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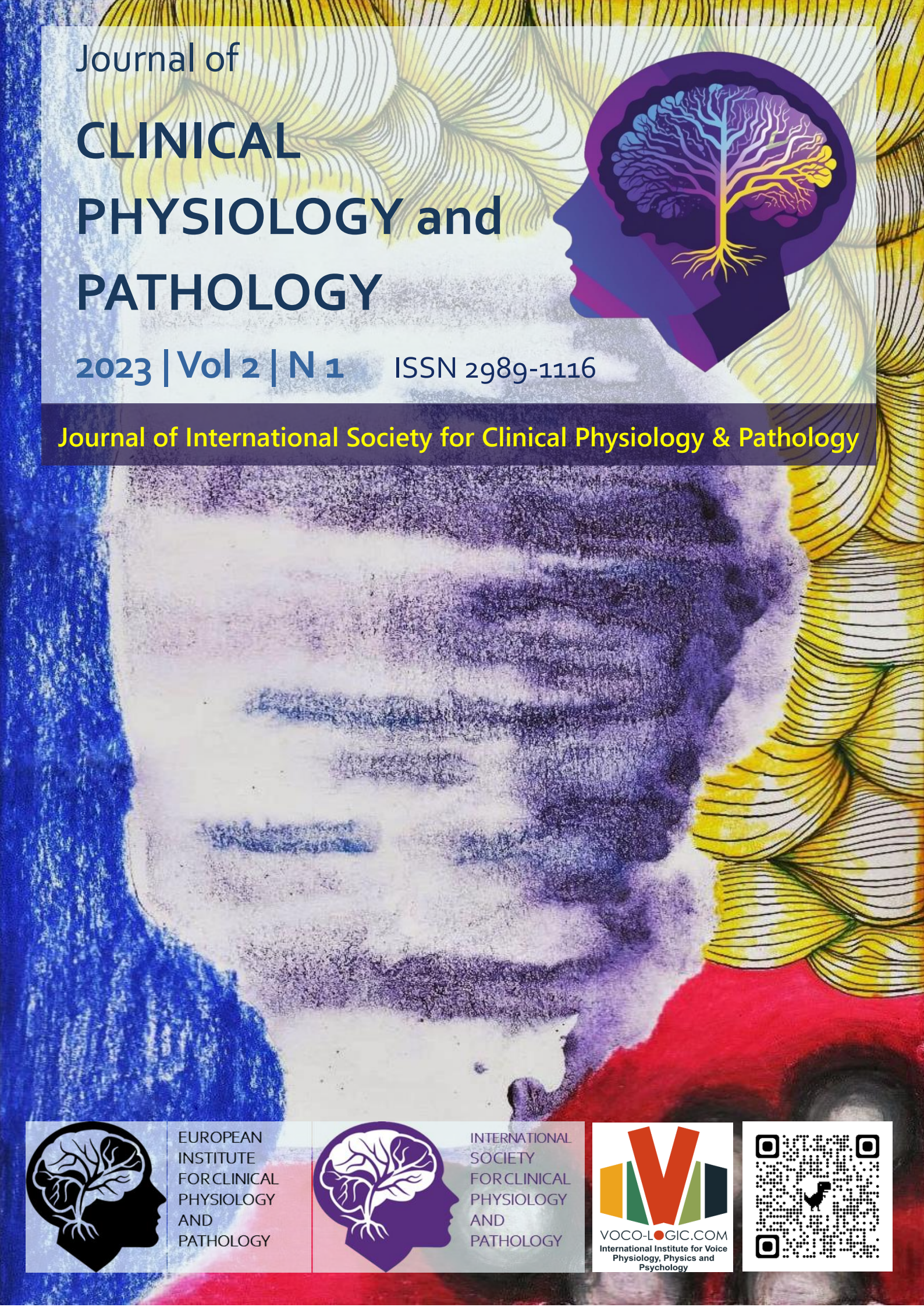

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Article

Pathological changes in traumatization of the upper jaw under the conditions of sinus lifting simulation in rats

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Abstract: Background. Simulation of surgical interventions in the maxillofacial region provokes a number of physiological reactive changes in the body of experimental animals. Thus, it was revealed that there are changes in the balance of the autonomic nervous system, activation of the hypothalamic-pituitary-adrenal and adrenergic systems, changes in behavioral reactions, as well as the occurrence of anxiety state. At the same time, the morphological causes of such reactions are not fully understood. Aims. The study provides data on morphological changes in the area of experimental trauma of the upper jaw during modeling of sinus lifting, dental implantation in rats. Materials and Methods. The study used male rats of the Wistar line weighing 210-280 g. Surgical interventions in all groups were performed under general anesthesia with the introduction of a solution of Zoletil 100 into the tail vein. In the first group, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa according to the standard method. In the second group (n=10), dental implantation with a titanium implant was performed after the hole was formed using a drill. In the third group (n=10), only a hole was made in the alveolar process of the upper jaw without subsequent manipulations. This group was a comparison group for groups with dental surgical interventions. In the fourth group, 10 rats underwent sinus lifting with bone chips with simultaneous implantation of a titanium implant. In the fifth group (n=10), with the help of a microdrill through a pre–formed hole in the alveolar process of the upper jaw, maxillary sinus was performed with damage to the mucous membrane of the ipsilateral maxillary sinus. Results. First group. On day 2, there was focal desquamation of a single-layer multi-row ciliated epithelium with local defects up to the basement membrane, multiple hemorrhages (extensive, with the presence of blood clots) in the mucosal lamina proper, mucosal edema (common), moderate diffuse infiltration (polymorphocellular). On the 4th day, signs of acute exudative serous inflammation were revealed. Second group. On the 2nd day, the wound surface contained cellular detritus, leukocytes, blood clots and a scab that did not adhere to the wound surface. (Fig. 2). On the 4th day, the signs of inflammation were not significant, macrophages, fibroblasts and lymphocytes predominated at the site of injury. On the 6th day, the formation of a clear demarcation line in the area of damage was noted with the formation of a shaft containing leukocytes and fibroblasts. Third group. On the 2nd and 4th days, the condition of the damaged tissues was characterized by the formation of scabs consisting of cellular detritus, necrotized tissue, leukocytes, erythrocytes (Fig. 4). On the 6th day, an accumulation of fibroblast-like cells, macrophages, and the formation of fibers of newly formed connective tissue was observed in the area of damage. Fourth group. On the 2nd and 4th days, extensive hemorrhages, the formation of scabs consisting of cellular detritus, necrotized tissue, leukocytes, erythrocytes were noted in this group. Fifth group. On the 2nd and 4th days, multiple hemorrhages with the presence of exudate blood clots were observed in the area of injury. Cellular detritus and necrotic tissue were present. Mucosal edema was widespread with extensive polymorphocellular infiltration. Conclusion. Different surgical interventions lead to different morphological changes, which probably affects the severity of physiological reactions under surgical stress.

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Keywords: septoplasty, deviated septum, sinus lift, dental implantation, inflammation.

1. Introduction

Simulation of surgical interventions in the maxillofacial region provokes a number of physiological reactive changes in the body of experimental animals [1-3]. Thus, it was revealed that there are changes in the balance of the autonomic nervous system, activation of the hypothalamic-pituitary-adrenal and adrenergic systems, changes in behavioral reactions, as well as the occurrence of anxiety state [4-12]. At the same time, the morphological causes of such reactions are not fully understood [13-14].

2. Materials and Methods

The study used male rats of the Wistar line weighing 210-280 g. Surgical interventions in all groups were performed under general anesthesia with the introduction of a solution of Zoletil 100 into the tail vein. In the first group, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa according to the standard method [4, 5]. In the second group (n=10), dental implantation with a titanium implant was performed after the hole was formed using a drill (Fig. 1a).

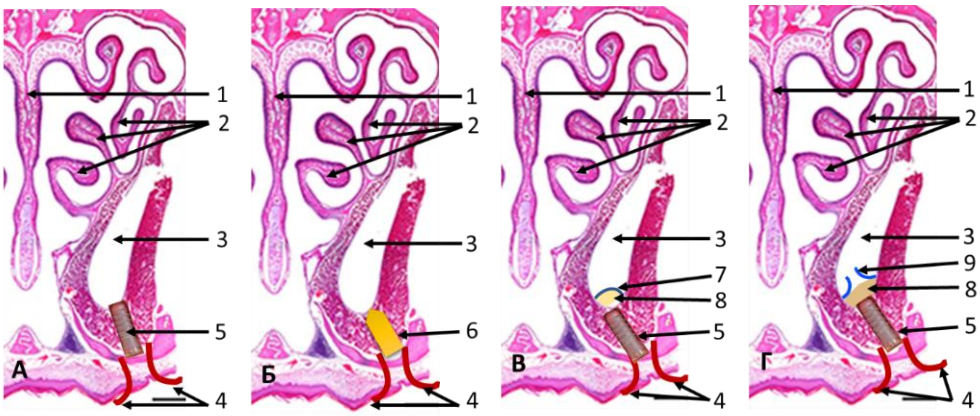

Figure 1. Schemes for modeling dental implantation (group 2) (a), the formation of a well in the alveolar process of the upper jaw (group 3) (b), sinus lifting with simultaneous implantation (group 4) (c) and sinus lifting complicated by maxillary sinusitis (group 5) (d).
Note: 1 – nasal septum; 2 – nasal concha; 3 – maxillary sinus; 4 – mucous-periosteal leaves after incision; 5 – implant; 6 – hole; 7 – mucous membrane of the paranasal sinus; 8 – bone chips; 9 – damaged mucous membrane of the paranasal sinus.

In the third group (n=10), only a hole was made in the alveolar process of the upper jaw without subsequent manipulations (Fig. 1b).

This group was a comparison group for groups with dental surgical interventions. In the fourth group, 10 rats underwent sinus lifting with bone chips with simultaneous implantation of a titanium implant (Fig. 1c).

In the fifth group (n=10), with the help of a microdrill through a pre–formed hole in the alveolar process of the upper jaw, maxillary sinus was performed with damage to the mucous membrane of the ipsilateral maxillary sinus (Fig. 1d).

3. Results

3.1. First group

On day 2, there was focal desquamation of a single-layer multi-row ciliated epithelium with local defects up to the basement membrane, multiple hemorrhages (extensive, with the presence of blood clots) in the mucosal lamina proper, mucosal edema (common), moderate diffuse infiltration (polymorphocellular). On the 4th day, signs of acute exudative serous inflammation were revealed. The exudate in damage is cloudy, with an admixture of erythrocytes, leukocytes, mucus. On the surface of the mucous membrane is an accumulation of cellular detritus containing necrotized epithelial cells, neutrophils and eosinophils. Hyperemia of the mucous membrane is moderate with diapedetic hemorrhages, moderate edema, widespread. Inflammatory infiltrates in the

own plate of the mucosa are multiple, abundant, mainly neutrophilic. On the 6th day, the exudate in damage was insignificant, there were also foci of cellular detritus. Hyperemia of the mucous membrane at this time was moderate along with minor local edema. The inflammatory infiltrate in the mucous membrane was moderate, polymorphocellular with the representation of macrophages.

3.2. Second group

On the 2nd day, the wound surface contained cellular detritus, leukocytes, blood clots and a scab that did not adhere to the wound surface. (Fig. 2). On the 4th day, the signs of inflammation were not significant, macrophages, fibroblasts and lymphocytes predominated at the site of injury. On the 6th day, the formation of a clear demarcation line in the area of damage was noted with the formation of a shaft containing leukocytes and fibroblasts. (fig. 3)

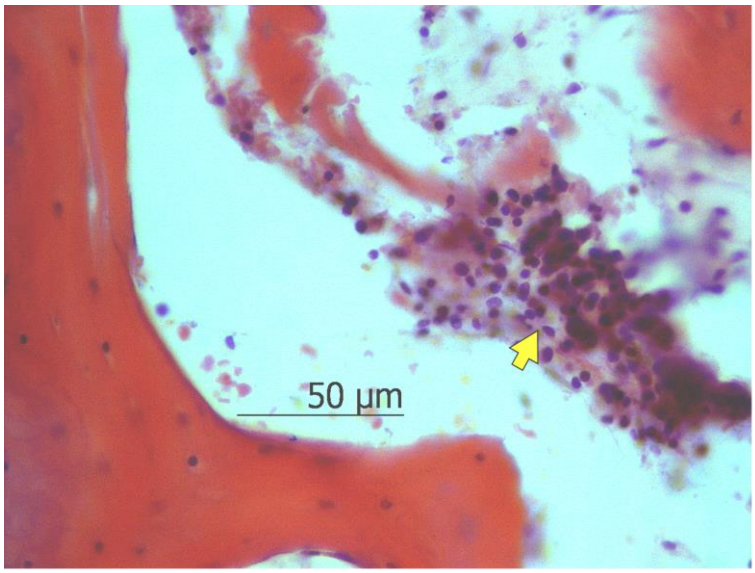

Figure 2. The arrow indicates a scab that is not adjacent to the surface of the bone.

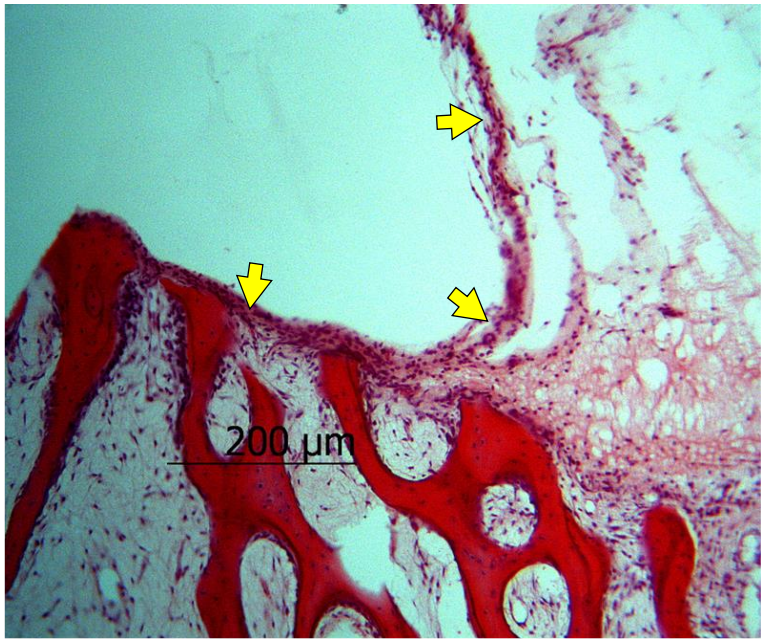

Figure 3. Yellow arrows indicate the demarcation line in the area of damage to the upper jaw.

3.3. Third group

On the 2nd and 4th days, the condition of the damaged tissues was characterized by the formation of scabs consisting of cellular detritus, necrotized tissue, leukocytes, erythrocytes (Fig. 4). On the 6th day, an accumulation of fibroblast-like cells, macrophages, and the formation of fibers of newly formed connective tissue was observed in the area of damage (Fig. 5).

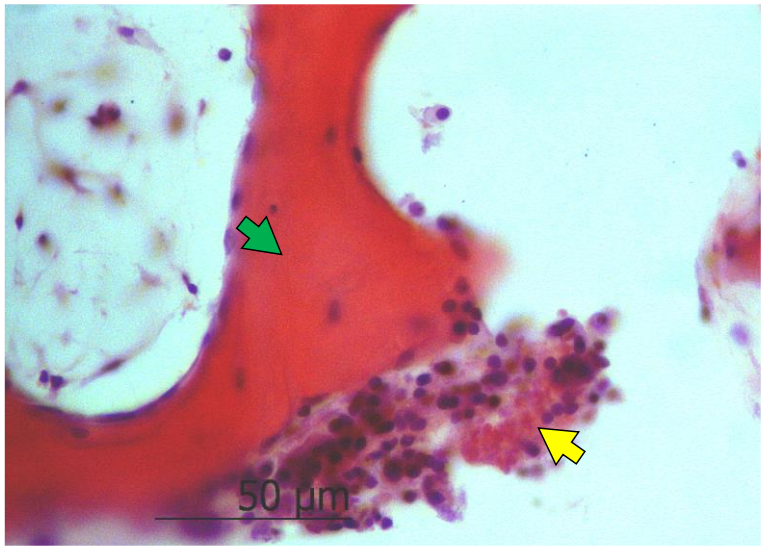

Figure 4. The yellow arrow indicates a scab adjacent to the surface of the spongy bone (green arrow)

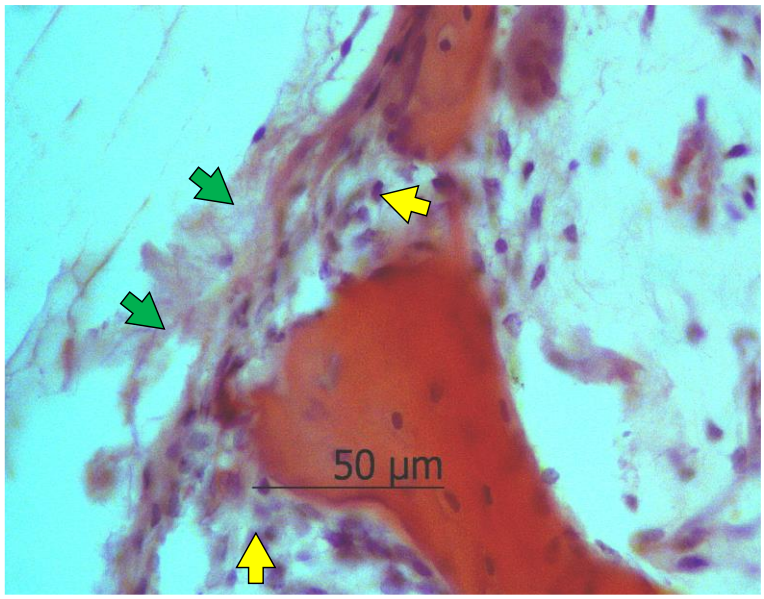

Figure 5. Fibroblasts (yellow arrows), connective tissue fibers (green arrows).

