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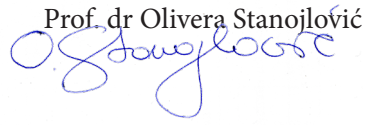

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REVIEW

Supervisor education and quality of PhD studies: current status and future challenges

Petar Milovanović [1], Tatjana Pekmezović [1]

[1] University of Belgrade Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Tatjana Pekmezović, MD, PhD
Faculty of Medicine University of Belgrade,
Dr Subotica 8, 11000 Belgrade, Serbia
Phone: +381 11 3636 300
E-mail: tatjana.pekmezovic@med.bg.ac.rs

Summary

Supervision is a specific relationship, where an experienced senior researcher provides guidance, support, and advice to navigate a junior colleague through the barriers to becoming an independent researcher. While supervision is clearly a rewarding duty, it is also associated with a number of challenges. It is clear that supervision involves many responsibilities, which means that the supervisor needs to possess a certain set of skills. While many of these skills are learned in the direct interaction with PhD candidates, it would be beneficial if a more formal and structured training was offered to supervisors, especially at the beginning of their supervision careers, so as to avoid frequent mistakes in the supervisor–PhD candidate relationship. Hence, the idea is to shift from experience-based supervision to professionalization, believing that such an approach would reduce the risk of poor supervision. At present, many universities offer formal education of supervisors. The practice of organized education of supervisors at University of Belgrade Faculty of Medicine started in 2019 with the aim of preparing future supervisors to establish productive and responsive relationships with PhD candidates. After a break due to the COVID-19 pandemic, a revised supervision course was organized in 2022. The survey conducted among the attendees of the two organized courses supported the need for better education of university teachers in terms of supervision skills and leading of PhD candidates. Indeed, considering the fact that PhD outcomes are largely dependent on the supervisor and the successful supervisor–PhD candidate relationship, supporting supervision through formal training and education may be an important step in improving PhD experience and outcomes for both supervisors and PhD candidates.

Keywords: supervision, supervisor skills, challenges, PhD studies, education

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INTRODUCTION

Supervision is a specific relationship between two individuals, an experienced senior researcher/teacher who shares critical information with a less experienced junior colleague, navigating through the barriers to his/her successful career (1). A supervisor is a person who can support, advise, and guide a candidate. Supervisor has the potential to become a lifelong friend, or the relationship might only last until the PhD candidate has achieved their goal. Supervision implies specific responsibilities such as creation of a relationship that pairs experience, wisdom, and expertise with new ideas, questions, and obstacles that accompany the research process. Modern definitions indicate that supervision is a dynamic, collaborative, reciprocal, and sustainable relationship, focused on the acquisition of values and attitudes, knowledge and skills, as well as the adoption of the behavior of junior colleagues, so that they become successful independent researchers (2). Recently, supervision of PhD candidates has been recognized as one of the factors that foster research integrity (3).

According to the Standards for PhD education in Biomedicine and Health Sciences in Europe, developed by a joint Organization for PhD Education in Biomedicine and Health Sciences in the European System (ORPHEUS) and The Association of Medical Schools in Europe (AMSE) Task Force (4), supervision is one of eight essential areas in the organization of PhD program (5). In this document, it is emphasized that supervisors need to be scientifically qualified and active researchers in the relevant field, with a continuous scientific production that contributes to scientific literature. Additionally, it is highlighted that universities should ensure that training in supervision is available for all supervisors and potential new supervisors, with the aim of becoming familiar with the local regulations of the PhD program as well as basic duties of supervision (6).

SUPERVISION SKILLS

It is generally accepted that the quality of supervision is a major predictor for successful PhD projects (7). Specifically, a recent study (8) has shown that solid research environment, including good supervision, is the strongest predictor of PhD candidates' outcomes during their PhD studies, provided that the candidates met certain minimum admission criteria. This highlights the role of a supervisor, not only as a supervisor of a doctoral thesis but also as a provider of the research environment, including patients or specimens, equipment, and consumables, grant support and international contacts and recognition.

Therefore, providing skills development guidance to PhD candidates considering their aptitudes and weaknesses is an important responsibility of a PhD supervisor. Sufficient information on specific knowledge, skills, or attitudes required from supervisors is not widely available in literature. However, Abedin et al. identified major categories of supervisor characteristics: leadership, empowerment, strategic perspective, integrity and judgment skills, creative thinking, and communication skills (9). These characteristics and skills further allow supervisors to train PhD candidates in data analysis, problem solving, scientific writing, and oral presentation.

It is very important to underline that supervision in clinical context appears to require additional competences. Therefore, a PhD supervision program should take into account the requirements of different professional specialties and backgrounds (7).

Communication is certainly one of the most important skills of supervision. Therefore, being able to identify specific characteristics of effective communication becomes important in order to maximize each supervisor–PhD candidate relationship. Handelsman et al. considered that elements of effective communication are those that include providing constructive feedback, communicating effectively across diverse backgrounds, disciplines, generations, ethnicities, and positions of power, identification of different communication styles, and engaging in active listening (10). Madan outlined several key topics that all PhD supervisors should consider, including calibration of expectations, management styles, and tailoring of the supervision experience (11).

EXPERIENCE-BASED SUPERVISION VS FORMAL TRAINING IN SUPERVISION

Not all PhD candidates are excellent, but not all supervisors are exceptional either. Previous studies evaluating the level of satisfaction of PhD candidates with their supervisors emphasized that in many cases the candidates were not satisfied with the received guidance, and complained of poor or inadequate supervision. Moreover, more than 50% of dropout cases in Denmark were related to the poor supervision received (12). Investigation of the first 23 individuals who completed the new PhD course at University of Belgrade Faculty of Medicine (UBFM) established in 2006 revealed that almost 50% of the candidates were not fully satisfied with how much their supervisors acknowledged their contribution, and almost 15% of the candidates would not recommend their supervisor to another colleague (13). Therefore, there is a huge need for improving the overall level of PhD supervision.

Supervisors may base their supervision style and expectations not only on their own personality but also on previous supervision relationships, including the supervision they received when they were PhD candidates (1). PhD supervision is a two-way learning street, where a candidate receives guidance from their supervisor towards fulfilling the thesis requirements but also "pro-

vides" the supervisor with a practical training opportunity to learn supervision skills along the way. Indeed, most supervisors acknowledge that they learned a lot through interaction with their PhD candidates, but it would be beneficial if more formal and structured training was offered to supervisors, especially at the beginning of their supervising careers, in order to avoid frequent mistakes in the supervisor–PhD candidate relationship. Furthermore, apart from training programs, a form of continuous or sporadic support to supervisors may be of great significance. The entire idea is to shift from experience-based supervision towards professionalization, as it is believed that such an approach would diminish the risk of poor supervision. Indeed, in contrast to the past when supervision was usually acquired through experience, many universities at present offer formal education to supervisors (7). In this context, supervisor education programs are essential, but they should take into account the needs of supervisors as well as specific needs of certain science fields, such as clinical medicine (7).

CHALLENGES OF SUPERVISION

While supervision is indeed a rewarding duty, it is also a very challenging process. Supervisors need to satisfy conflicting requirements when balancing between the need to ensure their candidates meet the criteria required in order to complete their PhD and the need to respect candidates' independence and their individual dynamics. Hence, they simultaneously support and demand, which may be frustrating and bring about anxiety and exhaustion of supervisors. While there has been a lot of interest in emotional coping of PhD candidates during their PhD studies and the preparation of their doctoral thesis, the fact that supervision is not just a cognitive but also an emotional endeavor has been largely neglected. A recent study by Han and Xu (14) has focused on supervisors' emotions during the supervising process and their emotional regulation strategies. In a qualitative study that involved 17 supervisors from China, the authors concluded that negative emotions such as anxiety, frustration, and exhaustion were commonly reported by the interviewed supervisors. The authors also identified and extensively discussed two main emotional regulation strategies of these supervisors, including antecedent-focused approach (where they try to avoid or modulate problematic situations so as to avoid experiencing negative emotions) and response-focused approach (where the focus is rather placed on suppression and relaxation techniques after the emotion has been felt) (14). Clearly, there is room for education of supervisors to help them optimize their emotion regulation strategies to ensure an optimal supervision experience and a successful supervisor–PhD candidate relationship.

