B-F1 distance ($p=0.017$).

A comparison of jaw cast model parameters through the groups undergoing early orthodontic treatment produced the following significant differences: lower BC values in the main group (10.3±0.9 mm vs. 16.0±2.3 mm in the comparison group, $p=0.013$); EB (29.4±1.5 mm vs. 34.5±1.3 mm in the comparison group, $p=0.033$) as well as higher DE values (36.6±0.3 mm vs. 34.0±0.7 mm in the comparison group, $p=0.001$).

a *b* *c*

Fig. 4. *Impression from the upper jaw produced with a specifically designed spoon (a); inner surface of the dental obturator used to perform orthodontic treatment of CBCUL in children (b); dental obturator in the baby's oral cavity (c)*

The designed obturator helps improve feeding as well as the maxillary alveolar arch shape. There was no protrusion of the jawbone observed, whereas the vomer was located on the symmetry axis.

The statistical processing of the obtained data revealed that before the treatment was started, the groups were comparable in terms of their major indicators, with no statistically significant differences to be observed. Following the treatment, the babies' age,

The study implied effectiveness quantitative assessment of treatment offered to babies with CBCULP based on a specifically developed method, matched against patients treated through a conventional method. Low treatment effectiveness, which manifested itself through insufficient capacity of milk-sucking and eating independently, was observed in 11 babies from the comparison group (27%) and only in 2 patients in the main group (5%). The absolute risk

reduction (ARR) was 22% at a CI of 95%: 6.7–37.7%. This ARR value corresponds to a NNT of 5 (95% CI: 3–15). This means that it would take offering the newly developed EOT to 5 children, in order to guarantee respective improvement in one extra child. The relative risk reduction was 82.7% (95% CI: 26.4–95.9%); the odds ratio was 0.13 (95% CI: 0.03–0.63). The results were considered statistically significant at p=0.012.

CONCLUSION

The study described above was the first focusing on the frequency and prevalence of CBCULP in babies, embracing the period of 2009–2019 in the municipal areas of Tajikistan. The questionnaire survey carried out among the babies' parents revealed the effect that related marriages have on an increase in the CBCULP occurrence and prevalence rate. The study offered the first ever explanation to the method of employing early orthodontic treatment for babies with CBCULP (RF patent # 2735063) performed with the dental obturator for orthodontic treatment of children with CBCULP (Republic of Tajikistan patent for invention # TJ 941) and the obturator for early orthodontic treatment of children with CBCULP (RF patent # 199314), all this aimed at improving the spatial ratio of the maxillary bone and upper jaw fragments, taken as a preparatory stage for comprehensive treatment. If matched against the conventional treatment, early orthodontic treatment relying on a modified dental obturator used to treat babies with CBCULP, yielded significantly better outcomes.

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