3.4. Fourth group

On the 2nd and 4th days, extensive hemorrhages, the formation of scabs consisting of cellular detritus, necrotized tissue, leukocytes, erythrocytes were noted in this group (Fig. 6). On the 6th day, there was a representation of macrophages, fibroblasts, mast cells in the area of surgical damage, and the absence of scabs, hemorrhages and detritus (fig. 7).

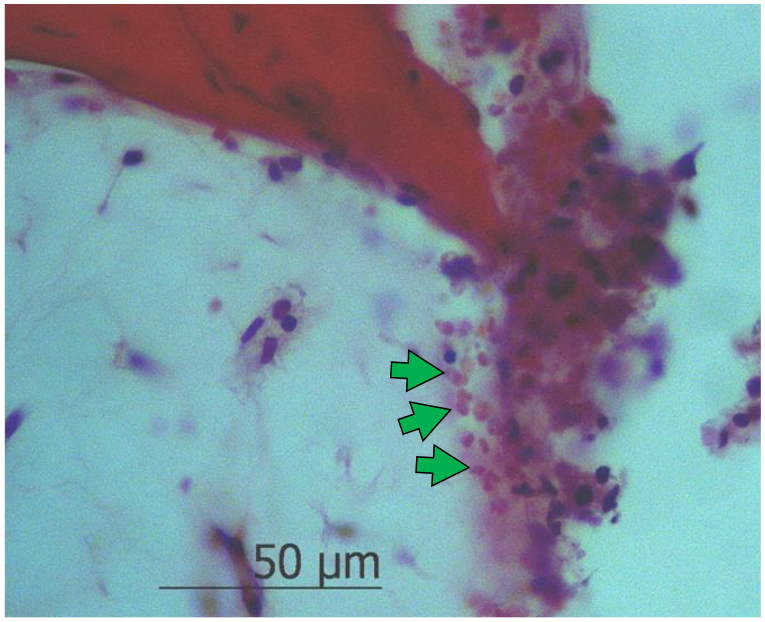

Figure 6. The arrows indicate the leukocytes in the scab.

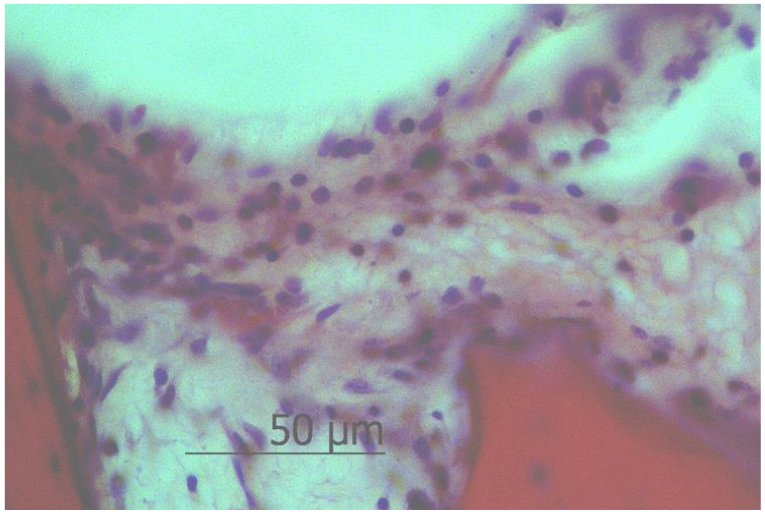

Figure 7. The healing process after sinus lifting with bone chips with simultaneous implantation of a titanium implant.

3.5. Fifth group

On the 2nd and 4th days, multiple hemorrhages with the presence of exudate blood clots were observed in the area of injury. Cellular detritus and necrotic tissue were present. Mucosal edema was widespread with extensive polymorphocellular infiltration (Fig. 8). On the 6th day, mucosal hyperemia was moderate, cellular infiltration was insignificant with a predominance of macrophages. In some foci, a significant representation of fibroblasts and vascular neoplasm in the resorption niche was noted (Fig. 9).

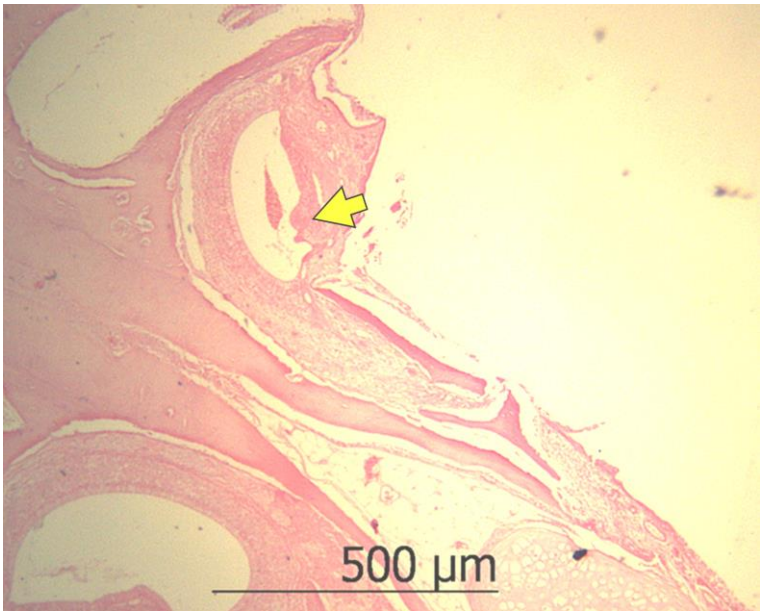

Figure 8. A section of the damaged mucous membrane of the maxillary sinus.

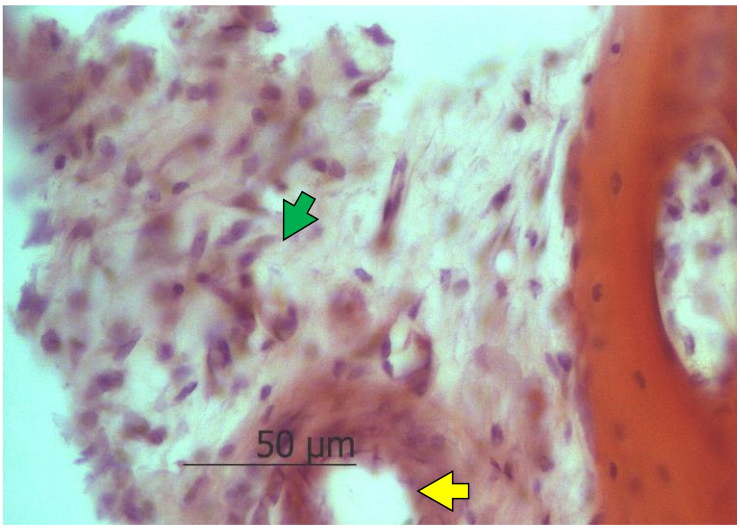

Figure 9. A newly formed vessel (yellow arrow) in the resorption niche, surrounding connective tissue (green arrow).

4. Conclusions

Different surgical interventions lead to different morphological changes, which probably affects the severity of physiological reactions under surgical stress.

Conflicts of Interest: The authors declare no conflict of interest.

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Clinical case

Implant-prosthetic dental rehabilitation after autopolytrauma

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Abstract: With extensive damage of the facial skeleton, multiple bony and soft tissue cicatricial defects and deformations are formed. Traditional methods of reconstructive are reliably not able to restore the defects fully. Often the bony structures of the facial skeleton can't be restored in one stage. Additional reconstructive surgeries are needed. A problematic situation is the condition after multiple surgeries in the defect area. Failure of bone grafting is associated with cicatricial deformities and lack of soft tissue, lack of gingiva, defects in the vestibule and damaged periosteum. The main problem is constriction and subsequent atrophy and deformation of the soft tissue in the area of the defect. This complicates further treatment and often it isn't possible to restore the bone volume required for a successful dental implantation. Implant prosthetic rehabilitation in the area of extensive bone defects after a facial injury requires preparation that is more careful, design and prototyping of the outcome with the use of computer programs and diagnostic models. Biocompatible materials for dentistry and maxillofacial surgery are clinically proven and recommended for usage in patients at the treatment stages. Clinical experience with individual temporary endoprosthesis, so called "tissue expander", produced by layer-by-layer synthesis (3D-printing) from biologically inert plastic based on CT data of the patient is presented in this article. The expander is made in the form of a 3D element to form the required soft tissue volume in the patient for 4-6 months and is fixed in place subcutaneously, in the area of mandibular frontal defect, using intraosseous screws. Dental implants were placed laterally on both sides. The following was carried out intraoperative direct replacement, fabrication and placement in the mouth of a temporary screw-retained prosthesis.

Keywords: facial trauma; fracture; maxillofacial defect; soft tissue constriction; endoprosthesis; autosseous plasty of the jaw; dental implantation.

1. Introduction

The question regarding the search for the optimal method of defect reconstruction and restoration of the integrity of the skull and facial skeleton remains topical. The works devoted to the study of the possibility of facial skeleton reconstruction by free bone autografts with one-stage or subsequent dental implantation are of interest [1,2]. The possibility of obtaining significant amounts of autologous material is very limited, and the donor is usually subjected to serious surgical interventions during its harvesting. The most important in autologous bone grafting is the recipient area, especially after significant traumatic injuries [2,3,13,15]. Violations of bone grafting protocols and lack of soft tissues can lead to autologous bone blocks eruption, suture discrepancy, and loss of the graft. The key factor of success is the work with tissue flaps and their passive positioning. With significant bony defects of the face and jaws, the soft tissues are deformed and not always sufficient to cover the flap. The possibilities of preliminary volume augmentation and quality of soft tissues in the area of the bone defect are studied [4,16]. Tissue silicone expanders have been used in oral surgery for quite a long time, but the result is not always stable [5]. 3D-printing of bioinert materials is actively being introduced in bone surgery [6,7,18]. Positive experience has been accumulated in the use of bioinert plastic and composite materials objects (experimental animals) [8,17]. In addition, the most important criterion is the possibility of protecting the augmentation area in the clinic of dentistry and maxillofacial surgery with temporary prosthetic constructions. This will improve healing and is a prevention of suture divergence [9,14]. Important criteria are treatment time and its reduction and the quality of life of the patient, especially for interventions in the frontal zone of the jaws [10]. We present clinical experience with the use of an individual temporary endoprosthesis, the so-called "tissue expander", manufactured using additive technologies (3D-printing). The expander was fabricated by layer-by-layer synthesis from a biologically inert plastic to form the required soft tissue volume for a period of four-six months. In a clinical example the possibilities of 3D-printing as a creation of an individual temporary endoprosthesis were realized, which allowed to increase the quality of surgical intervention and optimize conditions for subsequent autologous bone grafting and successful implantation in the area of the defect. In addition, the possibility of dental implants installation in the area of the defect and making a temporary screw prosthesis in the shortest possible time was realized [11,12]. All this has shortened the treatment period and improved the patient's quality of life.

2. Patients and Methods

The anamnesis data established: auto polytrauma, with extensive damage to the facial skeleton bones in April 2021. On April 30, 2021, he was delivered from the accident site to Sochi Hospital with complaints of asymmetry and pains in the facial area, disorder of teeth occlusion. Allied specialists examined the patient. Final diagnosis was closed craniocerebral injury. The patient had a concussion of the brain, bilateral fracture of the zygomatic-orbital complex. Fracture of the upper jaw in the type of Le Fore 2-3. Fracture of the lower jaw in the frontal region. Bone defect in the region of teeth 3.4 - 4.3. ICD 10 S02.7. On admission: general condition is severe. Internal organs were within the physiological norm. Locally: the configuration of the face was changed due to post-traumatic edema in all areas of the face. Infraorbital hematomas were on the right and left side. Lacerations of the lower lip was on the left side, 10 cm long. Oral side: skeletonized lower jaw in the area of missing teeth 3.4 - 4.3, also pathological mobility of the jaw. The bite is displaced and was classified as open bite.

Surgical treatment. Repositioning, metal osteosynthesis of the upper and lower jaws, zygomatic-orbital complex with titanium plates. Intermaxillary splinting was made according to Tigerstedt. Primary surgical treatment and suturing of wounds were done. The patient underwent a course of anti-inflammatory therapy. The mouth opened within 20 mm. The patient was discharged under the supervision of a dental surgeon at the place of residence. On May 14, 2021 in Krasnodar, the patient underwent additional treatment of metal osteosynthesis of zygomatic-orbital complexes. The cause of the complaint was deformity of the zygomatic-orbital regions and recurrent diplopia. It was recommended: to solve the problem of the possibility to eliminate the bone defect in the frontal part of the alveolar part of the lower jaw - augmentation with the purpose of further implantation and prosthetics.

The patient was admitted to the University Clinical Hospital № 1 of the First Moscow State Medical University named after I.M. Sechenov in March 2022. Facial skeleton CT: extensive defect in the alveolar part of the lower jaw in the area of missing 3.4 - 4.3 teeth (Fig. 1).

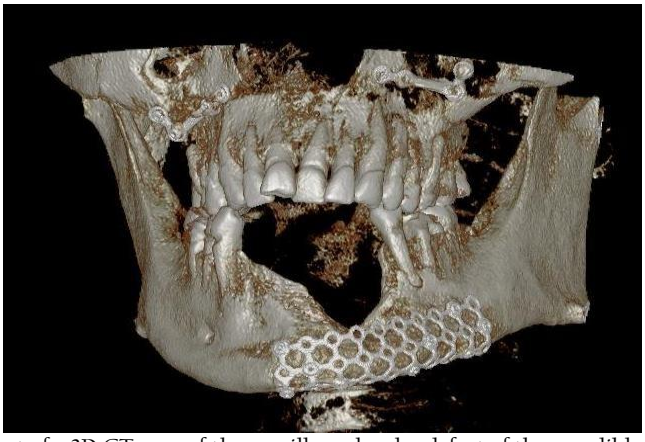

Figure 1. Screenshot of a 3D CT scan of the maxillary alveolar defect of the mandible.

Complaints: absence of teeth on the lower jaw in the frontal aspect, functional and aesthetic discomfort, difficulty in chewing and difficulties in eating and speaking.

The patient is a doctor by occupation. During the planning stage of the surgery, the following activities were performed:

- polymeric models of expanders and jaws were investigated,
- the size, insertion path, and fixation zones of an individual temporary endoprosthesis (tissue expander) are coordinated
- size and number of screws for fixation
- the directions and channels in the endoprosthesis for inserting screws are set in the software package.

Planned Intervention:

1. Design and prototyping of the intervention on 3D-models, coordination of size, shape, insertion path, and points of fixation of an individual endoprosthesis-expander
2. Removal of the metal structure.
3. Dental implantation in the lower jaw area. Dental implantation in the lower jaw area of teeth 35,36 removed and 42,43
4. Installation of an individual endoprosthesis-expander in the region of the lower jaw in the frontal part of the lower jaw-area of the defect.
5. CAD/CAM fabrication of a temporary implant-supported screw-retained prosthesis

We made prototypes for planning the surgery - samples of expanders and jaw models, coordinated the size, the path of insertion and fixation zones of the endoprosthesis, the size and number of screws for fixation (Fig. 2)

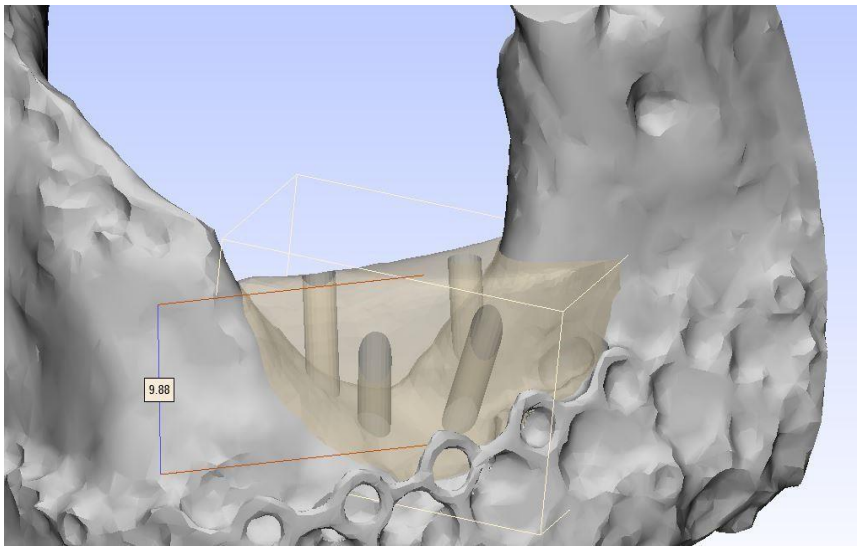

Figure 2. Digital 3D-modeling of the endoprosthesis.