An important and frequent challenge of supervision is disagreement between supervisors and candidates. While this is very individual and depends on the supervisor's and the candidate's personal characteristics and relevant actions, there are several important objective reasons when a candidate would disagree with their supervisor. A qualitative study in Sweden and England emphasized that the nature of disagreement between supervisors and candidates changes over time, from the beginning of PhD studies towards the final thesis submission. For example, as candidates mature, they would often like to take a more active participation in making decisions related to the work on their thesis (15). There are also other objective sources of candidate's disagreement. Supervisors are often not up-to-date with the candidate's work, especially when they are too busy and have many candidates to supervise, which may lead to inadequate guidance and consequent candidate's frustration; supervisors may offer inadequate or misleading advice due to ignorance or lack of careful consideration of the candidate's work; there may be conflicting advice or requests from two co-supervisors, where candidates often have to try to balance these contradictory expectations; and personal incompatibility may become apparent during PhD studies (15). Considering these are the situations where candidates would expectedly disagree with their supervisor, it would be essential for supervisors to understand these and other sources of disagreement, so as to either prevent them or recognize them as early as possible. Hence, it has been suggested that the education of supervisors should also include these topics so that they could avoid objective reasons for PhD candidate's disagreement.

Although providing feedback is an important duty of supervisors, there is not enough relevant research on it, and many supervisors and PhD candidates are often not sufficiently aware of its importance. Feedback is an important pedagogic skill, which is essential for guiding a PhD candidate during their PhD studies; however, it is often a challenge for supervisors (16) and may be a serious source of discomfort and poor relationship between supervisors and PhD candidates (17). Rather than simply evaluating the current status of a PhD candidate, PhD candidate's research work, or paper writing, providing feedback is important to guide the PhD candidate towards growing and improving. However, this is a very sophisticated skill, and it is not equally developed in everyone. Moreover, different PhD candidates may differently respond to the same feedback from a supervisor. As supervisors are often not skilled enough in providing constructive and appropriate feedback, there has been growing awareness of the fact that supervisors need special training on providing feedback (18). One of the suggested formats is a micro-feedback session, where supervisors are trained to develop or improve appropriate feedback skills using feedback-based scenarios, simulated candidates, and standardized checklists (18).

Another challenge is to ensure the compliance with good research practice. It has been shown that research environment is particularly important for PhD candidates' good research practice (3, 19). Specifically, research misconduct is more common in cases with poor supervision (20). In this context, a supervisor should be a 'role model' for their PhD candidate and lead them towards adhering to good research practice and avoiding any form of research misconduct (3, 21). However, not all supervisors are sufficiently aware of the provisions of good research practice; with this in mind, it is important to provide training of supervisors on the topics of research integrity so that they can confidently discuss topics of research misconduct and guide their PhD candidates on the path of research integrity (19). This is of particular importance to young supervisors (3).

SUPERVISOR TRAINING

The role of a supervisor has often been adopted through experience, but today, universities offer more formal sources of learning such as supervisor training courses (5), as recommended by ORPHEUS (4). Education can be organized at an international level and a local level. The course program usually includes standard topics such as the supervisor's role, the correlation of supervisor and PhD candidate's expectations, methods and approaches in supervisor–PhD candidate communication, conflict management, etc. Courses usually consist of lectures, structured group exercises, and plenary discussions.

The practice of organized education of supervisors at UBFM started in 2019 with the aim to prepare supervisors in biomedical research and help them to establish productive and responsive relationships with their current or future PhD candidates. The first such educational event was organized for 25 newly appointed Assistant Professors on February 20, 2019, as a one-day course including three lectures and two workshops. The lectures were related to new trends in PhD education in Europe, and the structure and characteristics of PhD program at UBFM. The workshops were oriented towards challenges of supervision (led by a psychologist), and assessments of the originality of PhD thesis (led by a university librarian). Due to the COVID-19 pandemic, there was an interruption in organizing supervisor training events. In line with the received feedback from the first supervisor training course, a revised course was prepared and organized on March 22, 2022. Like the 2019 course, the 2022 course included 25 newly appointed Assistant Professors. In addition to the program of the 2019 course, the 2022 course included three case studies (all related to common real-world problems in supervisor–PhD candidate relationships), which allowed additional and fruitful discussion with the attendees on concrete examples from university practice. All of the participants who successfully completed one of these courses received certificates and fulfilled evaluation forms that comprised 13 questions about the quality of the course content, lecturers, time, duration, and organization of the course (22). The course organized in 2022 was rated as excellent by 76% of attendees (vs. 56% for the 2019 course; p=0.209), and 80% of the participants reported that they had received high-quality information regarding the topic (vs. 52% for the 2019 course; p=0.037). It should be noted that 88% of participants who attended the course in 2019, and 76% of attendees in 2022, admitted that they had not attended any course for pedagogic development before. Twelve percent of participants after the 2019 course considered that it would have been useful if more psychological topics had been included, especially in the field of the supervisor–candidate relationship; although such topics were additionally developed for the 2022 course, 14% of the 2022 course attendees still felt that these topics could be further expanded. Moreover, about a third of future supervisors suggested that additional education about supervisor skills might be very useful, especially in the form of thematic online courses (22). These findings implicate a need for better and continuous education of university teachers in terms of supervision skills and providing guidance to PhD candidates.

CONCLUSIONS

While supervision is doubtlessly a rewarding duty, it is also associated with a number of challenges. Considering that PhD outcomes are largely dependent on the supervisor and the successful supervisor–PhD candidate relationship, supporting supervision through formal training and education may be an important step in improving PhD experience and outcomes for both supervisors and the PhD candidates.

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Conflict of interest

None to declare.

Author Contributions

PM and TP conceived and wrote the paper, revised it for important intellectual content, and approved its final submission.

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EDUKACIJA MENTORA I KVALITET DOKTORSKIH STUDIJA: TRENUTNO STANJE I BUDUĆI IZAZOVI

Petar Milovanović[1], Tatjana Pekmezović[1]

Sažetak

Mentorstvo je specifičan odnos, gde iskusniji, stariji istraživač daje smernice, podršku i savete mlađem kolegi/nici kako bi mu/joj pomogao da uspešno savlada sve prepreke na putu ka nezavisnosti. Iako je mentorstvo u osnovi vrlo lepa dužnost, ono je povezano i sa mnogobrojnim izazovima. Mentorstvo podrazumeva brojne odgovornosti, što od mentora zahteva određeni skup veština. Iako se mnoge od ovih veština uče u direktnoj interakciji sa kandidatima, korisno je mentorima ponuditi i formalnu, struktuiranu obuku, naročito na početku njihove mentorske karijere, kako bi se izbegle česte greške na relaciji mentor–kandidat. Samim tim, u uverenju da bi takav pristup smanjio rizik od lošeg mentorstva, raste podrška ideji da mentorstvo ne treba zasnivati samo na ličnom iskustvu i intuiciji već, pre svega, na profesionalnoj obuci. Mnogi univerziteti danas nude formalno obrazovanje mentora. Praksa organizovane edukacije mentora na Medicinskom fakultetu Univerziteta u Beogradu je počela 2019. godine sa ciljem da se budući mentori pripreme za uspostavljanje produktivnih i odgovornih odnosa sa kandidatima. Nakon pauze zbog pandemije COVID-19, 2022. godine je organizovan novi kurs za unapređenje mentorskih veština. Anketa polaznika ova dva organizovana kursa je podržala potrebu za boljim obrazovanjem univerzitetskih nastavnika u pogledu mentorskih veština i vođenja studenata doktorskih studija. Zaista, s obzirom na to da rezultati doktorskih studija u velikoj meri zavise od mentora i uspešnog odnosa mentora i kandidata, podrška mentorstvu kroz formalnu obuku i edukaciju može biti važan korak u poboljšanju ishoda doktorskih studija kako za kandidate tako i za same mentore.

Ključne reči: mentorstvo, mentorske veštine, izazovi, doktorske studije, edukacija.

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ORIGINAL ARTICLE

Skeletal metastases and pathological fractures of long bones

Stanislav Rajković[1, 2], Lazar Mičeta[1, 2], Ljubica Simić[1, 3], Goran Đuričić[1, 4], Zoran Baščarević[1, 2], Nenad Lujić[2], Jelena Sopta[1, 3]

[1]University of Belgrade, Medical Faculty, Belgrade, Serbia
[2]Institute for Orthopedics "Banjica," Belgrade, Serbia
[3]Institute for Pathology, Belgrade, Serbia
[4]University Children's Hospital, Belgrade, Serbia

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Correspondence to:
Stanislav Rajkovic
Institute for Orthopaedis "Banjica," Mihaila Avramovica 28, 11040 Belgrade, Serbia
tel. +381 64 120 95 64
email: stanbgd@hotmail.com

Summary

Introduction. The most common cause of pathological fractures are skeletal metastases. Ten percent of patients with diagnosed skeletal metastases will sustain a pathological fracture. Skeletal metastases can be treated by non-surgical methods, including analgesics, bisphosphonates, and radiotherapy, with the primary goal of relieving pain and slowing down tumor growth. Surgical treatment is indicated for impending or existing fractures. It includes stabilization with internal fixation using various nails, plates, and screws with or without osteoplasty, and endoprosthetic joint replacement, especially in lesions around major joints – hip, knee, and shoulder.

Material and Methods. The study included patients operatively treated at the Institute of orthopedics "Banjica" and pathohistologically analyzed at the Institute of pathology in Belgrade during the period from February 2021 to January 2022. Inclusion criteria were an existing or impending pathological fracture of long bones, operative treatment with tissue sampling, and the consequent pathohistological diagnosis of metastatic carcinoma. Patients with biopsy-proven processes other than metastatic carcinomas were excluded from the study. The total number of patients included in the study was 69.

Results. The mean age of patients at the pathological fracture occurrence was 67.7 (ranging from 42 to 88). Malignant diseases diagnosed were: breast cancer 36.1%, lung cancer 24.5%, kidney cancer 14.5%, prostate cancer 13.1%, colorectal cancer 2.9%, other cancer (8.9%). The radiological presentation was in the form of lysis in 75.4% and in blastic form in 24.6%. Operative treatment included arthroplasty in 53.6% of patients and stabilization with nail or plate in 46.4%.

Conclusion. Pathological fractures represent the final outcome of tumor activity in a bone and cause significant suffering in patients expressed through severe pain and often immobility, which accelerates all the pathological processes and leads to death. Joint methods of contemporary chemotherapy, radiotherapy, and surgery enabled a significant life quality improvement and extension in these patients.

Keywords. skeletal metastases, pathological fracture, surgical therapyn

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INTRODUCTION

Pathological fracture is a fracture of bone previously affected by a pathological process. These processes can be of metabolic, hormone, developmental or neoplastic origin. The most common cause are skeletal metastases (SM) of various carcinomas – lung, breast, prostate, kidney, and thyroid gland carcinoma have the highest incidence of bone metastases, although skeletal metastases are found in every other carcinoma. (1) During the course of the disease, 60–75% of carcinoma patients will get SM. (2, 3) Ten percent of patients with SM will sustain a pathological fracture. (3) These fractures have a significant impact on morbidity and mortality. Previous studies suggest a one-year survival rate of 40%. (4, 5) These reasons make pathological fractures an important medical and social issue, and studies are directed towards researching risk factors for their occurrence and methods of prevention and treatment. (6-8)

Pain is the leading symptom of SM, followed by movement difficulty and swelling. Spinal cord compression can cause neurological dysfunction, and bone destruction can lead to hypercalcemia and blood aplasia. (6) Pathological fracture is the outcome of a metastasis presence in a bone. It may occur after several months of complaints or a very short period, sometimes even without any previous problems. (9) Various methods are used in the diagnostic process – X-ray, skeletal scintigraphy, PET scan, MSCT, and MRI. (10, 11) Scintigraphy with 99mTc has special significance as a highly sensitive method indicating possible SM before their clinical occurrence. X-ray shows a lesion in its' later stage but is essential for presenting the exact location, the type of bone reaction (lytic or blastic), the degree of bone destruction, and an existing or impending pathological fracture. (10)

SM are treated by non-surgical and surgical methods. Non-surgical treatment includes analgesics, bisphosphonates, and radiotherapy. For pain control, non-steroid anti-inflammatory drugs are used, but most commonly, opioid analgesics are needed. Bisphosphonates are used to decrease bone resorption. Radiotherapy is performed in a single dose 8Gy regimen or a multiple fractionated treatment 16-30Gy. The main goal of this therapy is pain relief, but also slowing down tumor growth and, with this, a decrease in pathological fracture incidence, nerve decompression, and aplasia prevention. (7, 12, 13)

Surgical treatment is indicated in existing or impending fractures and includes internal fixation using various nails, plates, and screws with or without osteoplasty, usually with bone cement. Next to fixation is an endoprosthetic joint replacement, especially in lesions around the hip joint – hemiarthroplasty (HA), total arthroplasty (TA), and megaprosthesis (MP). (14-16)

The aim of this paper is to present a series of patients with pathological fractures of long bones of extremities that occurred on the basis of SM.

MATERIAL AND METHODS

The study included patients operatively treated at the Institute of orthopedics "Banjica" and pathohistologically analyzed at the Institute of pathology in Belgrade for one year (February 2021 – January 2022). Inclusion criteria were as follows: an existing or impending pathological fracture of long bones of extremities according to Mirels classification (17), an operative treatment with biopsy, and pathohistologically proven metastatic carcinoma tissue at the fracture site. Patients excluded from the study were those with biopsy-proven processes other than metastatic carcinomas (lymphoma, myeloma, primary tumor, solitary bone cysts, brown tumor). The total number of patients included in the study was 69.

This retrospective, observational study presented clinical, radiological, and pathohistological features: age, previous knowledge of the malignant disease, localization, radiographic presentation (lytic/blastic), and pathohistological diagnosis. A series of various operative methods are also presented.

Statistical analyses were performed using SPSS v.28.0 software (SPSS Inc., Chicago, IL, USA). All data were categorical. Descriptive data were expressed as a percentage of a group for discrete measures.

The study was approved by the Ethical committee of the Faculty of Medicine, University of Belgrade (1322V-3) and the research was carried out in compliance with the Declaration of Helsinki.

RESULTS

The mean age of patients at the pathological fracture occurrence was 67.7, with the youngest patient being 42 years old and the oldest 88 years old. Distribution was: <50 y. 5 pts, 51-60 y. 6 pts, 61-70 y. 28 pts, 71-80 y. 18 pts, and >81 y. 6 pts. Male were 34 (49.3%) and female 35 (50.7%).

Twenty-four (34.8%) patients did not know they had a malignant disease, and skeletal-related events (pain and pathological fracture, both simultaneously or separately) were the first manifestation. Other 45 (65.2%) knew they had a tumor, and pathohistological analysis of tumor tissue from the bone confirmed SM. Malignant diseases diagnosed were: breast cancer in 25 pts. (36.1%), lung cancer in 17 pts. (24.5%), kidney cancer in 10 pts. (14.5%), prostate cancer in 9 pts. (13.1%), colorectal cancer in 2 pts. (2.9%), esophagus cancer in 1 pt. (1.5%), stomach cancer in 1 pt, laryngeal cancer in 1 pt, urinary bladder cancer in 1 pt, squamous cell skin cancer in 1 pt, and skin melanoma in 1 pt.