Mock-ups of the jaw and expanders were made:

- Additive technology: SLS (selective laser sintering) - layer-by-layer fusion of polymer powder with a laser beam. The jaw model is also quite adequately obtained by FDM-printing (fusing deposition modeling) - layer-by-layer extrusion of polymer thread (filament), for example, from polycarbonate or ABS plastic.
- Expander fixation was planned with titanium screws to the body of the jaw. sizes 1.5-12 mm
- Equipment for making layouts: additive unit EOSINT, EOS company (Germany)
- Layout materials: biocompatible polymer powder polyamide 12 (PA2200) (Fig. 3).

Figure 3. Mock-ups of the jaw and endoprosthesis-expander.

Under endotracheal anesthesia and local anesthesia with 4% articaine the mucosal-periosteal flap was detached. When making the incision, it was important to preserve the keratinized area of the attached gingiva in the implant area. The mesh metal construction in the frontal area of the lower jaw region was removed (Fig. 4).

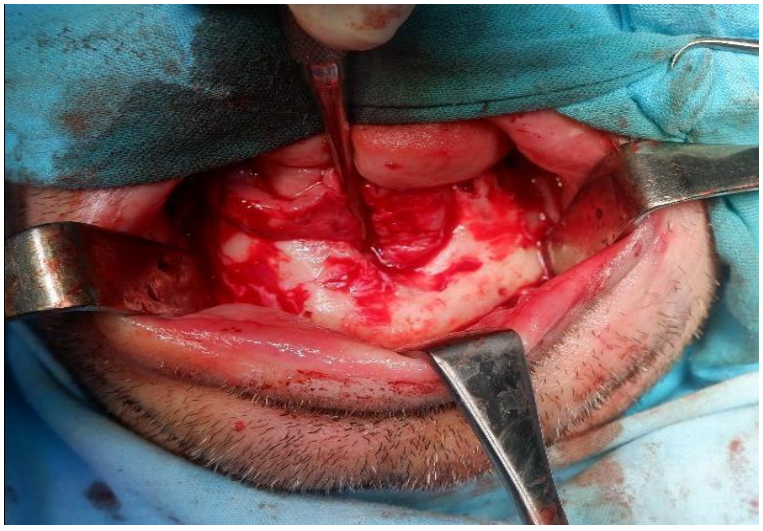

Figure 4. Skeletonized lower jaw, removed titanium plate, appearance of the defect.

Teeth 35, 36 were extracted, dental implants were placed in the cavity of tooth 35, anterior root of tooth 36 and 42, 43. Pterygoid I-implant BioLine implants with next coming measures: 36 - 3/75-18 mm 35 - 4/2 -20, 42 - 4.2-22 and 43 - 4.2/22 mm, respectively, were placed into the dental sockets.

Conical screw abutments with a neck height of two mm were placed in the implants and covered with protective caps. The individual temporary endoprosthesis, "tissue expander", was fixed subcutaneously, in the area of the mandibular frontal defect with intraosseous screws 1.5 mm-12 mm (Fig. 5).

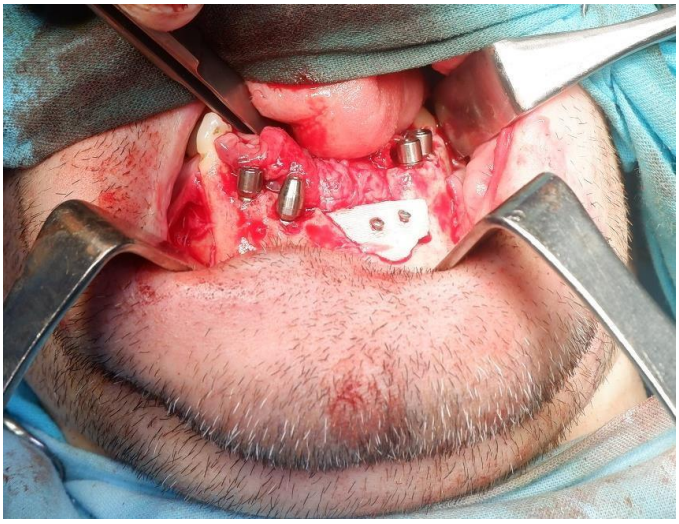

Figure 5. Implants, screw abutments and caps were placed, and the endoprosthesis was fixed.

Resorbable 5.0 Monisin Resorba sutures were stithed. Intraoperatively, impressions were taken using a custom-made spoon and transfer-checks. The bite was determined. Temporary screw dentures were made in the dental laboratory in 24 hours by CNC milling from PMMA polymer composite (Fig. 6).

Figure 6. PMMA bridge, which was made by milling.

Direct intraoperative prosthetics was performed, the prosthesis was placed in the oral cavity, fixed with M1.4 screws to the abutments. The wells of the screws were sealed with A-silicone (Fig. 7). Control radiological diagnostics was carried out (Fig. 8).

Figure 7. View of a patient with a prosthesis in the oral cavity.

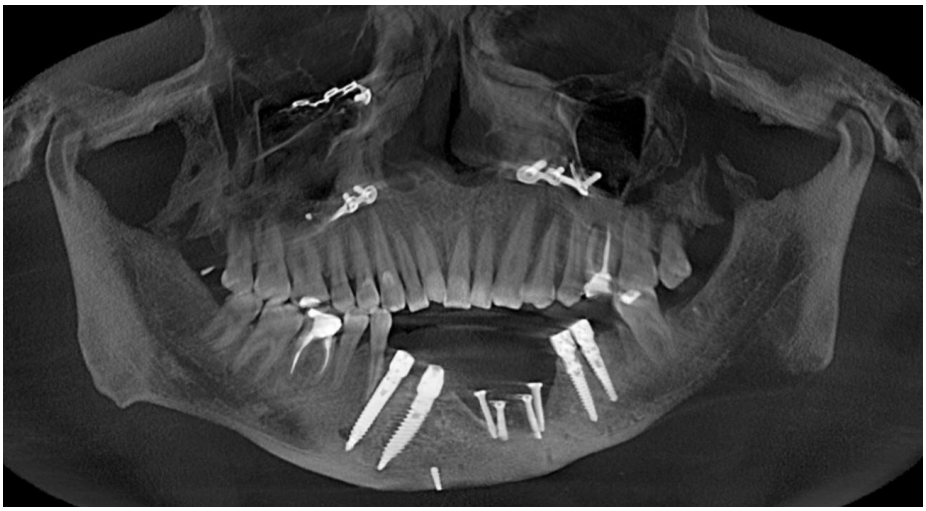

Figure 8. Control CT-scan after surgery, implants and expander have been placed.

The patient was referred for rehabilitation. In 5 months, the patient is scheduled to have the expander removed, autologous bone grafting with bone chips in height, and placement of two implants in the defect area.

3. Results

At the stage of surgical intervention, the main difficulties arose in the removal of the reticular metalwork in the frontal area of the lower jaw. Tooth extraction had to be carried out as atraumatically as possible. During the implants placing, a previously fabricated polymer template was used. This allowed to place the implants in the most correct position for the fabrication of prosthesis, taking into account the significant deformation of the upper and lower jaws. Individual temporary polymeric endoprosthesis, fixed in the area of frontal defect of lower jaw with intraosseous screws with significant compression. After slight immobilization, the flap was passively placed and sutured. No clinical manifestations were detected in the area of the endoprosthesis. A significant reduction of more than four mm in height of the intermediate part of the temporary screw bridge was required due to an increase in the tissue level in the area of the installed expander. The patient noted high quality of life, restoration of chewing function and aesthetics. Referred for rehabilitation in Sochi. After six months, removal of the tissue expander, autologous bone grafting, and placement of two implants in the area of the defect is planned.

Orthodontic treatment on the upper jaw is also recommended. According to the data provided by the dentists observing the patient, there were no clinical manifestations in the area of the endoprosthesis during the period from the operation to September 2022.

4. Discussion

A progressive trend in maxillofacial and bone surgery is the possibility of personalizing implantprosthetic structures [13-16]. Application of additive technologies for manufacturing individual maxillofacial implants makes it possible to design and prototype complex solutions on models, optimize prosthesis fixation systems taking into account elasticity modulus and bone density. The size and configuration of the "prosthetic body of fixation elements and orthopedic platforms" is determined by the attending physician or the consilium of specialists. The parameters for the necessary angulation of orthopedic interfaces are set [17]. When implants are on the design stage, it is important to consider the degree of roughness of the sternal and intraosseous parts of the body and fixation elements [13]. The hypothesis that bioinert temporary constructions replacing bone defects prevent soft tissue constriction and are promising for atrophy, trauma, and post-cancer defects of the jaws has been presented for discussion [18]. In the presented clinical case, we relied on the fact of an almost complete absence of the oral vestibule after trauma and a significant lack of bone tissue in this area, which will not allow a full restoration of function and aesthetics. Also of great importance in making the decision was the patient's motivation and age - a young man and a physician.

5. Conclusions

In the presented case it is particularly important to remove the screws from the expander without breaking them. This is dictated by the possible positioning of dental implants in this area at the stage of subsequent autosseous augmentation. The possibility of wider use of additionally formed soft tissues and passive placement of the flap on the bone augmentation is realized. The possibilities of personalization of medical approaches in bone surgery allow making qualitative changes in the work of specialists and, most importantly, reducing the rehabilitation period and improving treatment results. In order to study the processes of reparative osteogenesis we analyzed micro preparations of peri-implantation zone tissues. As a result, the signs of osteo- and fibro-osteointegration were revealed. The obtained data are considered as a prerequisite for further clinical trials of the developed protocols of sequential replacement of jaw defects using 3D-printing.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

The research of the effect of the interaction of molybdenum, cobalt, piracetam and ascorbic acid on cognitive processes in rats

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Abstract: The problem of combined effects on animals of a combination of drugs with heavy metals (HM) is considered. The study was carried out at the K.L.Khetagurov North Ossetian State University (Vladikavkaz, RSO-Alania) and the Lomonosov Moscow State University (Moscow). The effect of lead diacetate and ammonium molybdate on the training of rats was studied separately, as well as in combination with ascorbic acid and piracetam. It has been found that lead and molybdenum salts inhibit avoidance reactions and inter-signal reactions. The combined effect of these salts with ascorbic acid and piracetam led to mixed results. The nootrope counteracted the inhibition of avoidance reactions by metals, but increased the inhibition of inter-signal reactions, which serve as an important characteristic of learning. In contrast, ascorbic acid reduced the inhibition of both avoidance reactions and inter-signal reactions caused by HM. The use of 2 drugs with HM led not only to an increase in the positive effect exerted by each of the drugs on training, but also to its weakening. The results obtained indicate that the interaction of drugs and HM, taking place in real conditions, is fraught with unpredictable consequences and may pose a danger to human and animal health. This justifies the need for further analysis of the combined effects of several drugs with HM.

Keywords: molybdenum, cobalt, ascorbic acid, piracetam, training, rats.

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1. Introduction

In recent years, the anthropogenic load on the environment has increased catastrophically. Among the wide variety of pollutants, heavy metals (HMS) play a special role, representing a serious danger in industrialized regions [1]. For a number of reasons, HM is particularly dangerous for the central nervous system (CNS), causing severe neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [2? 3].

Until recently, the effect of HM was studied independently of other factors. However, in order to fully understand the meaning of HM for living organisms, it is necessary to take into account that in real life they do not affect the body in isolation, but simultaneously or sequentially with other factors. As a result, the importance of the influence of HM with each other gradually began to be emphasized [4, 5], with drugs [5], with stress [6], etc. It was shown that the effects of joint and separate exposure to agents differ. In particular, it was found that nootroppiracetam used to protect the central nervous system from various adverse effects, instead of countering the neurotoxic effect of heavy metals, can lead to its aggravation [6, 7]. This is an additional danger for industrialized areas with a high content of HM in the environment.

The main mechanism of the negative action of HM consists in the oxidative stress caused by them [8, 9]. This opens up prospects for the use of antioxidants as a means of countering the neurotoxic effects of HM. To date, separate studies have been carried out showing such a potential of antioxidants [7, 8].

In contrast to the study of the interaction of HM with each other, the joint use of drugs in the presence of heavy metals has not yet been analyzed sufficiently to date. In this paper, the features of the effect on learning and memory of rats of the combined use of ascorbic acid and piracetam with lead and molyb-denum salts are analyzed.

2. Materials and methods of research

Experiments were conducted on 11 groups of male white mongrel rats (20 animals per group) weighing 180-200 g by the beginning of the experiment. The first group was injected with piracetam at a dose of 300 mg/kg; the 2nd and 3rd groups were injected with aqueous solutions of lead diacetate (10-7 mol/l) and ammonium molybdate (10-5 mol/l), respectively; the 4th group was injected with ascorbic acid (250 mg/kg), which serves as a comparison drug in as an antioxidant; 5th and 6th - ascorbic acid in combination with lead and molybdenum salts, respectively; 7th served as a control; The 8th and 9th groups were injected with piracetam in combination with lead and molybdenum salts, respectively; the 10th and 11th groups in

combination with piracetam and ascorbic acid were injected with lead and molybdenum salts, respectively. HM salts were administered intraperitoneally 5 hours before the experiments, ascorbic acid was administered 3 hours later, and piracetam was administered 1 hour later. Control animals were injected with an equivalent volume of distilled water an hour before the experiment.

The experiments were carried out in a chamber divided by a partition with an opening into 2 equal halves. In animals, for 5 days (25 stimuli presented daily), a conditional reaction of active avoidance was developed, which serves as an experimental model of learning and memory. A sound conditional stimulus was turned on and after 10 seconds a current (0.5-0.7 mA) was applied to the floor wiring of the half of the chamber in which the rat was located. If the rat did not move to the safe half of the chamber, then after 10 seconds both stimuli were turned off; after 30 seconds, the stimuli were presented again. The transition during the isolated action of the sound led to its shutdown and avoidance of current exposure, and during the current – to the shutdown of both stimuli.

The dynamics of learning in groups was assessed using a one-factor nonparametric Kruskall–Wallis analysis of variance; the difference between groups was assessed using the Wilcoxon criterion.

3. Results

The results shown in Fig. 1 show that lead diacetate caused inhibition of the development of the avoidance reaction. The maximum value of avoidance was only 19.2 ± 2.9% of the number of presentations, that is, the animals "missed" more than 80% of the shocks during the experiment. The use of the Kraskel-Wallis analysis of variance showed that there was no statistically significant increase in the number of avoidance reactions against the background of lead salt, starting from the 2nd experiment, which indicates a deep inhibition of learning. Ammonium molybdate reduced the number of avoidance reactions relative to control only in the last three experimental days; on the 1st day, their growth was observed. Piracetam and ascorbic acid accelerate the production of the avoidance reaction, and in the first 2 days to the same extent.

The acqisition of an avoidance reaction with the combined administration of both ascorbic acid and piracetam with HM salts throughout the experiment occurred statistically significantly faster than with the introduction of metals separately. At the same time, the combination of piracetam with lead diacetate turned out to be more effective than the combination of acid with this salt (Fig. 2). The positive effect of ascorbic acid in these conditions is consistent with the previously described data [10, 11], which confirms the role of antioxidants in overcoming the negative effects of HM. The positive effect of piracetam in these conditions differs from the previously described effect [6, 10, 14].

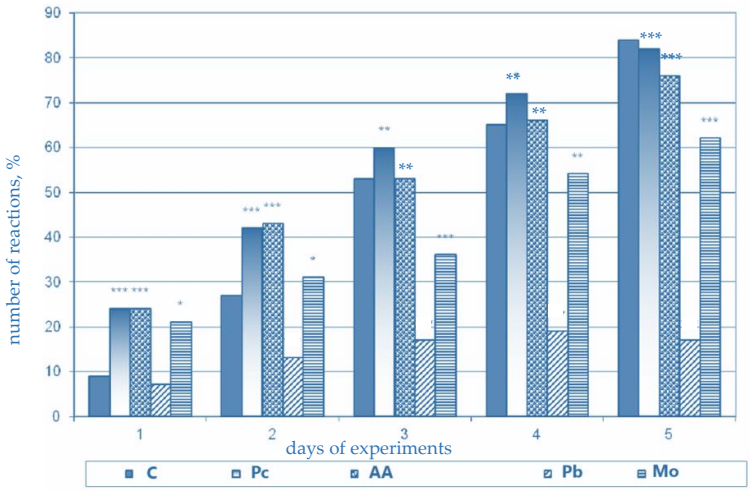

Figure 1. The effect of piracetam, ascorbic acid, lead diacetate and ammonium molybdate on the acqisition of the avoidance reaction. Abscissa – days of experiments; ordinate – the number of reactions as a percentage relative to all presentations. Designations: *,**,*** – p<0.05, p<0.01, p<0.001 relative to the control values. C – control, Pc – piracetam, AA – ascorbic acid, Pb – lead, Mo – molybdenum.