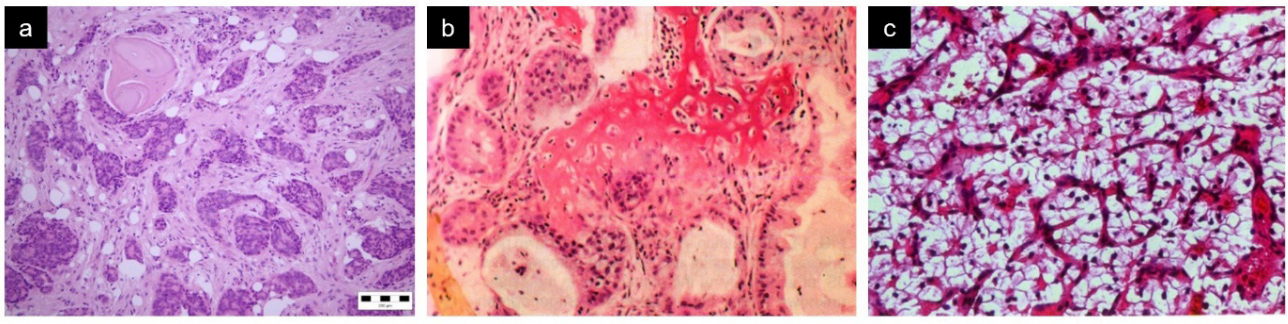

Figure 1. Microphotographs showing a variety of metastatic cancers in bone: a) Clasters of atypical cells with basophilic cytoplasma and nuclear hyperchromasia. Cancellous bone spherule also present - breast cancer SM (HE staining, 200x); b) Adenoid structures in bone tissue. Hypercellular bone with signs of remodeling – lung cancer SM (HE staining, 200x); c) Large cells with light cytoplasma and small excentric nuclei. Characteristic fields of haemorrhage in bone - renal cell carcinoma SM (HE stain, 200x)

The radiological presentation was in the form of lysis in 52 (75.4%) cases and in mixed blastic-lytic form in 17 (24.6%). Blastic-lytic lesions were present in some cases of breast cancer SM, and pure blastic forms were present in all the cases of prostate cancer. All other cancers' SM were lytic.

Operative treatment included arthroplasty in 37 (53.6%) patients and stabilization with nail or plate in 32 (46.4%) patients. Hip hemiarthroplasty and total arthroplasty were used in cases of a femoral neck fracture, and resection megaprosthesis was used in trochanteric region fractures, as in cases of neck fracture where a significant part of the trochanteric region was affected.

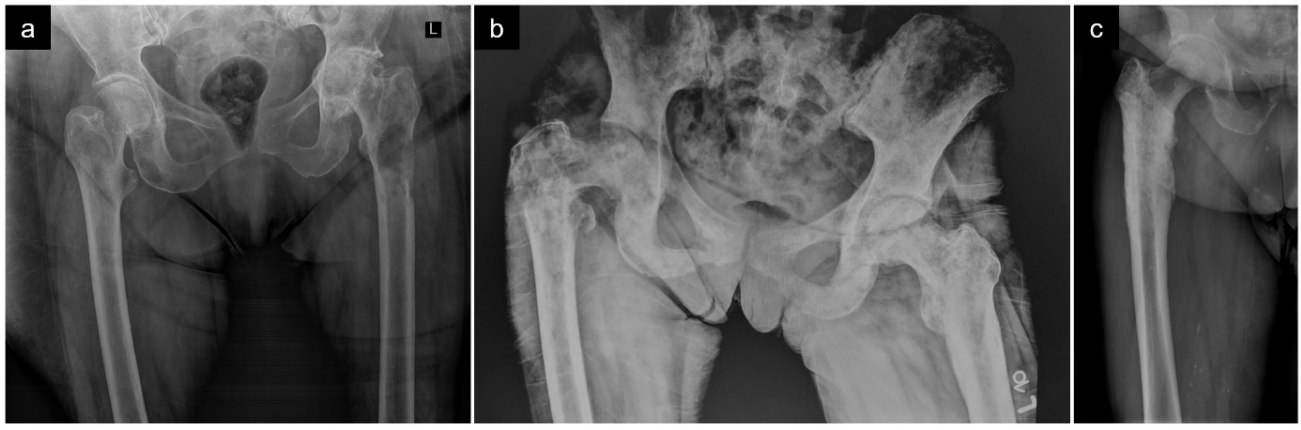

Figure 2. X-ray presentation of bone metastases: a) Lytic lesion in proximal femur – lung cancer SM; b) Mixed lesion with pathological fracture of trochanteric region – breast cancer SM; c) Blastic lesion involving trochanteric region and proximal diaphysis – prostate cancer SM

Table 1. Distribution of bone metastases and type of operative treatment

Bones				Operation			
				RA	IMS	P&S	
Humerus	12 (17.4%)	Proximal	2	2	/	/	
		Diaphysis	10	/	9	1	
					P&S		
Radius	1 (1.4%)	Diaphysis	1		1		
				HA	TA	RA	IMS
Femur	54 (78.2%)	Neck	13	7	4	2	/
		Trochanteric	22	7	7	22	7
		Diaphysis	19	7	7	7	19
					P&S		
Tibia	2 (2.8%)	Proximal	1		1		
		Distal	1		1		

RA – Resection Arthroplasty, IMS – Intramedullary Nailing Stabilisa tion, HA – Hip Hemiarthroplasty, TA – Hip Total Arthroplasty, P&S – Plates and Screws Stabilisation

DISCUSSION

The mean age of the patients in this study was 67.7 years. Previous studies showed different ages, most similar to our results (16, 18) and, in rare cases, younger. The mean age of 53.1 years in patients with triple-negative metastatic breast cancer was reported. (19) Most patients in this study were above 50, a significant number even above 70, which is related to bone atrophy (osteopenia/osteoporosis) that can be an important factor in pathological fracture development. (20)

The malignant diseases diagnosed in this study align with earlier findings. (1, 6) Most patients (36.5%) had breast cancer, followed by lung cancer (24.5%) and this incidence matches the familiar data that breast cancer is the most frequent in female population and lung cancer in male population. (21) Colorectal cancer is also widespread in the general population, but it is known that it more often gives visceral metastases than SM, which might be the reason for the low incidence of pathological fractures when it comes to this tumor. (22)

The femur stands out as the most common localization of pathological fractures, with 78.2% of all long bone fractures. As a lower extremity bone, it bears the weight of the entire body, which is especially true of the neck and the trochanteric region of the femur that are exposed to forces unevenly deployed through the bone cortices, making them particularly vulnerable; so even a small loss of the bone tissue in the critical zone can result in a fracture. (23, 34)

Radiological presentation of SM is usually in the form of lysis, although breast cancer SM are present in a blastic form in 20-40% of cases, and prostate cancer SM are always blastic. (9, 25). An earlier standpoint was that lysis represented a higher risk for fracture (17), but recent studies showed that blastic SM also carried a high risk, especially in the proximal femur. (23, 24) The results of this study confirm these findings.

Operative methods used for patient treatment in this series are in line with contemporary standards. (26, 27) The question of osteosynthesis or arthroplasty is still open. (28) The method of choice depends on SM localization, the existing or impending fracture, the degree of bone tissue loss, the patient's general condition, and expected survival. (27) Diaphysis fractures are usually treated by stabilization using an intramedullary nail. Depending on the tissue loss, part of the bone affected by SM can be resected and the defect filled with bone cement. Proximal femur fractures (trochanteric and subtrochanteric region) can be treated by intramedullary stabilization in cases where bone destruction is not significant and femoral neck and head are preserved. (28, 29) In cases where meta-epiphysis is affected, particularly in femoral neck fractures, arthroplasty is indicated. Hemiarthroplasty, total arthroplasty or resection, and megaprosthesis implantation are used in these cases. Besides localization and bone loss, general condition and expected survival of the patient are the factors influencing the choice of the operative method – as a less demanding procedure, intramedullary stabilization is used in cases with more significant bone destruction but where the general condition does not allow the extensive surgical procedure. (27, 29, 30)

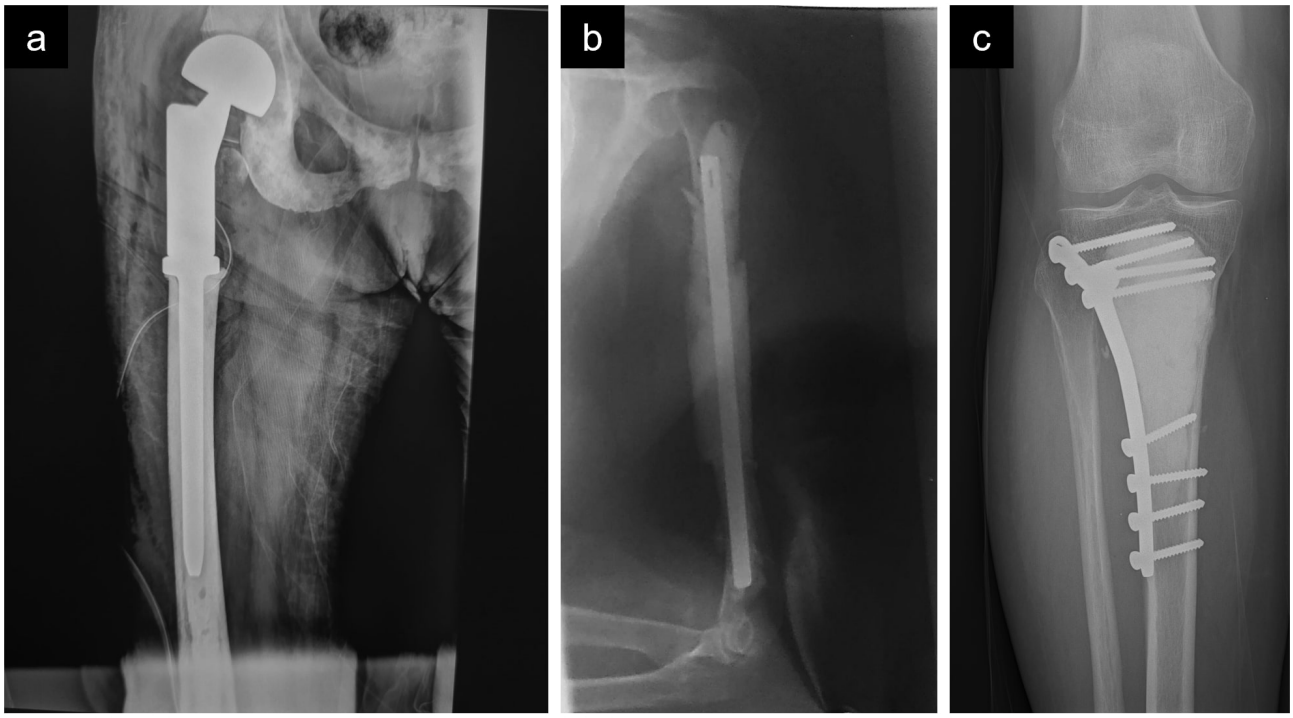

Figure 3. Postoperative X-ray showing different methods of surgical treatment: a) Resection of proximal femur with megaprosthesis arthroplasty – breast cancer SM; b) Intramedullary stabilization with cementing of humerus – lung cancer SM; c) Plate and screws stabilization with cementing of proximal tibia – melanoma SM

In our series, femoral neck fracture was treated by cemented hemiarthroplasty. Cemented total arthroplasty was used in cases of femoral neck fracture with the concomitant degenerative condition or acetabulum damage of any origin. Also, patients with a solitary metastasis in the femoral head or neck in good general condition and with long-expected survival were treated by cemented total arthroplasty. Resection and megaprosthesis implantation were performed in cases where the pathological process was located in meta-epiphysis: head and surgical neck of the humerus and the trochanteric region of the femur. This method was used in cases of femoral neck fracture where pathological processes significantly affected the trochanteric region. Intramedullary stabilization was used in all cases of humerus and femur diaphysis fractures, as well as in some cases of subtrochanteric femoral fracture in patients with the poor general condition and short expected survival. Stabilization using plate and screws with bone defect cementing was used in radius and proximal tibia fractures.

CONCLUSION

Pathological fractures represent the final outcome of tumor activity in a bone. Their occurrence was also the final stage of the disease since patients after these fractures suffered severe pain and were often immobile, which accelerated all the pathological processes and led to death. In the last few decades, joint methods of contemporary chemotherapy, radiotherapy, and surgery enabled significant life quality improvement and extension in these patients.

Acknowledgements

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Conflict of interest

None to declare.

Contributors

SR was responsible for designing and writing the protocol, conducting the search, collecting surgical data, reviewing other studies in this field, extracting and analyzing data, interpreting results, and writing the report. LM helped in collecting surgical data, reviewing studies, conducting statistical analysis, interpreting the results, and writing the report. LS was responsible for pathologic diagnostics, collecting pathological data, analyzing and interpreting results, and writing the report. GD took part in collecting and analyzing radiological data and analyzing and interpreting results. ZB supervised the collection of surgical data and helped interpret results. JS took part in designing and writing the protocol, supervising pathological data, reviewing previous studies, and analyzing and interpreting results.

Ethical approval

Study was performed with the appropriate participants' informed consent in compliance with the Helsinki Declaration. The Medical Faculty University of Belgrade Research Ethics Committee issued an approval (1322V-3).

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SKELETNE METASTAZE I PATOLOŠKI PRELOMI DUGIH KOSTIJU

Stanislav Rajković[1, 2], Lazar Mičeta[1, 2], Ljubica Simić[1, 3], Goran Đuričić[1, 4], Zoran Baščarević[1, 2], Nenad Lujić[2], Jelena Sopta[1, 3]

Sažetak

Uvod. Najčešći uzrok patoloških preloma kostiju su metastaze. Deset odsto pacijenata sa dijagnostikovanim metastazama na skeletu će zadobiti patološki prelom. Skeletne metastaze se mogu lečiti nehirurškim metodama, uključujući analgetike, bisfosfonate i radioterapiju, sa primarnim ciljem ublažavanja bolova i usporavanja rasta tumora. Hirurško lečenje je indikovano za postojeće ili preteće prelome. Obuhvata stabilizaciju sa unutrašnjom fiksacijom različitim klinovima, pločama i šrafovima sa ili bez osteoplastike i endoprotetsku zamenu zgloba, posebno kod lezija oko velikih zglobova – kuka, kolena i ramena.

Materijal i metode. Studijom su obuhvaćeni pacijenti operativno lečeni u Institutu za ortopediju „Banjica" i patohistološki analizirani u Institutu za patologiju u Beogradu u tokom jedne godine, u periodu od februara 2021. do januara 2022. Kriterijumi za uključivanje su bili postojeći ili preteći patološki prelom dugih kostiju, operativno lečenje uz uzimnje uzorka i posledičnu patohistološku dijagnozu metastaze nekog karcinoma. Iz studije su isključeni pacijenti sa patohistološki dokazanim procesima koji nisu metastatski karcinomi. Ukupan broj pacijenata uključenih u studiju bio je 69.

Rezultati. Prosečna starost pacijenata u vreme nastanka patološkog preloma bila je 67,7 godina (u rasponu od 42 do 88 godina). Dijagnostikovane maligne bolesti su: karcinom dojke 36,1%, pluća 24,5%, bubrega 14,5%, prostate 13,1%, kolorektalni 2,9%, ostali (8,9%). Radiološki prikaz je bio u obliku osteolize u 75,4% slučajeva i blastičnom obliku u 24,6%. Operativno lečenje uključivalo je artroplastiku kod 53,6% pacijenata i stabilizaciju klinom ili pločom kod 46,4%.

Zaključak. Patološki prelomi predstavljaju krajnji ishod tumorske aktivnosti u kosti i izazivaju značajnu patnju kod pacijenata izraženu jakim bolom i često nepokretnošću, što ubrzava sve patološke procese i dovodi do smrti. Zajedničke metode savremene hemoterapije, radioterapije i hirurgije omogućile su značajno poboljšanje i produženje kvaliteta života ovih pacijenata.

Ključne reči: skeletne metastaze, patološki prelom, hirurška terapija

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ORIGINAL ARTICLE

Treating refractory chronic spontaneous urticaria with omalizumab – real life case series

Rada Mišković[1,2]; Žikica Jovičić[1,2], Vesna Tomic Spirić[1,2], Maja Stojanović[1,2], Aleksandra Plavšić[1,2], Sanvila Rašković[1,2], Aleksandra Dašić[1], Aleksandra Perić Popadić[1,2]

[1] The Clinic of Allergy and Immunology, University Clinical Centre of Serbia, Belgrade, Serbia,
[2] Faculty of Medicine, University of Belgrade, Belgrade, Serbia

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Correspondence to:
Aleksandra Dasic
The Clinic of Allergy and Immunology, University Clinical Centre of Serbia
Koste Todorovica 2, 11000 Belgrade, Serbia
Phone: +381652174027
aleksandra.dasic777@gmail.com

Summary

Introduction: Patients with refractory chronic spontaneous urticaria (CSU) may pose a significant challenge to the treating physician. Although many studies have investigated the effects of omalizumab in refractory CSU, many issues remain unanswered.

Aim: To describe our experience in treating refractory CSU with omalizumab in a real-life setting.

Material and methods: We present a series of eight patients with refractory CSU treated with omalizumab during a 2-year period.