This can be explained by the fact that this salt, when interacting with piracetam, may, under certain conditions uncontrolled by the experimenter, undergo changes with the formation of intermediates that significantly affect the functional properties of the nootrope and impair animal learning [14].

Evaluating these two results in general, it is necessary to agree that the data obtained in this work do not deny the possibility of aggravating the neurotoxic effect of lead when combined with piracetam.

Moreover, they are consistent with the results presented below on the aggravation of the inhibition of inter-signal reactions (ISR) by the combined use of these agents.

As the results shown in Table 1 show, both HM salts inhibit ISR, which reflect the essential role of the avoidance development process [15], which emphasizes the negative role of these agents in learning. At the same time, as in the case of avoidance reactions, the negative effect of molybdenum salt is less pronounced than lead salts. Combined with molybdenum salt, the use of piracetam led to increased inhibition of ISR, so that their number throughout the experiment was less than with a separate introduction of the metal. This

distinguishes the effect of the combination of these agents from their combined positive effect on the avoidance response.

The combined use of piracetam with lead salt also differs from the positive effect of this combination on the avoidance reaction. In the first 3 days, there is no effect, and on the 4th day, the number of ISR under the influence of agents was even less than with a separate exposure to lead. Consequently, nootropics not only do not counteract the depressing influence of metals on the specified characteristic of learning, but also aggravate this oppression. The effect of the combination of ascorbic acid with the HM used is of a different nature. The number of ISR when exposed to this combination of agents exceeds the value that is observed when exposed to each of the metals separately.

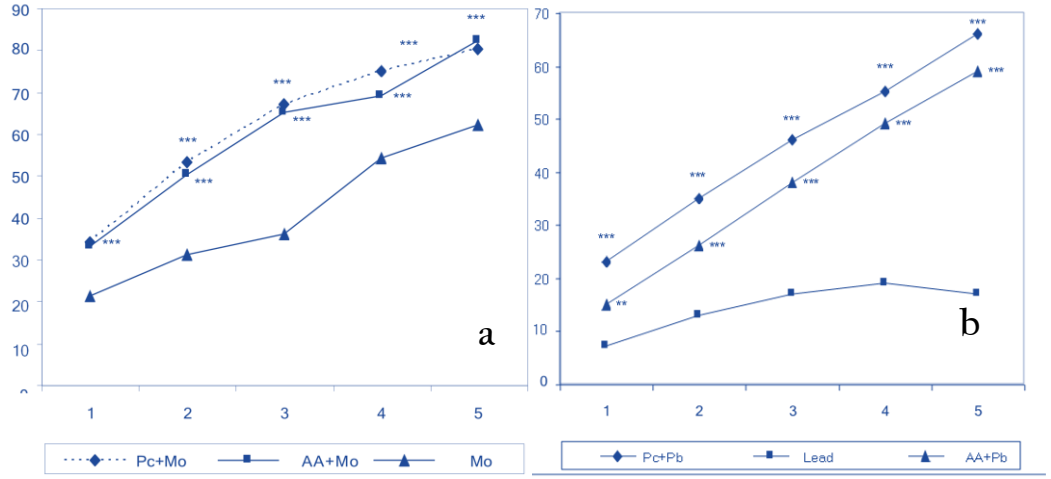

Figure 2. The combined effect of piracetam and ascorbic acid with lead diacetate (a) and ammonium molybdate (b) on the acqisition of the avoidance reaction. Notation – as in Fig. 1.

Since in real life HM works together not only with one, but also with several medicines, we investigated the combined effect of two medicines with molybdenum and lead. As shown above, the combined effect of both piracetam and ascorbic acid with each of the HM leads to the fact that rats develop an avoidance reaction more successfully than it occurs against the background of metal salts, which indicates the positive role of the drugs used. The combined effect of piracetam and ascorbic acid with lead diacetate provided a further increase in the positive effect of the combination of acid with lead, which reached a statistically significant level in the last 2 experimental days (Table 2). At the same time, the effect of the combined effect of two drugs with lead did not exceed the effect of the effect of piracetam with metal.

Table 1. Effect of heavy metal preparations and salts on inter-signal reactions. Note: *,**,*** - p<0.05, p<0.01, p<0.001 relative to control animals; +, ++, +++ - p<0.05, p<0.01, p<0.001 relative to animals receiving the corresponding drug;*, **, *** - p<0.05, p<0.01, p<0.001 relative to animals receiving the corresponding metal.

Agent	Days of experience				
	1	2	3	4	5
Solvent	8,8±1,8	19,2±2,1	29,2±2,8	19,8±1,5	10,4±1,2
Pyracetam	16,6±2,1**	30,6±2,9**	35,8±5,3*	35,8±5,3**	21,4±2,7***
Lead diacetate	2,4±0,9**	3,8±1,2***	4,2±1,7***	3,2±1,0***	2,8±1,4***
Ascorbic acid	3,2±0,9*	4,0±1,1***	2,4±0,9***	2,2±0,7***	3,2±1,0***
Ammonium molybdate	10,0±1,6	7,8±1,0***	6,8±1,2***	4,6±1,1***	5,6±1,0**
Lead diacetate + piracetam	1,8±0,5**, ++	4,4±1,5*,+++	5,2±1,3***,+++	0,6±0,3***, +++, #	4,8±1,1**, +++ ,#
Lead diacetate + Ascorbic acid	3,8±1,1*	8,6±1,7**, +, #	8,4±2,6***, +, #	5,2±2,1***	4,8±1,1***
Ammonium molybdate + piracetam	4,0±0,6*, +++, ##	3,8±0,7***, +++,##	0,6±0,3***, +++, ###	0,6±0,3*****, +++,###	1,0±0,5***, ###, +++
Ammonium molybdate	7,8±1,7+	11,4±2,9*, +	12,6±4,5**, +	10,6±3,3***, ++	9,8±2,4+

+ ascorbic acid					

Table 2. Combined effect of two drugs with heavy metal salts on avoidance reactions and inter-signal reactions. Note: *,**,*** - p<0.05, p<0.01, p<0.001 relative to control animals; #, ##, ### - p<0.05, p<0.01, p<0.001 relative to the combination of the corresponding metal with ascorbic acid; ^,^^,^ - p<0.05, p<0.01, p<0.001 relative to the combination of the corresponding metal with piracetam.

Agent	Days of experience				
	1	2	3	4	5
	avoidance reactions				
Lead diacetate + piracetam	23,0±2,6***	35,2±2,9*	46,2±2,2*	55,4±2,0**	65,8±3,1***
Lead diacetate + ascorbic acid	15,4±2,6*	26,4±2,9	37,8±4,3**	48,5±4,3**	56,2±3,4***
Ammonium molybdate + piracetam	34,0±3,4***	56,2±2,1***	66,6±2,9***	75,2±2,0***	79,6±2,4
Ammonium molybdate + ascorbic acid	33,0±4,5***	50,4±3,4***	64,6±3,1**	88,8±3,1	82,2±1,9
Lead diacetate + ascorbic acid + piracetam	16,8±1,9**	33,0±3,3	46,4±4,7	59,8±3,4#	69,8±3,5***,#
Ammonium molybdate + ascorbic acid + piracetam	16,4±3,0##, ^^^	34,8±3,4*, ##, ^^^	48,0±3,5##, ^^^	60,6±4,1#	75,4±2,0**, #, ^
Inter - signal reactions					
Lead diacetate + piracetam	1,8±0,5***	4,4±1,5***	5,2±1,3***	0,6±0,3***	4,8±1,1***
Lead diacetate + Ascorbic acid	3,8±1,1*	8,6±1,7**	8,4±2,6***	5,2±2,1***	4,8±1,1***
Ammonium molybdate + piracetam	4,0±0,6***	3,8±0,7***	0,6±0,3***	0,6±0,3***	1,0±0,5***
Ammonium molybdate + ascorbic acid	7,8±1,7	11,4±2,9*	12,6±4,5**	10,6±3,3*	9,8±2,4+
Lead diacetate + ascorbic acid + piracetam	4,2±1,2*,##	6,0±1,8***	7,6±2,4***, ##	5,0±2,0***, #,^^	3,2±0,9***
Ammonium molybdate + ascorbic acid + piracetam	5,2±1,6#,^	8,6±1,6***, ^	11,4±3,5***, ^^^	7,2±1,9***, ^^^	3,4±0,8***, #, ^^^

With the combined use of drugs with ammonium molybdate, instead of enhancing the positive effect, the opposite result was observed. In fact, the use of piracetam, ascorbic acid and HM salt combined led to the suppression of avoidance regarding the use of both piracetam and ascorbic acid with this salt.

As shown above, the number of ISR when exposed to piracetam with both ammonium molybdate and lead acetate decreased relative to the effects of each of these salts. The addition of ascorbic acid to this combination changed the situation, and the number of ISR increased.

On the contrary, the combined effect of the two drugs was less than the effect of one ascorbic acid with molybdenum. Consequently, an increase in the number of drugs, in addition to strengthening the counteraction to the negative effects of HM, can lead to a weakening of the influence of each of them on both avoidance reactions and ISR.

5. Conclusions

It was found that lead and molybdenum salts inhibited avoidance and ISR reactions. The combined effect of these salts with ascorbic acid and piracetam led to mixed results. The nootrope counteracted the inhibition of avoidance reactions by metals, but increased the inhibition of ISR, which serve as an important characteristic of learning. In contrast, ascorbic acid reduced the HM-induced inhibition of both avoidance reactions and ISR. The use of 2 drugs with HM led not only to an increase in the positive effect provided by each of the drugs, but also to its weakening. The results obtained indicate that the interaction of drugs and HM, which takes place in real conditions, is fraught with unpredictable and poorly studied consequences and may pose a danger to human and animal health.

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Article

Social health in the aspect of fractal determinism and the changing world

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Abstract: The paper consider the problems of a changing world in the areas of natural and climatic, ecology, migration of ethnic groups, education and their impact on the health of society. Research has revealed that the idea of bifurcations and the principle of fractal determinism allows us to look at one of the most significant problems of humanity: its health and adaptive capabilities in a changing world. We still understand these changes at the level of any one science, and not holistically. Therefore, it is so important to comprehensive study health problems from the standpoint of modern synergetic methodology in a changing world.

Keywords: health of society, changing world, ecology, natural and climatic conditions, education, ethnos, migration, bifurcation, fractal determinism, synergetic methodology.

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1. Introduction

In 2008, the book "Human Ecology in a Changing World" published, for which the team of authors received the Government Prize. The introduction states that "People's health and the quality of their life are largely determined by the state of the time-varying environment-natural, anthropogenic and social. At the same time, the reaction to its impact of various categories of the population (by gender, age, genetic characteristics, profession, place of residence, social conditions, diseases) can be purely individual and changeable over time" [6, p. 4]. One of the significant social values is not only the health of society as a whole but also the health of a particular person who performs labor activity in those natural and social conditions in which he has to carry it out.

The concept of "changing world" considered in the work of Ervin Laszlo "Age of Bifurcation. Comprehension of the changing world" [5]. The concept of "changing world" which is considered in Ervin Laszlo's work "Age of Bifurcation. Comprehension of the changing world" [5] has undoubted interest due to the fact that the society has moved to a different stage of its development in the 21st century, which can no longer explained by the principle of linear determinism.

The appearance in science of the concept of "synergetic" as an interdisciplinary area of scientific research, made it possible to take a different look at the development of society, its value orientations in the conditions of intensively developing scientific and technological progress [4]. Synergetic studies the patterns and principles underlying self-organization in systems of different nature: physical, chemical, biological, psychological, social, technical, and others. Bifurcation is a basic concept that allows the scientific community to understand current development trends, including biological and psychological knowledge about a person and his activities. In modern scientific terminology, this term is the name of a fundamental feature of the behavior of complex systems subject to strong influences and stresses, sometimes destructive forces. It considered bifurcation as a qualitative restructuring or metamorphosis of various objects with a change in the parameters on which they depend. A living system has the ability to self-organization and instability to the influence of the conditions of novelty in which it finds itself, which allows it to adapt to the changed conditions of the external or internal environment. Physiology may manifest a different reflex path that changes human behavior, reflecting in the psychology of behavioral actions as an event in one time and space.

The purpose of this work is to analyze the health of society in the aspect of fractal determinism and the changing world.

2. Methods

It considered the health of society from interdisciplinary positions in medicine, biology, psychology, philosophy and other sciences. Our research and analysis of literary sources let us address some elements of social health from the point of view of self-organization theory. The idea of bifurcations and the principle of fractal determinism used in the methodology of the non-invasive method of heart rate variability. The analysis of attractors of phase portraits, as a geometric pattern, allows us to analyze human health not only in 5-minute cardio intervals, ultradian, circadian rhythms, but also to predict diseases associated with disorders of both the cardiorespiratory system and the body as a whole.

It uses the principle of fractal determinism in sociological, psychological research, analysis of historical events, which makes it possible to model not only social development, but educational space.

The bifurcation point is one of the important concepts of the theory of self-organization. For society, this is the moment in the history of the system when it passes from one system of certainty into another. An example of such a social event is the collapse of the Soviet Union, with its transition from one system of socially significant values to a new system of values. The period of transition is the bifurcation point at which it doomed the old values to change. And society and a particular person can adapt to these changes faster, thanks to socio-psychological adaptation, due to the awareness of new values and the acceptance or non-acceptance of them. Another thing is the evolutionarily established mechanism of biological adaptations. In this case, the living system has the genetic potential of adaptive mechanisms. However, the transition from the bifurcation point to the equilibrium system takes a significant amount of time, and, in a certain period, may experience an adaptive breakdown. If there are enough resources in the system, it reaches equilibrium due to resistance, If not, then the system, at the individual level, can self-destruct, but is able to survive population due to the genetic reserve of adaptive mechanisms.

3. Results

In the theory of dynamical systems, there is the concept of "phase space" - this is the number of attractors in space and time that determine the totality of all conditions in which the system can be. The non-invasive method of heart rate variability (HRV) uses the concept of "phase portrait" in pre-nosological conditions. The system responds to these "attractors", or forces, that determine the trajectories in the phase space. Since such attractors act on the whole system, they force it to change its dynamic properties, forming an orbit of the attractors. In physiology and psychology, they make it possible to determine the rate of stress of the body and its adaptive capabilities (Fig.).

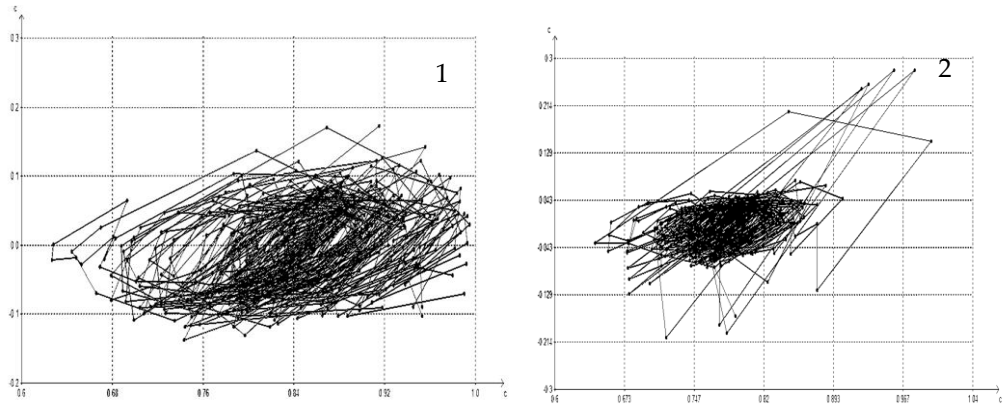

Figure. Phase portraits of the students under conditions of mental load according to attractors of cardio intervals using HRV (1 - normal; 2 - tension of regulatory systems).

If we are considering the characteristics of a person (subject / personality) in a group, then the phase space allows you to identify risk groups or a marginal group. But anyway, the system will strive for equilibrium / homeostasis.

Currently, a person has to perform labor activities in various environmental conditions, including migration, through a search for work in the current trends of world globalization. Let us designate some problems in which a person finds himself in his activity. Thus, the lack of holistic knowledge creates sufficient problems within which society cannot solve the global problems that

it has fallen into because of fragmentation of knowledge. We can see this in the example of the problems of adaptation of migrants to the new conditions of climatic and geographical latitudes.

N.A. Agadzhanyan noted that the peculiarity of climate, topography, nutrition, magnetic anomalies, photoperiodism affect the structural and physiological organization of people whose ancestors from generation to generation lived in relatively little changing environmental conditions [2]. "When studying the ecological portrait of each individual, it is necessary to regard the ethnicity of a person and the biochemical characteristics of the environment" [1, p. 6]. There is information in the literature about the existence of ethnic differences as the most important physiological constants of the body in the functioning of not only individual enzymatic systems but also the response of the neuro-immune-endocrine system to the impact of inadequate exogenous and endogenous factors. It clearly manifested ethnic differences in the temporal - chronophysiological features of the reproductive function. For example, the level of tension in the regulatory systems of the body in different ethnic groups, the direction and severity of changes in the dynamics of the cardiovascular system, depends on the ethnic characteristics of adaptation to natural and climatic conditions.

In connection with the anthropogenic impact on the climate, active migration processes associated with professional activities, various ethnic groups will face the risks of failing the evolutionarily established adaptive resources and adaptive reactions of the body to specific natural and climatic conditions, if we consider systems in the aspect of linear determination. If we turn to fractal determinism, then adaptation to climate change will require a fundamental rethinking of the socio-economic development strategy and ecosystem management strategy from states that are actively included in the world community today in terms of the concept of bifurcation. It should note that, at present, in order to solve the problem of the impact of climate change on the health of an ethnic group, it is required to develop indicators that could help determine future risks and diseases. Such developments are necessary to create corrective models of health security and evolutionarily formed adaptive responses to a complex of stress factors of various nature in ethnic groups in new conditions of life and professional implementation.

Thus, the outlined issue is associated with Edward Lorenz's "butterfly effect," which was found during the simulation of global climates. He occurred to the conclusion that weather conditions are unstable, like the flapping of the wings of a danaid butterfly, as atmospheric turbulence generates a whole series of bifurcations. Today, Russia assumes the intensive development of not the Far North, but the Arctic latitudes, which can also cause a "butterfly effect" not only of weather, but of climate change and lead to a bifurcation of the evolutionarily established mechanisms of nature, including the organization of life for people in other regions, which so far is only possible predict.

The modern problem of education, aimed at preparing future labor resources, loses sight of socially significant values in professional activity - human health. Introducing the innovative educational technologies, the pedagogical community does not consider adaptive reactions to stimuli. The modern school provides knowledge that is not subjected to critical analysis. In Russia, it built a unified state exam using a testing system on their isolation from practical significance in choosing a future profession and, as a result, fragmentation and inability to use them in future professional activities. Scientists mention that educational institutes share knowledge systems based on the picture of the world, divided into physical reality and the sphere of human goals and actions, which hinders the formation of a holistic worldview [3]. Holistic knowledge of society is the moral basis of our responsibility for actions in the world around us. The implementation of global projects that do not consider the integrity of existing knowledge can lead to irreversible processes, both in the biosphere and in the viability of the human population in it.

4. Discussion

Currently, holistic education is becoming increasingly popular, focused on the practical holistic value of knowledge, including the integration of the highest achievements of modern sciences and arts. The formation of holistic knowledge is a very difficult task in holistic education. In Russian universities, there is an attempt to introduce practice-oriented learning into the system of higher education. However, the system of subject education itself, where we are considering the training of a narrow specialist, does not solve the problem of its development.

5. Conclusions

Thus, the idea of bifurcations and the principle of fractal determinism gives us the opportunity to look at one of the most significant problems of humanity: its health and adaptive capabilities in a changing world. We still understand these changes at the level of a single science, and not holistically. Therefore, complex studies of health problems from the standpoint of modern synergetic methodology in a changing world are so important.

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XI INTERNATIONAL INTERDISCIPLINARY CONGRESS OF HEAD AND NECK DISEASES

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Article

Acute urticaria in children: course of the disease, features of skin microbiom

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Abstract: Quantitative and qualitative changes in the microbiome of the skin affect the emergence and course of allergic diseases, in particular, of acute urticaria. Aims: to investigate the taxonomic composition of the skin microbiota in children with acute urticaria and to study its effect on the course of the disease. In total, 75 children with diagnosed acute urticaria at the age of 7-14 years were examined. The average age of children was 10.83±0.95, of which 44 were boys (58.7%), and 31 were girls (41.3%). The control group consisted of 30 virtually healthy children of the appropriate age, of whom 16 were boys (53.3%), and 13 were girls (46.7%). Regardless of the severity of the disease, the examined children suffering from acute urticaria had sensitization in history with a significant prevalence of food sensitization ($p<0.05$). The occurrence of a severe episode of acute urticaria is associated with allergens of drug origin in 52.6% of cases and the action of unidentified triggers in 47.4% of cases. In children with acute urticaria, S. epidermidis, S. aureus, bacteria of the genus Peptococcus, and Peptostreptococcus dominated on a non-affected skin area, while for affected skin area, the Propionibacterium, S. aureus, S. epidermidis, bacteria of the genus Peptococcus, Propionibacterium, and Peptostreptococcus were denoted as dominating. High frequency of S. aureus detection on affected and non-affected skin areas in children with acute urticaria is a predictor of the disease's severity.

Keywords: keywords. acute urticaria in children, features of acute urticaria, sensitization and acute urticaria, skin microbiota and urticaria

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1. Introduction

Children's allergic diseases (AD) are quite a sensitive problem for modern medicine and the global health system being the reason for significant socio-economic expenses due to their high prevalence, which has increased dramatically in recent years [1]. The ADs have a negative impact on life quality, increasing the frequency of concomitant pathology and the risk of death, such as in bronchial asthma, for example [2]. Negative economic consequences of AD are associated with significant direct (visit to a doctor, hospitalization, intensive care unit treatment, laboratory and instrumental diagnostics, conservative treatment, etc.) and indirect medical expenses (work and study absences, resulting in lower production volumes, worse productivity, and poor performance) [3]. The prevalence of AD is quite difficult to study due to its difference within the country depending on the region, which is explained by the interaction of genetic and environmental factors [1]. Allergic diseases include several genetically heterogeneous and immunologically determined diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis, food allergies, and acute urticaria (hives). Almost 700 million people worldwide suffer from respiratory ADs alone (bronchial asthma and allergic rhinitis) [4-6].

For many years, acute urticaria (AU) has been considered as nearly the most relevant problem in allergology, especially among children [7,8]. The peak of morbidity of this pathology in children occurs in the age period from 14 to 16 years, although, over the last 5 years, a tendency to higher morbidity is denoted among children of preschool and primary school age. In general, the prevalence of AU among children is 2.1–6.7% (in Great Britain – 3.4%, in Germany – 4.4%, and in Denmark – 5.4%), and among children with atopic dermatitis, the incidence rate is higher and amounts to about 16.2%. This disease was observed at least once in 10-20% of children, and in 5.4% of cases, it was diagnosed in preschool-aged children [8]. Besides, more than half of the children with AU are diagnosed with other allergic pathologies as well [9].

Infective agents, food, and medicines are among the main trigger factors for AU emergence in children [10-12]. Acute spontaneous urticaria occurs in preschool children with atopy. Infection in

children is probably the most common predictor of AU compared to adults, with infection being the most frequently documented cause of this allergic pathology in children (about 40% of cases) [12,13]. Among infectious agents associated with the emergence of AU are viral (rotavirus, rhinoviruses, herpes simplex virus, Epstein-Barr, hepatitis A, B, and C, and human immunodeficiency virus), bacterial (streptococcus, mycoplasma, Helicobacter pylori), and parasitic (protozoa, helminths). Aspirin and other non-steroidal anti-inflammatory drugs, β-lactam antibiotics, vancomycin, and opiates are the drugs most often associated with the occurrence of AU and cause the disease through direct degradation of mast cells. In most cases, the cause of acute urticaria is possible to establish [13].

The pathogenesis of AU is based on allergic reactions of immediate type, i.e., type I, less often type II and III. In such allergic reactions, allergens interact with specific antibodies-reagents of basophilic membranes and adipose cells, resulting in degranulation of these cells with the release of biologically active substances that cause typical symptoms of the disease. In particular, histamine is associated with itching, edema, and hyperemia on the periphery of the bladder. Histamine, cytokines, platelet activation factor incites the expansion of blood capillaries, plasma sweating, and also the migration of macrophages, neutrophils, T-lymphocytes in the area of the urticant lesion. Among other mediators affecting the development of AU are prostaglandin D2, calcitonine binding peptide, substance P, and eicosanoids [8,9]. Non-immune mechanisms of AU are much rarer and arise as a result of 1) an increase in the concentration of histamine due to its non-specific release from mast cells by the non-immune way, for example, at eating or taking some medicines; increase in the concentration of this mediator through inhibition of the enzyme activity of diamin oxidase, which directly participates in its destruction; as a result of its oversupply with certain foods (smoked food, cheeses, tuna, cod, chocolate, nuts, spinach, avocado, tomatoes, beer) and its increased synthesis in the body (e.g., in intestinal dysbiosis); 2) arachidonic acid metabolism disorders as a result of non-steroidal anti-inflammatory drugs intake; 3) excessive acetylcholine secretion due to physical and psycho-emotional exhaustion or high-temperature action; 4) complement system activation when injecting X-ray-contrast substances); 5) bradykinin accumulation in blood, when angiotensin-converting enzyme inhibitors are taken) [8,9,14].

The AU is manifested by the sudden appearance of wheals which is associated with the influence of the trigger factor, and the duration of this condition is less than 6 weeks. Wheals do not have a certain typical localization, are accompanied by itching, and can merge in places of close contact with clothes [15]. The wheal is edema of one of the skin layers – dermis, has a limited character, and usually disappears in 24 hours. Its diameter varies from a few millimeters to several centimeters, and it is characterized by intense hyperemia of peripheral part and swelling of the central part. Sometimes the pathological process may extend to deeper layers of the dermis and subcutaneous adipose tissue or mucous membranes resulting in the formation of angioedema, or Quinque's edema, for which painfulness and a longer regression of up to 72 hours are typical. Isolated form of hives in the form of urticaria is found in 40% of cases, the Quinque's edema in 11% of cases [16], and the combination of urticaria and Quinque's edema is revealed in 49% of cases [13]. Besides the local skin manifestations, children with edema may experience increases in body temperature to febrile values, dyspepsia, abdominal and joint pain, which may lead to erroneous hospitalization to an infectious disease hospital [17].

The AU is diagnosed based on the clinical symptomatology of the disease, namely the presence of the typical urticanthropic hives described above, as well as anamnesis data relationship of its occurrence to the action of a certain agent [15]. Usually, it is sufficient for diagnostics of AU, and there is no necessity to perform additional routine laboratory examinations. Only in case of suspicion of drug hypersensitivity or IgE-dependent mechanism of food intolerance, it is required to admit the child to allergologist's consultation for allergy diagnostics [13,15].

Treatment tactics for AU should be aimed primarily at the elimination of the triggering agent from the child's body. Of great importance is the therapeutic nutrition excluding food referred to as histamine liberators [13,15]. Among medicines of the first line are antihistamines (non-sedative), and glucocorticosteroids are recommended in case of their ineffectiveness. Noteworthy is that for symptomatic treatment of AU in children, it is allowed and recommended to use only drugs with reliable evidence, which have proven clinical efficacy [13,15,17].

Considering the increasing prevalence of allergic diseases among children, including AU, the issue of studying and revealing new pathogenetic links of their origin and progression is of current importance as it can improve the diagnostic algorithm and increase the efficiency of treatment of allergic conditions. In particular, the study of the influence of the skin microbiome on the emergence and course of AU has attracted the special attention of scientists in recent years [18-20]. Such interest to the skin microbiome is due to its extreme diversity (enrolling about 1014 taxonomic units) and absolutely unique ecosystem, the peculiarities of which depend on sex, comorbid pathology, environmental factors, a region of residence, etc. [20]. The growth of Streptococcus and/or Propionibacterium ratio in the skin microbiome was established to correlate with the appearance of atopic dermatitis, while some Acinetobacter species, in contrast, protect the skin from

allergic sensitization and inflammation and participate in maintaining the balance of Th1 and Th2 [4,19]. The studies proved the Staphylococcus aureus, Escherichia coli, Helicobacter pylori, and Pseudomonas aeruginosa to be capable of releasing histamine from the reserves of the human body, while some taxon representatives of Acinetobacter, Serratia, Pseudomonas, Staphylococcus, Corynebacterium, and Micrococcus demonstrate histidine decarboxylating effect, which indicates that quantitative and qualitative changes of skin microbiome influence the appearance and flow of AU [21]. However, very few studies have been performed on this issue, and most of them have examined the influence of skin microbiota on the origin and course of atopic dermatitis [22,23]. The lack of sufficient data on acute urticaria (hives) specifies the necessity of further research on this issue.

The study aimed to examine the taxonomic composition of the skin microbiota in children with acute urticaria and study its effect on the course of the mentioned disease.

2. Methods

A total of 75 children at the age of 7-14 years with the diagnosis of acute urticaria were examined. The average age of children was 10.83±0.95, of which 44 were boys (58.7%), and 31 were girls (41.3%). The control group consisted of 30 virtually healthy children (VHC) of the appropriate age, of whom 16 were boys (53.3%), and 13 were girls (46.7%). Surveys were conducted between 2017 and 2019, and the number of children in this age group was 16 boys (53.3%) and 13 girls (46.7%). The disease was verified following the recommendations of the European Academy of Allergology and Clinical Immunology, the European Global Allergy and Bronchial Asthma Network, the European Dermatological Forum and the World Allergy Organization (The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria) [15].

All studies were conducted in compliance with the Convention of European Counsil "On Human Rights and Biomedicine" (04.04.1997), the Helsinki Declaration of the World Medical Association "On Ethical Principles for Medical Research involving Human Subjects" (1964–2013), and ICH Good Clinical Practice (1996).

The study included children who met the following criteria: age from 7 to 14 years, verified diagnosis of acute urticaria, voluntary informed consent to participate in the study signed by the child's parents or legal guardian.

Children, who had at least one of the following criteria, were not included in the study: age under 7 years and over 14 years, concomitant dermatological disease, history of an infectious disease suffered earlier than a month before being included in the study, intestinal infection within the last three months, antibiotic therapy within the last three months, presence of other pathology of internal organs in the acute stage, oncopathology, and mental disorders.

The level of AU severity was assessed with 0 to 3 points considering such as the number of morphological elements of the rash, duration of the rash, and severity of itching. With a total score of ≤3, the course of AU was assessed as mild, that with 4-6 scores as moderate, and with ≥7 scores as severe [24] .

The study of the skin microbiome in VHC was performed on the middle third of the forearm (on its inner surface), and in children with AU – on the affected area of the skin and on a non-affected surface symmetrical to the affected one. The material for the bacteriological study was extracted through a bacterial seal (Murray PR2015). Extracted material was sown within one hour to nutrient and differential-diagnostic media produced by HiMedia Laboratories Pvt. Ltd, India, namely, HiGrome Aureus Agar Base, Endo Agar, HiGrome Enterococci Agar, HiGrome Candida Differential Agar, Blood Agar Base – for facultative anaerobic bacteria, Schaedler Agar, Bacteroides Bile Esculinum Agar, and Anaerobic Agar – for non-clostridial anaerobic bacteria. After 24 hours of incubation in a thermostat at 37°C, the grown pathogenic colonies of microorganisms were identified by examining their morphology, tinctorial features, and biochemical properties.

The Student T-criterion and Wilcoxon non-parametric T-criterion were applied for statistical analysis. The differences were considered statistically significant at $p< 0.05$. The $\chi 2$ criterion was used to numerically interpret the qualitative features and compare the detection rates of individual skin microorganisms. All statistical operations were performed using Statistica for Windows 10 Pro (Stat Soft inc., USA) and Microsoft Excel 2013 (Microsoft, USA) software packages.

3. Results

While studying the anamnesis, the food products were established as the main cause of AU development in 34 children (45.3%), then medicines – in 22 children (29.4%), and other factors, such as plant pollen, contact allergens, etc., in 7 children (9.3%). At that, for 12 children (16%), no triggering factor for AU has been detected. Noteworthy is that the majority of children with acute urticaria had an aggravated allergic history, i.e., 68 children (90.7%), of whom 46 children (61.3%) had a history of food allergy, 29 children (38.7%) had drug intolerance, 19 children (25.3%) had

atopic dermatitis, 8 children (11.7%) had allergic rhinitis, and 6 children (8%) suffered from bronchial asthma.

In considering the specifics of the disease flow, 18 children under examination (24%) were diagnosed with the mild form of AU, 38 children (50.7%) had moderate AU, 19 children (25.3%) had severe AU. The incidence rate of moderate flow of disease was significantly higher in comparison with the mild ($p<0.05$) and severe ($p<0.05$) form of acute urticaria. No statistically significant differences in the severity of disease between girls and boys were recorded ($p> 0.05$).

In children with mild form, the main cause of the disease was food allergens determined in 8 children (44.4%), then pollen and contact allergens – in 7 children (38.9%), significantly less often ($p<0.05$) compared to the triggers mentioned above the cause of the mild OK episode were medicines – only in 3 (16.7%) children. For all children with mild AU, the triggering factor for the episode was possible to establish.

For moderate severity, the occurrence of the AU episode in most cases was associated with food allergens in 18 children (47.4%), medications in 13 children (34.2%), and undefined allergens in 7 children (18.4%).

All children (100%) with severe AU had allergic anamnesis, while in the past, sensitization with food products prevailed significantly more often ($p<0.05$) – in 9 (47.4%) children. The development of severe AU episodes in the examined children was mainly related to allergens of medication origin, namely, in 10 children (52.6%), which is significantly more frequent, than with mild form ($p<0.05$). The influence of unidentified triggering agents was noted in 9 children (47.4%), which is significantly more frequent, than with mild ($p<0.05$) and moderate ($p<0.05$) degree of severity. Severe AU in response to food allergens was not recorded in the study performed.