Results: The average duration of CSU was 49.9 months (3-180). A high average 7-day Urticaria Activity Score (UAS7) of 31.3 (12-42) and a low average Urticaria Control Test (UCT) score of 4.1 (0-8) had been recorded before omalizumab therapy. Prior to omalizumab, all patients required fourfold dose of H1-anihistamines, montelukast and corticosteroids to achieve at least a partial disease control. Antimalarial was given to two patients and dapsone to three, with no response. Adverse effects of corticosteroids were noted in most patients. Patients received 150 mg or 300mg of omalizumab subcutaneously every 4 weeks, for at least 3 months. All patients responded well to omalizumab and discontinued corticosteroid therapy. There were no significant side effects during omalizumab treatment.

Conclusion: Omalizumab is an effective corticosteroid sparing treatment, enabling disease control in patients with refractory CSU, even in lower doses (150 mg) and when given for a short period of time. This is especially important when the availability of the drug is determined by economic issues.

Key words: chronic spontaneous urticaria, refractory, omalizumab

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INTRODUCTION

Urticaria is a mast cell-driven disease with heterogenous and insufficiently known activating signals (1). Chronic spontaneous urticaria (CSU) is characterized by recurrent occurrence of wheals, angioedema, or both, for more than six weeks, without an obvious external trigger. It is a highly disabling disease with a major influence on the quality of life and a significant cost for health care system and patients (2). The global prevalence of CSU varies between 0.5 and 1% depending on the population studied (3-4). In the majority of cases it lasts between 2 and 5 years. However, in approximately 20% of patients it can persist for more than 5 years (4). Intensive pruritus, frequent recurrence of symptoms and unpredictive clinical course lead to sleep deprivation and common psychiatric comorbidity (5).

The EAACI/GA²LEN/EuroGiuDerm/APAAACI guideline recommends stepwise therapeutic approach, starting with non-sedating H1-antihistamines once a day and increasing up to the fourfold dose in non-responders. In patients who remain uncontrolled, omalizumab is recommended as a second-line therapy (1). Refractory forms of CSU can be especially challenging for the treating physician and for the patient, causing frustration and uncertainty. Patients with severe active disease frequently receive corticosteroids (CS), developing many CS adverse effects over time. Cyclosporin, another guideline recommended treatment, also carries the risk of serious side effects, especially if taken over a long period of time. However, such patients have been frequently excluded from clinical trials that require strict inclusion criteria, permitting in most cases just the inclusion of patients with severe disease activity treated only with antihistamines.

Omalizumab is the first licensed biological therapy available for CSU. It is a humanized anti-IgE monoclonal antibody that recognizes C3 domain of Fc region of IgE molecule, forming omalizumab-IgE complexes and reducing the level of free IgE. It is hypothesized that this process leads to the down-regulation of high affinity FcƐRI receptor on mast cells and circulating basophils, decreasing mediator release, and consequently reducing the symptoms of CSU. Additional mechanisms of action, independent of the level of IgE have been proposed as well (6). Several studies evaluated the effectiveness of omalizumab in refractory CSU, but many issues remain unresolved. The aim of this study was to describe our case series of patients with refractory form of CSU treated with omalizumab and to discuss some practical issues regarding its use in a real-life settings.

MATERIAL AND METHODS

Patients

We retrospectively reviewed medical records of patients with refractory CSU treated with omalizumab at the Clinic of Allergy and Immunology between January 2018 and December 2019. Main demographical, clinical and laboratory data of the patients were recorded, as well as the clinical evolution of CSU. The Institutional Review Board approved the study (approval number 570/4).

Disease and patient assessment

Disease activity was assessed using the standard 7-day Urticaria Activity Score (UAS7) and the medication scoring system. The UAS7 quantifies the number of wheals (from 0 - none to 3 – severe) and pruritus intensity (from 0 – none to 3 – severe) on daily bases for 7 consecutive days. The total score ranges from 0 to 42, allowing to classify disease activity as a complete response (0), well-controlled (1-6), mild (7-15), moderate (16-27), or severe (28-42). The UAS7 was recorded by each patient during the period of 7 days prior to each visit (7).

The quantitative medication score was calculated before the application of omalizumab therapy and at every subsequent visit. This score is a sum of weighted scores for antihistamines (2 points: regular dose, 8 points: four-fold dose), oral glucocorticoids (5 points: <11mg, 10 points: 11-25mg, 15 points: >25mg), cyclosporine 3.0mg/kg (8 points), hydroxychloroquine (6 points) and montelukast (2 points) (8).

Disease control was assessed using the standard Urticaria Control Test (UCT). This is patient-based, 4-item questionnaire with a 4-week recall period. It assesses the control of physical signs and symptoms of urticaria, impairment of the quality of life, the efficacy of the treatment and overall disease control. The questions are rated from 0 to 4, with the total score ranging from 0 (no control) to 16 (complete control). The patients having score of ≥12 are considered to have well-controlled urticaria (9).

In our study, the patient was considered to have refractory CSU if the disease was uncontrolled despite using non-sedating H1-antihistamines in fourfold dose, leukotriene receptor antagonists (LTRA) and oral corticosteroids or if the patient could not discontinue corticosteroids without losing control over disease.

Total serum IgE was measured by immunonephelometric assay. Measurements were done before (bIgE) and 4 weeks (w4IgE) after the first omalizumab injection. We calculated w4IgE/bIgE ratio and applied the '2x4' rule proposed by Ertas et al. as a predictor of the response to omalizumab. According to this rule, when bIgE fails to double within 4 weeks of treatment, non-response is to be expected (10).

Treatment protocol and the evaluation of treatment response

Patients received 150 mg or 300mg of omalizumab subcutaneously every 4 weeks, for at least 3 months. The response to the treatment and safety were assessed before each application. A 'complete response' was defined as a reduction of 90% or more in the UAS7, 'significant improvement' as a reduction in UAS7 of 90%-30%, and 'no significant improvement' as less than 30% reduction in the UAS7 (11).

We used descriptive statistics to analyze the data considering that due to the small number of patients, it was not possible to apply analytical statistical methods.

RESULTS

Eight patients with refractory CSU were treated with omalizumab during the study period: 3 males and 5 females, mean age 51.12 (23-81) years. Mean disease duration was 49.8 (3-180) months and mean UAS7 was 31.3 (12-42), pointing to high baseline disease activity. All patients had a low UCT score (mean UCT 4.6) indicating poor disease control. Mean serum bIgE was 74.8 (5.8 -273) IU/ml. Patients' characteristics and treatment response are shown in **Table 1**.

Before omalizumab treatment, all patients required fourfold dose of H1-anihistamines and corticosteroids daily (dose range 10 - 40 mg) for symptom control. Three patients were given dapsone and two patients were given antimalarial with no response. One patient received immunomodulatory doses of intravenous immunoglobulins and another high dose of CS therapy (pulse doses), both with only short-term effects. Adverse effects of CS were noted in most patients (cushingoid features, fluid retention, sleep disturbance, anxiety, weight gain, hypertension, hyperglycemia, gastritis, acne).

Mean treatment duration was 5.5 (3-10) months. One patient (No.1) had complete resolution of urticaria (UAS7 0) several hours after his first omalizumab injection, which was maintained thereafter, allowing fast CS tapering and withdrawal. The remaining patients were also fast responders and their UAS7 decreased more than 30% on their second visit. Overall, after 3 doses of omalizumab, 6 patients achieved complete response (UAS7 of 0) and 2 experienced a significant improvement. Medication scores decreased in all patients.

All patients were able to discontinue CS therapy after starting omalizumab, with the time needed for CS withdrawal ranging from 1 to 12 weeks.

The patients were followed-up for at least 6 months after the termination of the treatment. One patient (No.3), with initially good response to omalizumab (UAS7 0), was switched to a lower dose (150mg) after 5 months, but experienced exacerbation of CSU (UAS7 18), although not as severe as at the starting point (baseline UAS7 39). He was not motivated to use cyclosporine, and he was given occasional CS burst for maintaining disease control. Another patient (No. 2) who achieved a significant reduction in UAS7 after 6 doses (300mg) of omalizumab, exacerbated one month after the termination of the treatment and was also introduced to cyclosporine therapy, but with no response. The patient further required prednisone daily (10mg/day). The patient number 5 achieved complete response, but experienced exacerbation three months after the completion of omalizumab treatment. As cyclosporine was not effective, she was given prednisone (15mg/day) to maintain disease control. In these 3 patients reintroduction of omalizumab was not possible due to financial reasons. The remaining 5 patients achieved complete response or a significant improvement and their disease was further maintained with antihistamine therapy only.

Total serum IgE was measured at baseline and 4 weeks after the start of the treatment. An average bIgE was 74.8 IU/ml (5.8-273), increasing to 230.2 IU/ml (10.1-680) 4 weeks after first omalizumab injection. Mean w4IgE/bIgE ratio was 4.2 (1.7-8.3) predicting a good treatment response. Only 2 patients had w4IgE/bIgE ratio lower than 2, but both responded to the treatment.

Overall, the treatment was well tolerated. One patient developed herpes zoster after the third omalizumab injection and was not motivated to continue omalizumab. After thorough literature search, we could not find any case of herpes zoster associated with omalizumab therapy. Furthermore, this patient had other risk factors for herpes zoster (advanced age, diabetes mellitus).

DISCUSSION

Our study describes the efficacy and the safety profile of omalizumab in a case series of patients with refractory CSU in a real-life settings. We included patients with severe disease activity requiring several medications for CSU, including CS daily or every other day to control the disease. All patients had good and fast response to omalizumab. Complete remission was achieved in 5 and a significant improvement in 3 patients at the end of the treatment. This was followed by a significant reduction in medication scores in all cases. Most importantly, all patients discontinued CS therapy.

Several real-life studies evaluated the efficacy of omalizumab in refractory CSU. However, only some of them included patients with a severe form of the disease who used several CSU medications, including CS frequently or daily. In a prospective open-label study, Sussman et al. showed that 150 mg of omalizumab was effective in difficult-to-treat patients with severe chronic urticaria refractory to the recommended treatments who frequently use prednisone (8). Similarly, Kulthanan et al. per-

Table 1. Main demographical, clinical and laboratory characteristics of patients and overall response to the treatment with omalizumab

Patient No/ sex/ age	Duration of CS (months)	AE	Anti-thyroid Abs	Asthma	Previous treatment	bIgE IU/ml	bUAS7	bUCT	Omb dose (mg)	Treatment duration (months)	w4IgE IU/ml	w4IgE/ bIgE	UAS7 end	UCT end	MS end	Time to CS withdrawal (weeks)	Time to serious relaps (weeks)
1/M/23	54	Yes	-	No	4xH1; LTRA; Ket; CS; Dap; AM; IVIG	21.1	42	0	5x150 5x300	10	98	4.6	0	16	2	1	*
2/F/53	12	Yes	-	Yes	4xH1; LTRA; CS	71	18	4	6x300	6	285	4.0	1	16	2	3	4
3/M/55	24	No	-	No	4xH1; LTRA; CS	177	39	2	5x300 2x150	7	680	3.8	19	10	18	2	3
4/F/48	48	No	NP	No	4xH1; LTRA; Ket; CS; MP pulse	6.8	40	7	6x150	6	23.4	3.4	0	15	10	4	*
5/F/45	180	Yes	NP	No	4xH1; LTRA; CS; Dap	273	15	8	3x150	3	477	1.8	0	14	2	12	12
6/F/47	72	Yes	-	No	4xH1; LTRA; CS	34.1	12	8	6x300	6	191	5.6	0	16	2	1	*
7/F/57	6	Yes	+	Yes	4xH1; LTRA; CS; Dap; AM	9.2	42	4	3x150	3	76.8	8.3	0	16	2	12	*
8/M/81	3	No	+	No	4xH1; LTRA; Ket; CS	5.8	42	4	3x150	3	10.1	1.7	6	12	2	3	*

AE – angioedema; Abs – antibodies; end – end of treatment; Dap- dapsone; Ket – ketotifen; MP- methylprednisolone; IVIG – intravenous immunoglobulin; AM – antimalarial; LTRA – leukotriene receptor antagonists; H1- H1 antihistamine; NP – not performed. CS –corticosteroids; b- baseline; Omb – omalizumab; MS – medication score; * - did not experience disease relapse requiring CS during follow up

formed retrospective analysis of omalizumab as an add-on therapy in uncontrolled CSU despite 4-fold dose of non-sedating antihistamines, LTRA, oral CS and cyclosporine, showing efficacy of initial dosage of 150 mg in most cases, with dosing up to 300 mg being effective in the remaining ones. Oral CS and cyclosporin were discontinued in all patients (12). A study from Portugal showed a good long-term efficacy of omalizumab in 6 patients with severe chronic urticaria, allowing discontinuation of CS in all patients. During the median treatment duration of 17.5 months, the main side effect of omalizumab was headache on the administration day (13).

There are currently no official guidelines or recommendations regarding the duration of omalizumab treatment, an optimal dose, or a dose interval in patients with CSU. Many authors suggest an individualized approach when using omalizumab in patients with refractory CSU. This approach considers different aspects of the disease and the patient and is frequently influenced by economic factors. Uysal et al. suggested starting the treatment with 150 mg dose every 2 weeks, prolonging the dose interval for 1 week when the patient achieves UAS7 < 2 up to the maximal dose interval of 8 weeks when the treatment should be paused and the patient further closely monitored for symptom recurrence. In patients with treatment failure, defined as UAS7 > 3 after 2 to 3 doses of 150 mg, they suggest increasing the dose to 300 mg (14). Kasperska-Zajac et al. suggested a treatment algorithm based on their own experience and literature review. They advise starting with 150 mg of omalizumab, and if the symptoms resolve completely, the subsequent dose should be administered on symptom recurrence. In patients with severe symptoms and poor response to CS, a 300 mg starting dose is advised and it can be reduced to 150 mg if remission is achieved. If symptoms recur after dose reduction, it should be increased again to 300 mg. When no remission has been achieved after 8 – 12 weeks of 300 mg dose, the omalizumab treatment should be discontinued (15). Some authors suggest repeating 300 mg dose after 2 weeks before treatment discontinuation in such cases (11). In our group of patients, both doses proved to be effective. Treatment response was visible soon after the first omalizumab dose in most patients. Three patients with good response experienced exacerbation during the follow-up. This is in concordance with other studies, suggesting that in some patients long-term treatment or retreatment with omalizumab is necessary (12, 16-17). It should be noted that dose and treatment duration in our study were significantly influenced by financial factors, and a prolonged or repeated treatment with omalizumab was not feasible in most patients.

The mechanism of action of omalizumab in CSU is not sufficiently elucidated, but it is assumed to be dependent on CSU endotype and reduction of circulating IgE. Binding of omalizumab to free IgE leads to down-regulation of FcεRI on mast-cells and basophils increasing the threshold for cell degranulation. After treatment discontinuation there is a gradual return of serum IgE to baseline values in some patients, which may be followed with CSU relapse. A recent study demonstrated that the clinical effect of omalizumab correlated with the reduction of $FcεRI^+$ cells and IgE^+ cells in the dermis of lesional and non-lesional skin, linking systemic effects of omalizumab to skin changes. Since the clinical response in some patients is much faster than observed histological changes, the authors speculate that an additional mechanism of action might be involved (18). Some of the proposed additional mechanisms include direct stabilization of effector cells, decreased B-cell activation and antibody production and reduction of coagulation activation (15). Although some of these mechanisms overlap with those of CS, they come with a significantly fewer adverse events.