In addition to the main skin manifestations of AU in the children included in the study, concomitant symptoms, such as general weakness, headaches, discomfort/ abdominal pain, nausea, single vomiting, and stool disorders, were also observed (Table 1). Most commonly children complained of general weakness, headaches, and nausea. In children with severe disease, concomitant symptoms were reported in 100% of cases, which is significantly more frequent ($p<0.05$) compared to moderate (concomitant symptoms were present in 24 children (68.4%)) and mild symptoms (concomitant symptoms were present in 7 children (38.9%)).

During the study of the species composition of skin microbiota, 11 species of microorganisms (7 facultative anaerobic (FA) and 5 non-clostridial anaerobic (NCA)) were detected in VHD and 12 species (6 FAs and 6 NCAs) were found in children with AU. The average bacteria insemination of the skin by FAs in VHD were (2.3 ± 1.2) CFU/sm2, by NCAs - (1.9 ± 0.8) CFU/sm2. The average bacteria insemination of the healthy skin by FAs in children with AU were (3.3 ± 1.7) CFU/sm2, by NCAs - (1.6 ± 0.5) CFU/sm2, and that of the injured skin by FAs - (3.0 ± 1.6) CFU/sm2, by NCAs- (1.6 ± 0.6) CFU/sm2. Among FAs, S. epidermidis was more frequently detected in 28 virtually health children (93.3%), Micrococcus genus microorganisms in 18 children (60%) (Fig. 1), Peptococcus bacteria in 13 (43.3%) children, and Peptostreptococcus in 9 (30%) children (Fig. 2). In children with AU on a non-affected skin area, S. epidermidis dominated in 53 children (70.7%), S. aureus was found in 40 (53.3%) children (Fig. 1), Peptococcus bacteria had 34 children (45.3%), Peptostreptococcus was visible in 21 children (27%), and Propionibacterium was revealed in 20 (26.7%) children (Fig. 2). Those with confirmed AU in the affected skin area, S. aureus dominated in 54 children (72%) and S. epidermidis – in 44 children (58.7%) (Fig. 1). Among the NSAs, Peptococcus bacteria prevailed in 47 children (62.7%), Propionibacterium – in 32 children (42.7%), and Peptostreptococcus – in 29 (38.7%) children (Fig. 2). Thus, in children with AU, S. aureus was detected 1.96 times more frequently ($p<0.05$) in the affected skin area as compared to VHD, and 1.45 times more frequently ($p<0.05$) in the non-affected skin area as compared to the non-affected skin area at AU. The S. epidermidis in children with AU was detected 1.3 times ($p < 0.05$) less frequently in the non-affected skin area compared to VHD, while in the affected area – 1.6 times ($p < 0.05$)) less frequently. Bacteria of genus Micrococcus were recorded 1.7 times ($p<0.05$) and 2.8 times ($p<0.05$) less frequently and that of genus Bacillus – 4.3 times ($p<0.05$) and 3.7 times ($p<0.05$) less frequently in the non-affected and affected skin area, respectively. Representatives of the genus Propionibacterium were 2.1 times ($p<0.05$) more frequently detected on the affected skin area of children with AU compared to VHD and 1.6 times ($p<0.05$) more often on the affected skin area at AU compared to healthy areas.

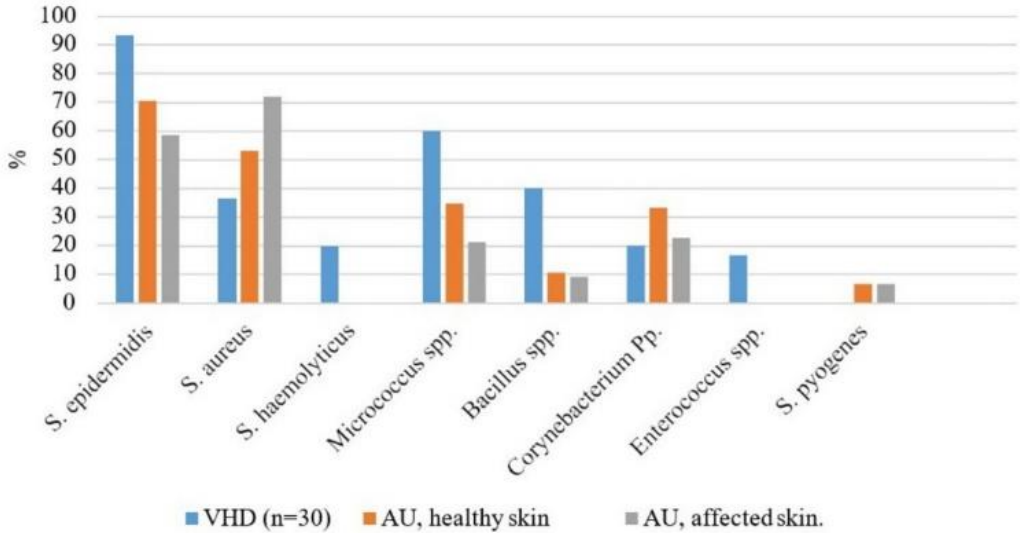

Figure 1. Emergence frequency of facultative anaerobic skin microbiotic taxons in children with acute urticaria (AU), %.

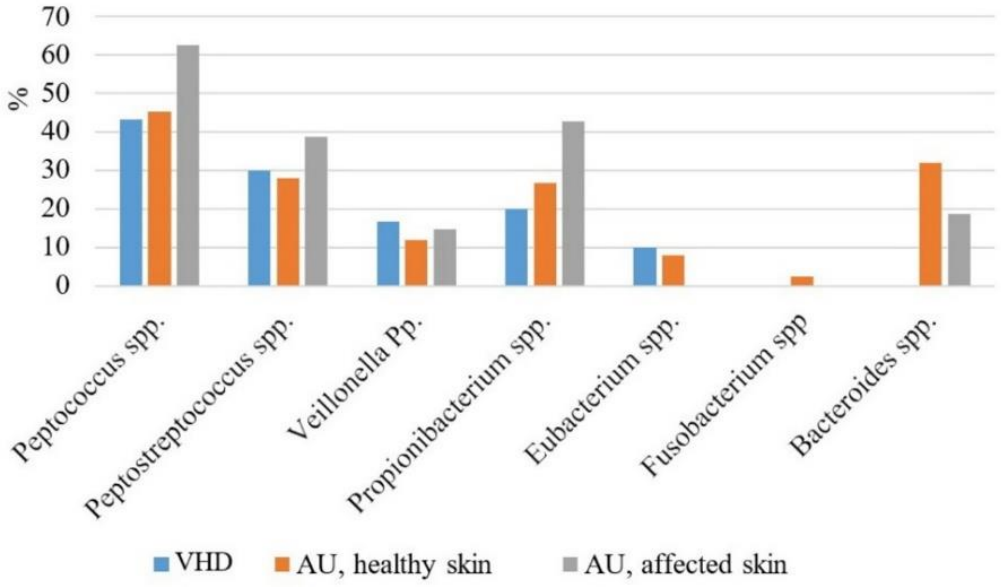

Figure 2. Emergence frequency of neclostridial-anaerobic skin microbiota taxons in children with acute urticaria (AU), %.

The Streptococcus pyogenes was found in 5 children (6.7%) ($p<0.05$) of with AU compared to VHD, as well as Bacteroides was detected in 14 children (18.7%) ($p<0.05$) with AU in the affected area of skin and 24 children (32%) ($p<0.05$) with AU in a healthy skin area compared to VHD. In contrast, 6 virtually healthy children (20%) ($p<0.05$) had Staphylococcus haemolyticus in the skin microbiome and 5 children (16.7%) ($p<0.05$) had Enterococcus genus, which was not recorded among children with acute urticaria.

The study of emergence frequency of certain microbiota taxons on the affected and non-affected areas of children's skin with AU depending on the severity of the disease has shown that in case of the moderate AU, bacteria of genus Bacteroides ($p<0.05$) were detected on the affected area of the skin significantly more frequent in comparison with VHD against the background of the decrease of Bacillus bacteria incidence ($p<0.05$). In the case of the severe form of the disease, the S. aureus bacteria ($p<0.05$) was noticed significantly more frequently. On non-affected skin areas in children with mild AU in comparison with VHD, the bacteria of genus Propionibacterium ($p<0.05$) were detected significantly more often, for the medium form, bacteria of genus Bacteroides ($p<0.05$) prevailed, and for severe forms – S. aureus ($p<0.05$). Besides, the emergence frequency of

bacteria of genus Micrococcus ($p<0.05$) decreased significantly in the case of a severe form of the disease.

4. Discussion

When studying the anamnesis and course of AU in children it has been established that in 90.7% of children, a burdened allergic anamnesis for both mild and severe course of the studied disease was observed. In general, among triggering agents of AU episodes development in this study, food sensitization significantly prevailed counting for 61.3% ($p<0.05$) of cases. At the same time, the development of a severe episode of this disease was associated with sensitization by drugs ($p<0.05$) and unidentified triggering allergens ($p<0.05$). Concomitant symptoms, such as general weakness, headache, nausea, vomiting, abdominal pain/discomfort, and stool disorders, were significantly more typical of severe form (100% of cases at $p<0.05$) compared to the moderate (68.4%) and mild (38.9%) forms.

When examining the composition of the skin microbiota in AU children, a significant increase in the frequency of S. aureus detection ($p<0.05$) both on the affected and non-affected skin areas was recorded compared to virtually healthy children. Besides, the emergence frequency of this microorganism increased with greater severity of the disease. It allows asserting that a higher incidence of S. aureus in children with AU is a predictor of the severity of this nosology.

Typical was also a significant reduction in the incidence rate of S. epidermidis ($p<0.05$) in children with AU, which is the most common microorganism on the skin of a healthy person. The S. epidermidis, together with other coagulase-negative staphylococci, can release antimicrobial agents that inhibit the growth and formation of S. aureus biofilm [21]. In addition to changes in the emergence frequency of these species of staphylococcus, the variations in the incidence frequency of other skin microbiome species (genus Micrococcus, Corynebacterium, Bacillus, Propionibacterium) has been revealed, which indicates the presence of complex relationships between different taxons of skin microbiota and the need for their comprehensive and detailed study. The production of S. epidermidis and S. aureus antimicrobial substances (bacteriocins, antimicrobial peptides) incites a decrease in the relative number of Micrococcus, Bacillus, and S. haemolyticus bacteria during the AU episode [23-25].

The data obtained concerning the main triggering factors of AU episodes development and its flow features are generally comparable with the results of other similar studies [17,24]. However, more research in the literature is devoted to the study of skin microbiome features in atopic dermatitis enrolling both adults and children [22,26]. In particular, a study involving 128 people aged 2-62 years revealed the predominance of healthy individuals of the bacteria of genera Staphylococcus, Propionibacterium, Corynebacterium, and Streptococcus on the skin microflora, and, S. aureus, Propionibacterium, and Peptococcus on the skin of patients with atopic dermatitis [26], which is consistent with the results of this research. A similar study was conducted in Russia with 61 AU children at the age of 3-12 years. It has been established that the severe flow of AU is associated with medication sensitization and increased frequency of S. aureus detection on the affected skin area in AU children with [24], which also corresponds to results of this study.

5. Conclusions

Thus, the results obtained through this study showed that, regardless of the severity of the acute urticaria flow, the surveyed children suffering from this disease had sensitization in their history, namely, 61.3% of children – food allergy, 38.7% – medication intolerance, 25.3% – atopic dermatitis, 11.7% – allergic rhinitis, and 8% – bronchial asthma. At that, food sensitization prevailed ($p<0.05$). The occurrence of a severe episode of acute urticaria is associated with allergens of medication origin (in 52.6% of cases) and the action of unidentified triggers (in 47.4% of cases), which is significantly more frequent in comparison with a mild form of the disease ($p<0.05$). In children with acute urticaria, S. epidermidis dominated in a non-affected skin area (in 70.7% of cases), while S. epidermidis. aureus (in 53.3%), bacteria of the genus Peptococcus (in 45.3%), Peptostreptococcus (in 27%), Propionibacterium (in 26.7%), S. aureus (in 72%), S. epidermidis (in 58.7%), bacteria of the genus Peptococcus (in 62.7%), Propionibacterium (in 42.7%) and Peptostreptococcus (in 38.7%) prevailed on the affected area. In children with AU, S. aureus was detected 1.96 times more frequently ($p<0.05$) in the affected skin area as compared to VHD, and 1.45 times more frequently ($p<0.05$) in the non-affected skin area as compared to the non-affected skin area at AU. The S. epidermidis in children with AU was detected 1.3 times ($p < 0.05$) less frequently in the non-affected skin area compared to VHD, while in the affected area – 1.6 times ($p < 0.05$)) less frequently. High frequency of S. aureus detection on the affected and non-affected skin areas in children suffering from acute urticaria can be considered as a predictor of the disease severity.

6. Prospects for further research

A prospect for further research is to examine the efficacy of probiotic use in children with severe and severe acute hives.

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Article

Influence of self-regulation breathing techniques on spectral indicators of heart rate variability in men students.

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Abstract: The purpose of the study was to study the influence of respiratory psychotechniques on the spectral indices of cadets' heart rate variability.

Materials and methods: 21 men aged 18-20 were examined. The standard method of breathing exercises was used, which is used in the training of mental self-regulation in the preparation of employees of the penitentiary system, during which, for 5 minutes, a gradual lengthening of the expiratory phase occurs. Using the hardware-software complex "Varicard 2.6", a 5-minute cardiointervalometry was performed before and after breathing exercises.

Results. There was a decrease in the high frequency component (High Frequency - HF) (at rest - 25.76 ± 4.85 ms, after breathing exercises - 20.04 ± 3.74 ms, $p < 0.01$), an increase in the low frequency (Low Frequency - LF) (at rest - 29.97 ± 3.21 ms, after exercise - 38.48 ± 5.12 ms, $p < 0.05$). The very low frequency spectral component (Very Low Frequency - VLF) did not change (at rest - 18.00 ± 2.63 ms, after breathing exercises - 18.53 ± 2.31 ms, $p > 0.05$). It should be noted that the total power (Total power - TP) in the HF, LF, VLF ranges also did not change statistically significantly (47.44 ± 5.49 ms at rest, 51.51 ± 6.05 ms after exercise, $p > 0.05$).

Conclusion: Respiratory exercises, characterized by an increase in the duration of exhalation in relation to the physiological norm, do not affect the heart rate, but lead to statistically significant changes in the spectral parameters of heart rate variability. The dynamics of HRV spectral parameters after exercise exposure is characterized by a decrease in high-frequency components (HF), and an increase in low-frequency components (LF). The indicators of the very low-frequency components of the spectrum (VLF) do not change statistically significantly. Indicators of the total spectrum power (TP) after exercise do not change, which is associated with a proportional change in the values of high-frequency (HF) and low-frequency (LF) components relative to each other.

Keywords: breathing techniques, mental self-regulation, spectral indices of heart rate variability, cadets.

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1. Introduction

At present, the role of psychological support for the professional activities of employees of law enforcement agencies has significantly increased, the most important component of which is the use of self-regulation methods. At the same time, when introducing these methods into practice, certain difficulties arise, often associated with the lack of objective criteria for assessing their impact on the human body.

The purpose of the study is to study the influence of respiratory psychotechniques on the spectral parameters of cadets' heart rate variability.

2. Patients and Methods

21 male students aged 18-20 were examined. The standard method of breathing exercises [2] was used, which is used in the training of mental self-regulation in the preparation of employees of the penitentiary system [1], during which, for 5 minutes, a gradual lengthening of the expiratory phase occurs. Using the hardware-software complex "Varicard 2.6", a 5-minute cardiointervalometry was performed before and after breathing exercises. The results were processed by the statistical package "Statistika 6". In order to normalize the distribution of the obtained data, their preliminary mathematical transformation (square root extraction) was carried out. Statistically significant differences were confirmed by Student's test for dependent samples.

3. Results and Discussion

It should be noted that studies on the effect of breathing exercises on heart rate variability (HRV) are very fragmented and are mainly devoted to studying the relationship between respiratory rate and HRV [4]. In our study, the influence of the ratio of inhalation-exhalation phases on HRV was assessed in the framework of the standard method of breathing exercises.

The results of the study showed that the heart rate (HR) did not change statistically significantly after performing breathing exercises. At rest, the heart rate was 77.09 ± 4.07 beats per minute, after exercise it was 78.64 ± 3.52 beats per minute ($p > 0.05$). At the same time, when analyzing the dynamics of HRV spectral indicators, statistically significant changes were revealed. For statistical studies of power indicators TP, HF, LF, VLF by parametric methods, their radical expressions were used. Thus, there was a decrease in the high frequency component (High Frequency - HF) (at rest - 25.76 ± 4.85 ms, after breathing exercises - 20.04 ± 3.74 ms, $p < 0.01$), an increase in the low frequency (Low Frequency - LF) (at rest - 29.97 ± 3.21 ms, after exercise - 38.48 ± 5.12 ms, $p < 0.05$). The very low frequency spectral component (Very Low Frequency - VLF) did not change (at rest - 18.00 ± 2.63 ms, after breathing exercises - 18.53 ± 2.31 ms, $p > 0.05$). It should be noted that the total power (Total power - TP) in the HF, LF, VLF ranges also did not change statistically significantly (47.44 ± 5.49 ms at rest, 51.51 ± 6.05 ms after exercise, $p > 0.05$).

Certain changes in HRV after breathing exercises were quite expected, since fluctuations in the high frequency range are closely related to the act of breathing and reflect respiratory sinus arrhythmia (RSA). Given that RSA is modulated by n. vagus, then the high-frequency component of HRV is a reflection of parasympathetic influences. At the same time, the presence of individual differences observed in various breathing patterns suggests that changes in spectral parameters are caused not only by the processes of autonomous regulation. In particular, significant changes in low-frequency HRV, observed after breathing exercises, are associated by some researchers with the resonant characteristics of the cardiovascular system, which affect the final result of the combined action of RSA and baroreflexes [3, 4].

4. Conclusions

1. The breathing exercises used in our study, characterized by an increase in the duration of exhalation in relation to the physiological norm, do not affect the heart rate, but lead to statistically significant changes in the spectral parameters of heart rate variability.

2. The dynamics of the HRV spectral parameters after the impact of exercises is characterized by a decrease in high-frequency components (HF), an increase in low-frequency components (LF). The indicators of the very low-frequency components of the spectrum (VLF) do not change statistically significantly.

3. Indicators of the total spectrum power (TP) after exercise do not change, which is associated with a proportional change in the values of high-frequency (HF) and low-frequency (LF) components relative to each other.

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Article

Hand-foot syndrome and nail changes caused by capecitabine chemotherapy.

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Abstract: The effects of targeted therapy are not limited with cancer cells and, unfortunately, are associated with many and numerous side effects. Dermatological manifestations are one of the most frequently observed, and in severe and/or prolonged they inevitably affect the quality of life of patients. The management of these various side effects is empirical and largely based on expert advice and consensus. Many cytotoxic and biological drugs are the cause of severe dermatological side effects, such as hand-foot syndrome (HFS). An oncological patient with HFS presents relevant symptoms that interfere with daily activities and with adherence to anticancer treatment. Control and treatment of HFRS are the most important goals of improving the quality of life of cancer patients.
Below we present the case of a 62-year-old woman undergoing treatment with capecitabine and paclitaxel for breast cancer.

Keywords: hand and foot syndrome, capecitabine, oncologists, chemotherapy, drug's reaction.

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1. Introduction

Capecitabine (Xeloda; Hoffmann-La Roche Inc, Nutley, NJ, USA), a fluoropyrimidine carbamate derivative that is a prodrug of 5-fluorouracil, is an orally administered tumor selective cytotoxic agent [1], [2]. It is used in combination with docetaxel or with paclitaxel for the treatment of locally advanced or metastatic breast cancer [3]. It is also used as a first-line treatment for metastatic colorectal carcinoma. Hand-and-foot syndrome (HFS) is listed as a well-known adverse effect on the patient information brochure. HFS is also seen with other chemotherapeutic agents and found that 92.9% of HFS developed within the first two cycles of treatment. HFS is usually self-limiting and rarely leads to hospitalization or life-threatening manifestations. However, it has an on treatment schedule and quality of life [4], and the cumulative nature of HFS difficult to ascertain [5].

A 62-year-old woman was seen in the outpatient Department one and a half years after undergoing a modified Mastectomy carcinoma of the left breast. She underwent chemotherapy with two cycles of injection of cyclofosfamide (750 mg), 5-fluorouracil (750 mg) and methotrexate (75 mg) before surgery and three more cycles after surgery. Then she began six cycles of radiation therapy. In the end, she was started on paclitaxel (240 mg in one pint of normal saline infused over 3 hours) and capecitabine (500 mg) three tablets twice a day for 14 days, followed by 7-day pill-free phase.

After the second cycle of paclitaxel and capecitabine, the patient complained on tingling in hands and feet associated with progressive burning. During the week, she also noted discomfort, tightness, soreness, and stiffness when holding objects. During the examination, swelling and hyperemia of the palms and soles were noted [Fig. 1]. It was thickening of the skin accompanied it, more on the pads of the toes and heels [Fig. 2 A,B]. Besides there was a pronounced peeling on the legs. The nail plates of the hands and feet significantly thickened and changed color. Some of the plates were flaking off.

The patient was the clinical diagnosis HFS Grade III intensity levels induced by capecitabine. She refused a skin biopsy on her hands. She was assigned a softening agent containing allantoin and thermal water, 2% salicylic ointment on areas of hyperkeratosis. She also started taking oral pyridoxine (40 mg) once a day. Third capecitabine cycle was delayed.

During the observation one week later there was a significant decrease in pain, stiffness, tingling and burning. Thickening, peeling and flaking decreased [Fig. 3 A,B]. However, there was only a slight decrease in hyperemia of the hands and feet. At this stage, treatment was resumed with a reduced dose of capecitabine, 1g twice a day, for 14 days. Fifteen days later, there was no recurrence of symptoms or there. The patient continued to receive chemotherapy.

Hand-foot syndrome, acral erythema, palmar-plantar erythrodysesthesia syndrome were first reported by Zuehlke in 1974 [6]. Since then syndrome is ofter reported such an adverse event in many chemotherapy regimens. 5-Fluorouracil, cytarabine, doxorubicin, methotrexate, etoposide and commonly used agents are associated with HFS [7]. Of the new agents, there have been many reports that capecitabine causes HFS [1], [2], [5].

HFS appears to be a drug-addicted dose. It is assumed that the reaction is spused by the accumulation of a large amount of the drug in the stratum corneum of the palms and soles that have sebaceous glands but do have a large number of eccrine glands. All this contributes to the local toxic accumulation of the drug. However, this fact has not been proven yet. HFS manifests itself initially as dysesthesia, paresthesia and increasing discomfort on the hands and feet. Patients complain of burning, pain, tenderness when holding objects that may be accompanied by difficulties in standing or walking. In the future there might be swelling, progressive erythema along with, we can witness the development of hyperkeratosis and calluses and corns on hands and feet. In very severe cases, blisters may be seen. The condition improves within a few weeks with the peeling on the hands and feet. HFS manifests initially as dysesthesia, paresthesia and an increasing discomfort in the hands and feet [8].

Some cases may be accompanied by nail changes such as onycholysis and nail discoloration. Acral skin lesion for the disorder was registered in less than 5% of the patients, who received capecitabine only and in about 15% of the patients who received during either capecitabine and docetaxel or docetaxel alone metastatic breast cancer treatment [9]. The colors and thickening of our patient's nail plates may be seen as part of the HFS. HFS has three grades of severity Grade1 shows erythema of lateral aspects of fingers, progressing to thenar and hypothenar eminences, with swelling, numbness, dysesthesia/paresthesia, and tingling, especially over the pads of distal phalanges. A similar picture may be seen on the feet. However, it does not interfere with the patient's normal daily activity. Grade2 shows a progression of manifestations of grade 1, along with the pain, tenderness and discomfort affecting daily activities. In grade 3, along with severe pain, there is also development of blisters, moist desquamation and ulcer formation. The histopathological findings are nonspecific, with mild focal spongiosis in the epidermis, mild epidermal atypia, and mononuclear cell infiltration of the upper dermis. Immunofluorescence studies did not reveal any particular criteria in diagnosis [10].

3. Discussion

The drugs that provoke HFS most often are part of the basic schemes of chemotherapy, which are widely used in the treatment of cancer pathology. HFS is caused by cupecitabine in 74% of patients, 5-fluorouracil (34%), idarubicin (48%) as well as by methotrexate, etoposide and a combination of agents [5]. Less frequently HFS occurs with continuous infusion of doxorubicin, treatment with high doses of interleukin-2, liposomal doxorubicin, cytarabine, idarubicin, cyclophosphamide, hydroxyurea, docetaxel, mercaptopurine, mitozatronom, paclitaxel, vinorelbine, floxuridine, tegafur. Targeted therapy with sorafenib, sunitinib and lapatinib also provokes the development of this syndrome.

The histopathological findings are nonspecific, and helude mild focal spongiosis in the epidermis, mild epidermal atypia, and mononuclear cell infiltration of the upper dermis [7]. Immunofluorescence studies do not yield any positive findings.

Simple topical care with wet dressings, topical steroids, and emollients is enough to improve the condition of some patients, without interrupting therapy [7]. In some patients, moderate reduction of the dose of the offending agent, along with an intensive local care regimen, may be required. In a third subset of patients, the offending agent needs to be stopped completely to avoid recurrences or worsening of the condition. Patients are also recommended to avoid excessive exposure to sunlight and heat.

Knowing the symptoms and methods of aid will help to avoid the HFS syndrome. This will allow to resume treatment without reducing the drugs dosage or withdrawing it.

Figure 1. Fig.1 Skin changes, specifically swelling and hyperemia of the palms.

Figure 2 (A, B). Skin lesions, in particular, thickening of the skin more pronounced on the fingertips and in the heel area.

Figure 3 (A, B). In the process of therapy one week later there was a significant decrease in pain, stiffness, thickening peeling and flaking decreased.

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Article

Studying the redox status of paramecium caudatum cells under influence of molybdenum, zinc, copper oxide nanoparticles and synthetic antioxidants

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Abstract: *Aims.* To study the effect of CuO, ZnO and MoO3 nanoparticles on the vital functions of the single cell organism Paramecium caudatum; to analyse the activity of antioxidant cellular enzymes: SOD and CAT, as well as to evaluate the possibility of cells protection against oxidative stress by endogenous antioxidants. *Methods.* Paramecium caudatum cells were cultured under standard conditions for this test subject [3-4]. The toxicity of metal nanoparticles, PMCO (20-60 nm), PM ZnO (40-80 nm) and PM MoO3 (5-20 nm) (Laboratory of Physical Modelling of Two-Phase Flows, United Institute of High Temperatures, Russian Academy of Sciences) - was evaluated by determining the LC50 lethality index of the concentration at which 50% of Paramecium caudatum population was killed. Free-floating cells were then exposed for 48 h to sublethal concentrations of NPs metal oxides in moderately hard water with dissolved antioxidant. The efficacy of emoxipine (10 mg/ml), mexidol (50 mg/ml) ascorbic acid AA (25 mg/ml) and nicotinic acid NA (10 mg/ml) was investigated; for this purpose cell number, cell membrane condition, changes of intracellular organelle shape were recorded (Levenhuk C310 digital camera microscope, 3.1 Mpixel). *Results.* We found that the presence of metal oxides induced a significant decrease ($p < 0.05$) in the number of viable Paramecium caudatum cells, in 24 h there were 58 % deaths from CuO, 43 % deaths from ZnO and 40 % deaths from MoO3, but in 48 h - 92 %, 88 % and 75 %, respectively. Copper oxide PM were the most toxic to cells, with an LC50 of 25 mg/l; for ZnO PM and MoO3 PM, the lethal concentration was equal and higher than 50 mg/l. negative pressure of metal-containing NPs led to osmotic disorganization, which was accompanied by an increase in vacuoles, abnormal bending and membrane rupture. *Conclusions.* Our results demonstrated that oxidative stress is one of the leading mechanisms of toxicity of PM oxides of transition metals such as copper, zinc and molybdenum. When the single-celled organism Paramecium caudatum was exposed to the studied NPs, destructive damages of membrane structures, changes in functions and morphology of organelles leading to cell death were observed. It should be noted that under such abiotic stress, the viability of Paramecium caudatum in general is the result of a complex interaction of the cells' own antioxidant system as well as the specific characteristics of NPs (size and solubility) and additional environmental factors, such as the presence of compounds with antioxidant activity in it.

Keywords: molybdenum, zinc, copper oxide nanoparticles and synthetic antioxidants.

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1. Introduction

The modern application of nanotechnology is accompanied by problems of nanosafety and the assessment of the impact of nanomaterials on human health and the environment. Among the various biological reactions used to assess the potential effects of nanoobjects on biota, the generation of reactive oxygen species (ROS), which disrupts the pro- and antioxidant equilibrium in cells and thus causes oxidative stress (OS), is currently the most accepted paradigm for the toxicity of various nanoparticles (NPs) to humans and the environment [1-2; 5]. Metal-containing

nanoparticles are used in various fields from technical to medical, for example, copper and zinc nanoparticles are widely used biocides and molybdenum nanomaterials also have antibacterial properties. It should be noted that molybdenum, zinc and copper are essential trace elements for living organisms and each of them has a specific function in the redox state of the cell. For example, molybdenum is a promoter of antioxidants, particularly ascorbic acid (AA). Copper and zinc are found in the cellular enzyme superoxide dismutase (SOD), a catalyst for the dismutation of the aggressive AFC superoxide. But in excess, these transition metal ions have a serious toxic effect on cells, primarily caused by OS.

To evaluate the ability of NM of these transition metals to cause OS in various ecologically relevant organisms, this work used biomarkers such as increased activity (SOD) and catalase (CAT), the most sensitive elements of the antioxidant system, the so-called first-line defense against AOS damage. In addition, since lipid molecules constitute approximately 30-80% of biological membranes by mass, lipid peroxidation in response to reactive oxygen species is a very likely scenario of OS, therefore, we additionally evaluated the condition of cell membranes by accounting for the secondary product of peroxidation, malondialdehyde MDA.

Our study was undertaken to better characterize the mechanism of action of metal-containing NPs at different levels of organization of living matter. The free-living freshwater infusoria Paramecium caudatum was chosen as a test object in this work, as this cell-organism provides an opportunity to study both cellular and organismal forms of response to chemical stressors simultaneously.

Aims. To study the effect of CuO, ZnO and MoO3 nanoparticles on the vital functions of the single cell organism Paramecium caudatum; to analyse the activity of antioxidant cellular enzymes: SOD and CAT, as well as to evaluate the possibility of cells protection against oxidative stress by endogenous antioxidants.

2. Methods

Paramecium caudatum cells were cultured under standard conditions for this test subject [3-4]. The toxicity of metal nanoparticles, PMCO (20-60 nm), PM ZnO (40-80 nm) and PM MoO3 (5-20 nm) (Laboratory of Physical Modelling of Two-Phase Flows, United Institute of High Temperatures, Russian Academy of Sciences) - was evaluated by determining the LC50 lethality index of the concentration at which 50% of Paramecium caudatum population was killed. Free-floating cells were then exposed for 48 h to sublethal concentrations of NPs metal oxides in moderately hard water with dissolved antioxidant. The efficacy of emoxipine (10 mg/ml), mexidol (50 mg/ml) ascorbic acid AA (25 mg/ml) and nicotinic acid NA (10 mg/ml) was investigated; for this purpose cell number, cell membrane condition, changes of intracellular organelle shape were recorded (Levenhuk C310 digital camera microscope, 3.1 Mpixel).

Activity of biomarkers SOD (by reduction of tetrazolium blue), CAT (by hydrogen peroxide reduction rate) and MDA (by Uchiyama-Michara method) was determined by spectrophotometric methods (SPECORD 50 plus). All data were statistically processed and valid (Statistica 12.6).

3. Results

We found that the presence of metal oxides induced a significant decrease ($p < 0.05$) in the number of viable Paramecium caudatum cells, in 24 h there were 58 % deaths from CuO, 43 % deaths from ZnO and 40 % deaths from MoO3, but in 48 h - 92 %, 88 % and 75 %, respectively. Copper oxide PM were the most toxic to cells, with an LC50 of 25 mg/l; for ZnO PM and MoO3 PM, the lethal concentration was equal and higher than 50 mg/l. It was shown in a number of works [1-2; 5] that metal oxide particles may deposit on cell wall causing mechanical damage; change of cell morphology, deformation of membranes and intracellular structures. In our experiments on Paramecium caudatum infusoria, negative pressure of metal-containing NPs led to osmotic disorganization, which was accompanied by an increase in vacuoles, abnormal bending and membrane rupture (Fig.). These results were consistent with the experimental literature [2; 5], which reported that in unicellular organisms, ZnO NPs increase membrane permeability, depolarize cells and/or perforate cell walls, allowing NPs to penetrate into the cytoplasm. The survival of Paramecium caudatum cells was dependent on the amount of NPs and their degree of aggregation within the cells. NPs were detected in the food vacuoles and cytoplasm but their accumulation varied depending on the size, concentration of NPs and time of exposure. The amount of accumulated PM in the cell was higher after 2 h of exposure than after 24 and 48 h. It is shown that the increase of CAT activity in the cells was observed after 2 h of incubation of Paramecium caudatum with metal-containing PM. This is due to the fact that catalase is considered a first-line

defense enzyme against the damaging effects of AFC. Indeed, catalase activity is the conversion of hydrogen peroxide (H2O2) into water and molecular oxygen (O2) initiated by the presence of exogenous components such as metal ions in the body.

Figure. Changes in Paramecium caudatum cell shape: a - cell in normal condition; b - disruption of the outer cell membrane by ZnO NPs; c - cell condition in the presence of the antioxidant emoxipine

Increased concentrations of NPs metal oxides (50 mg/l) in the environment contributed to the development of OS. At the same time, the level of MDA increased, while the levels of SOD and CAT activity decreased by about half. This indicates an intensive process of free oxygen radical formation and related cell damage.

The addition of the synthetic antioxidant emoxypine to the experimental medium with a population of Paramecium cauda tum (Fig.) reduced the toxic effect of NPs metal oxides, and the same positive effect on cells was exerted by mexidol. It is indicative that the effect of PM on cells cultured in medium with emoxipin or mexidol, which was evaluated by MDA level, was 3.5 times lower than that of cells that were in medium with metal-containing PM only. Nicotinic acid in our experiments proved to be ineffective in protecting the cells from exposure to the metal oxide NPs under study.

Earlier by us [3-4] on cells of Paramecium caudatum in model of OS was determined a strict concentration dependence of pro/antioxidant effect of AA. It was found that AA in the presence of Cu+2 and Zn+2 inhibited the activity of infusoria and promoted the development of OS resulting in cell death. The results of experiments with nanosized particles of copper, zinc, and molybdenum were similar to those obtained earlier [3-4].

5. Conclusions

Our results demonstrated that oxidative stress is one of the leading mechanisms of toxicity of PM oxides of transition metals such as copper, zinc and molybdenum. When the single-celled organism Paramecium caudatum was exposed to the studied NPs, destructive damages of membrane structures, changes in functions and morphology of organelles leading to cell death were observed. It should be noted that under such abiotic stress, the viability of Paramecium caudatum in general is the result of a complex interaction of the cells' own antioxidant system as well as the specific characteristics of NPs (size and solubility) and additional environmental factors, such as the presence of compounds with antioxidant activity in it.

We have developed an approach to assess the impact of nanomaterials on the living organism by monitoring the most sensitive biomarkers of oxidative stress such as superoxide dismutase, catalase and malondialdehyde - characteristic indicators of chemical pollution.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

Transcriptomic reaction of the rat hippocampus and spleen to singular and course injection of selank peptide

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Abstract: The *aim* of the study was to evaluate the effect of the regulatory peptide selank on the action and expression of the genome. *Methods*. In order to do this, we needed to locate the genes responsible for the change in expression in the hippocampus and spleen of a rat. Male Wistar rats were used in the experiment. The animals were split into 3 groups (of 8 rats with the average weight of 260 grams): control group (C), singular injected group (SI) and injected over a course (CI). 2 groups- C and SI were intranasally injected with water over the course of 5 days once a day, group CI was injected with a watered solution of selank (200 mcg/kg). *Results*. During the first stage, hybridization was carried out on a micromatrix for RNA from hippocampal tissues. The data obtained showed that both single and course administration of Selank changed the expression of 5 genes by more than 2 times. Since Selank is also an antiviral drug, of particular interest is the study of the mechanism of action of this peptide on the expression of these five genes in the rat spleen. A quantitative assessment carried out during the study showed that the effect of Selank on the expression of the five selected genes in the rat spleen was much more pronounced than in the hippocampus. In the spleen, there is an increase in the expression of all selected genes. The strongest increase (more than 4.5 times) was noted after a single injection of the peptide. With a course introduction, the effect of the peptide is less pronounced, the expression of selected genes increases by no more than 2 timesThe data obtained showed that both single and course administration of selank changed the expression of 5 genes by more than 2 times. The change of expression in the CX3CR1 gene is of particular interest because it is involved in the regulation of inflammatory processes. *Conclusions*. Our data indicate that selank may be involved in the regulation of inflammatory processes in the body. The complex biological effects of selank on the body may at least partially be due to the systemic effect of the peptide on genome expression. This mechanism of action of peptides opens up new opportunities for directed changes in the transcriptional profile under the action of oligopeptides, homologues of natural bioactive peptides. However, this will require further study of the mechanisms of action of peptides, including selank, on different systems of the body and the processes occurring in them.

Keywords: Transcriptomic Response, CX3CR1 Expression, Selank peptide.

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1. Introduction

An innovation in the field of pharmacology, is creating new drugs that are affectively able to lower the level of anxiety without side effects, using endogenous regulative peptides. "Selank"- is a new drug that has been synthesized at the laboratories of the Institute of Molecular Genetics of the Russian academy of sciences and the Research Institute of Pharmacology (im. Zakusova) of the Russian academy of medical sciences, the active substance of which is a synthetic peptide - an analogue of a short fragment of the heavy chain of human immunoglobulin G Thr–Lys–Pro–Arg, elongated from the C end with the tripeptide Pro–Gly–Pro. Selank has been proven to be an effective stable nootropic and anxiolytic drug, while promoting the survival of brain cells during hypoxia, and also having an antiviral effect. Research in the recent years has shown that many peptides like semax, can alter the expression of the genome. Therefore, given the selank is also a regulative peptide, it will be interesting to research its influence on the expression of the genome. In

order to do that, we had to localise the genes responsible for altering the expression of the genes in hippocampus and spleen of a rat under the influence of said peptide.

2. Methods

Male Wistar rats were used in the experiment. The animals were split into 3 groups (of 8 rats with the average weight of 260 grams): control group (C), singular injected group (SI) and injected over a course (CI).

2 groups- C and SI were intranasally injected with water over the course of 5 days once a day, group CI was injected with a watered solution of selank (200 mcg/kg). on the sixth day group SI was injected with the watered solution of Selank (200 mcg/kg). After one hour the animals were decapitated. Using the RNAgentsTM Total RNA Isolation System ("Promega", USA) a total strand of RNA was isolated out of the hippocampus and spleen, then using the "RevertAid™H Minus First Strand with DNA Synthesis Kit" ("Fermentas", Lithuania) a strand of coking DNA was synthesized. The influence of selank on the expression of genes was analyzed via a micromatrix SBC–R–RC–100–13, containing 12000 genes ("Shanghai Biochip™", China). A quantitative assessment of the level of expression of individual genes was carried out using real-time PCR on the device "Mx3000P™ RealTime QPCR System" ("Stratagene Equipment", USA) using the SYBR Green I ("Syntol", Russia) and primers RT2 qPCR Rrimer Assay SYBR® Green ("Super Array", USA). The obtained values of reaction cycle thresholds (Ct) were normalized to Ct of the gene of the ribosomal protein L3 and statistically processed using the software "Relative Expression Software Tool384", version 2 [8].

3. Results

During the first stage, hybridization was carried out on a micromatrix for RNA from hippocampal tissues. The data obtained showed that both single and course administration of Selank changed the expression of 5 genes by more than 2 times (Table 1).

Since Selank is also an antiviral drug, of particular interest is the study of the mechanism of action of this peptide on the expression of these five genes in the rat spleen. A quantitative assessment carried out during the study showed that the effect of Selank on the expression of the five selected genes in the rat spleen was much more pronounced than in the hippocampus. In the spleen, there is an increase in the expression of all selected genes. The strongest increase (more than 4.5 times) was noted after a single injection of the peptide. With a course introduction, the effect of the peptide is less pronounced, the expression of selected genes increases by no more than 2 times (Table 1).

Table 1. Relative changes in gene expression in the hippocampus and spleen of rats under the influence of a single (SI) and course (CI) administration of the selank peptide compared with the control.
*p<0.05;**p<0.01

Gene	Name of Gene	Hippocampus		Spleen	
		SI	CI	SI	CI
ACTN1	Actinin Alpha 1	0.42*	0.49*	15.96**	1.97**
CX3CR1	C-X3-C Motif Chemokine Receptor 1	0.46*	2.77*	15.93**	1.87**
FGF7	Fibroblast Growth Factor 7	2.35*	2.23*	8.15**	2.08**
PTPRN2	Protein Tyrosine Phosphatase Receptor Type N2	2.61*	3.01*	70.36**	1.09
XTRP3	Sodium- and chloride-dependent transporter XTRP3	3.98*	2.13*	4.47*	1.19

4. Discussion

The presented study is one It should be noted that for the ACTN1 and CX3CR1 genes, selank has a multidirectional effect on their expression in the rat hippocampus and spleen. The expression of the ACTN1 gene after a single and course administration and of the CX3CR1 gene after a single administration in the hippocampus is significantly reduced. In the spleen, on the contrary, there is an increase in the expression of these genes, which is especially significant after a single administration of the peptide. The greatest change in expression was observed in the spleen for three genes - PTPRN2, ACTN1 and CX3CR1 after a single injection of the drug. At the same time, the maximum increase in expression (by 70 times) was noted for the PTPRN2 gene. This gene encodes an integral glycoprotein involved in the regulation of transmembrane signaling [4]. PTPRN2 is an important autoantigen in insulin-dependent diabetes and may play a pathogenic role in the development of this disease [11]. For the ACTN1 and CX3CR1 genes, it was shown that a single administration of selank leads to a 16-fold increase in their expression level. The ACTN1 gene encodes a calcium-sensitive protein that cross-links F filaments of actin, which plays an important role in maintaining the viscosity and elasticity of the cytoplasm, which is necessary to preserve the integrity of macromolecules associated with the plasma membrane [12]. The change in the expression of the CX3CR1 gene that we found is of particular interest, since this gene is involved in the regulation of inflammatory processes. The CX3CR1 gene encodes a specific receptor for the fractalkine protein belonging to the serpentine receptor family and is involved in the maturation, transfer, and recycling of leukocytes and in the initiation of local inflammation as a result of the involvement of inflamatory cells in the chemotaxis process [5, 9].

The interaction of fractalkine with CX3CR1 can act as a regulator of communication between neurons and microglia in the brain and participate in the activation and migration of microglia [7]. Some data indicate that the CX3CR1 gene plays the role of a neuroprotector and is able to inhibit apoptosis [6]. In addition, studies show that CX3CR1 can function as a co-receptor for HIV1 entry into the cell [2].

5. Conclusions

Our data indicate that selank may be involved in the regulation of inflammatory processes in the body. The complex biological effects of selank on the body may at least partially be due to the systemic effect of the peptide on genome expression. This mechanism of action of peptides opens up new opportunities for directed changes in the transcriptional profile under the action of oligopeptides, homologues of natural bioactive peptides. However, this will require further study of the mechanisms of action of peptides, including selank, on different systems of the body and the processes occurring in them.

Conflicts of Interest: The authors declare no conflict of interest.

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In Memory

Inna Vlasova: scientist, researcher, teacher.

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On January 1, 2023, at the age of 89, DSc, Professor Inna Vlasova, whose pedagogical and scientific activities were inextricably linked with the Department of Physiology of RUDN University, left us.

Inna Vlasova was born on June 23, 1934 in Moscow. In 1958 she became a doctor at the Sechenov 1st Moscow Medical Institute. From 1958 to 1962 Inna Vlasova worked as a workshop physician in the medical sanitary unit N1 of the Likhachev Automobile Plant.

From 1962 to 2013, Inna Vlasova worked at the Department of Normal Physiology of the Medical Faculty of RUDN University, first as an assistant, then as a senior lecturer, associate professor, and since 1993 as a professor. Inna Vlasova was one of the founders of the Department of Normal Physiology at RUDN University. Together with Associate Professor Sofia Chesnokova and Head of the Department of Physiology Konstantin Kullanda, she participated in the organization of the educational process and the first scientific work at the Department of Physiology. In 1970 she defended her Ph.D. thesis "Characterization of properties and some mechanisms of corticopetal and corticofugal connections of non-specific systems of the brain stem", in 1981 she was awarded the academic title of associate professor. In 1992, Inna Vlasova defended her dissertation "Comparative characteristics of temporal and adaptive reactions of nerve cells to the action of extreme factors" and received a DSc degree. In 1994 she was awarded the academic title of Professor.

Inna Vlasova lectured and conducted classes with students in the specialties "Medicine", "Pharmacy" and "Dentistry", supervised the specialty "Pharmacy" at the Department of Physiology.

Inna Vlasova was known for her scientific work in the field of studying adaptive reactions to the action of extreme environmental factors (hypoxia, temperature, laser and electromagnetic radiation), as well as the mechanisms of biorhythms at the neuron level. She owned unique methods for studying the central nervous system: the cultivation of nervous tissue, surviving sections of the brain. She learned this technique in 1974 at the then advanced scientific laboratories in Canada. She performed with scientific in Austria, Switzerland, Italy. Inna Vlasova is the author of 160 scientific, educational and educational works, including 2 textbooks and 4 workshops, as well as 12 teaching aids, 2 certificates for rationalization proposals have been received. The textbook "Fundamentals of Human Physiology" and "Workshop in Physiology", which she co-authored and are now used in many medical universities.

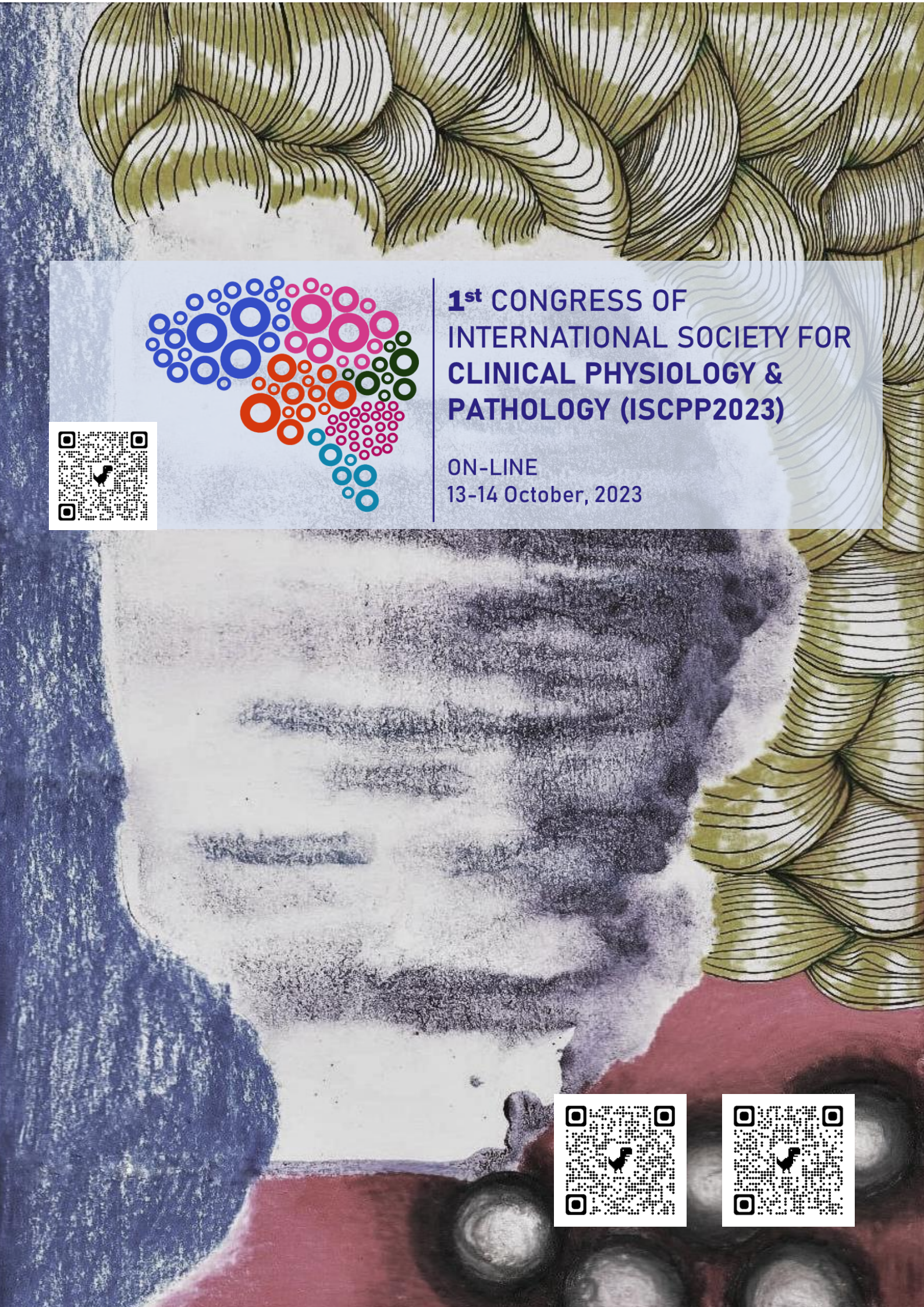
Inna Vlasova also did a lot of social work. Together with Associate Professor of the Department of Therapy Elena Polotskaya, she organized the first internship for students of the Medical Faculty of RUDN University at Clinical Hospital No. 64. She was the Deputy Dean of the Faculty of Medicine of RUDN University Fyodor Romashov on a voluntary basis for work with interns,

residents and graduate students, a member of the trade union committee of the Faculty of Medicine, the secretary of the faculty's expert commission, a member of the commission for work with students in the hostel of RUDN University. For many years she was responsible for extracurricular activities at the Department of Physiology of RUDN University, for which the Department of Physiology received prizes for 3 consecutive years in 2007-2008, 2009-2010, 2010-2011.

Inna Vlasova was awarded the badges "Honorary Worker of Higher Professional Education of the Russian Federation" and "Excellent Worker in Health Care", a bronze medal of the USSR Exhibition of Economic Achievements, was a "Veteran of Labour".

Inna Vlasova was an example of boundless devotion to her work, an experienced teacher and an interesting interlocutor, she had a stubborn character and incredible capacity for work. Many generations of students and staff of the Department of Physiology at RUDN University remember her with deep gratitude and reverence.

Rest in peace, dear Inna Vlasova!



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