Several biomarkers of CSU have been proposed to help identify disease endotypes and predict response to the therapy. Type I autoimmune CSU is related to the existence of autoreactive IgE antibodies to a wide range of self-antigens and high serum IgE. In patients with type IIb autoimmune CSU mast-cell degranulation is caused by IgG or IgM autoantibodies to the FcεRIα or IgE bound to it and there is a higher rate of low serum IgE, high C-reactive protein, eosinopenia and basopenia (1). Current evidence suggests high D-dimer and C-reactive protein level as predictors of poor response to antihistamines, while cyclosporine response is predicted by a positive basophil histamine release assay (19). There is robust evidence supporting low serum IgE as a predictor of poor response to omalizumab treatment (20). Ertas et al. found that patients with low bIgE level (< 43 IU/ml) have 33% risk of non-response within the first 12 weeks of treatment, as compared to only 5% risk in patients with IgE ≥ 43 IU/ml. However, w4IgE/bIgE ratio was a better predictor of response and patients having at least 2-fold increase of w4IgE responded to treatment (10). It is assumed that this increase in serum IgE is due to formation of omalizumab-IgE complexes, prolonging the half-life of IgE. Most of our patients had low bIgE level which significantly increased 4 weeks after omalizumab injection. We also calculated w4IgE/bIgE ratio and applied the '2x4' rule proposed by Ertas et al. Only two patients had w4IgE/bIgE ratio below 2, but they both responded to the treatment. A recent publication suggests differences in biology and function of IgE between different CSU endotypes. Modifications in glycosylation pattern of IgE molecule are noticed, possibly influencing 3-dimensional folding and lipophilicity of IgE. Whether these modifications are clinically significant and influence treatment response and disease relapse is what remains to be elucidated. If these modifications are clinically significant and weather they influence treatment response and disease relapse are the two things that remain to be elucidated (21).

This study showed that omalizumab is an effective treatment in patients with severe refractory CSU, en-

abling a significant reduction in disease activity parameters and discontinuation of CS therapy. It is limited by a small number of patients. However, the number of patients with this form of disease is relatively small in relation to the total number of patients with CSU. Our experience suggests that a lower dose (150 mg) and shorter treatment duration (3 months) are beneficial for patients. Considering many adverse effects of CS and cyclosporine, such a therapeutic approach seems to be rational from a clinical and economic point of view.

CONCLUSION

In conclusion, real-life experience with omalizumab confirms that it is a safe and effective therapeutic option in the majority of patients refractory to other available treatments. Some patients benefit from a lower dose and shorter treatment duration. We emphasize individualized approach that is based on patient's characteristics, disease manifestations and economic aspects.

Conflict of interest

The authors have no conflict of interest to declare.
We have no funding sources regarding this study to report.

Author contribution

Conception and design of the work: Rada Miskovic, Zikica Jovicic, Aleksandra Peric Popadic
Acquisition, analysis, or interpretation of data: Sanvila Raskovic, Maja Stojanovic, Aleksandra Plavsic, Aleksandra Dasic
Preparing the draft of the manuscript or interpretation of revised version of manuscript: Rada Miskovic, Vesna Tomic Spiric, Zikica Jovicic, Maja Stojanovic

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PRIMENA OMALIZUMABA U TERAPIJI REFRAKTORNE HRONIČNE SPONTANE URTIKARIJE - SERIJA SLUČAJEVA

Rada Mišković[1,2], Žikica Jovičić[1,2], Vesna Tomic Spirić[1,2], Maja Stojanović[1,2], Aleksandra Plavšić[1,2], Sanvila Rašković[1,2], Aleksandra Dašić[1], Aleksandra Perić Popadić[1,2]

Sažetak

Uvod: Pacijenti sa refraktarnim oblikom hronične spontane urtikarije (HSU) predstavljaju značajan izazov u kliničkoj praksi. Iako su brojne studije ispitivale terapijske efekte omalizumaba kod pacijenata sa refraktarnom HSU, mnoga pitanja su još uvek bez odgovora.

Cilj: Prikazati iskustvo primene omalizumaba kod pacijenata sa refraktarnim oblikom hronične spontane koprivnjače.

Materijal i metode: Prikazana je serija od osam slučajeva pacijenata sa refraktarnom HSU koji su lečeni omalizumabom tokom perioda od dve godine.

Rezultati: Prosečno trajanje HSU iznosilo je 49,9 meseci (3-180). Pre započinjanja terapije omalizumabom kod pacijenata su zabeleženi visoka prosečna vrednost sedmodnevnog testa aktivnosti koprivnjače (TAK7) koji je iznosio 31,3 (12-42) i nizak prosečan rezultat testa kontrole koprivnjače (TKK) - 4,1 (0-8). Kod svih pacijenata je pre uvođenja omalizumaba u terapiji bila potrebna primena četvorostruke doze antihistaminika, montelukasta i kortikosteroida za postizanje makar parcijalne kontrole bolesti. Terapija antimalarikom je pokušana kod dva pacijenta, a dapsonom kod tri, bez terapijskog efekta. Kod većine pacijenata zabeleženi su brojni neželjeni efekti kortikosteroidne terapije. Omalizumab je primenjivan u dozi od 150mg ili 300mg subkutano svake 4 nedelje tokom bar 3 meseca. Povoljan terapijski odgovor na omalizumab su imali svi pacijenti, uz obustavu primene kortikosteroida. Nisu zabeleženi značajniji neželjeni efekti terapije omalizumabom.

Zaključak: Omalizumab predstavlja efikasnu terapijsku opciju koja omogućava smanjenje upotrebe kortikosteroida i postizanje kontrole bolesti kod pacijenata sa refraktarnim oblikom HSU, čak i kad se primeni u nižim dozama (150mg) i tokom kraćeg vremenskog perioda. Ovo je od posebnog značaja kad je dostupnost leka određena finansijskim aspektom.

Ključne reči: hronična spontana urtikarija, refraktarnost, omalizumab

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ORIGINAL ARTICLE

Exploring e-health literacy among students of sports vs. medical students

Tatjana Gazibara[1], Jelena Cakić[1], Milica Cakić[1], Redžeb Zejnelagić[2], Aleksandra Popović[3], Anita Grgurević[1]

[1] Institute of Epidemiology, Visegradska 26A, Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia.
[2] Community Health Center "Niksic", Radoja Dakica bb, 81400 Niksic, Montenegro.
[3] Faculty of Sport and Physical Education, University of Belgrade, Blagoja Parovica 156, Belgrade 11000, Serbia.

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Correspondence to:
Assist. Prof. Tatjana Gazibara
Institute of Epidemiology
Faculty of Medicine
University of Belgrade
Visegradska 26A
Belgrade 11000, Serbia
Email: tatjanagazibara@yahoo.com, tatjana.gazibara@med.bg.ac.rs
Tel/Fax:+381113607062

Summary

Introduction/Aim: Data about electronic health (eHealth) literacy and potential differences in eHealth literacy between university students are lacking. The aim of this study was to evaluate eHealth literacy in students of sports and medicine and to assess the factors associated with better eHealth literacy.

Material and Methods: This cross-sectional study was carried out from April to October 2017 among final year students of the Faculty of Sports and Physical Education and the Faculty of Medicine, University of Belgrade, Serbia. A total of 89 sports students and 301 medical students were included. The eHealth Literacy Scale (eHEALS) was used to evaluate eHealth literacy.

Results: Compared with sports students, medical students had higher median eHEALS score (27 vs. 30, respectively, p=0.008). Medical students were twice as confident as sports students in their efforts to locate helpful online health resources and use online health information. A significant hierarchical linear regression model was not obtained in the sample of sports students regarding predictors of better eHealth literacy. In the sample of medical students, the following was associated with better self-perceived eHealth literacy: being female, residing outside of the capital before becoming a student, younger age at the time of the first Internet use, the use of health-related websites and smartphone apps as well as lower influence of online health-related information on decision making regarding health.

Conclusion: Medical students were more confident in perceiving their eHealth literacy skills compared to sports students. The factors associated with better eHealth literacy may depend on the fields of study.

Keywords: eHealth, literacy, medicine, sports, students.

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INTRODUCTION

Over the past years, the online health (eHealth) literacy has become increasingly relevant to successfully navigating health-related content on the Internet (1). Since various online platforms are continuously being developed, health-related information is readily available to the users with Internet access (2). As such, online health information may have a strong influence on their consumers. However, not all online health-related content is reliable. In fact, to navigate through online content, consumers need to have optimal eHealth literacy skills. The eHealth literacy entails uncovering, comprehension and evaluation of online health in order to make knowledgeable decisions regarding health (3). This skill is particularly important for people who are studying or working in the health care realm.

A previous study suggested that factors such as being a medical major in college and being more concerned about health were strongly associated with being eHealth literate (4), which is not surprising, because a greater knowledge level enables people to make conscious health-related decisions. Similar findings were reported by Hsu et al. in Taiwan (5), where better individual health status and greater concern for health were major predictors of better eHealth literacy and positive health-related behavior. Health issues such as balanced nutrition, exercise, safe sexual practice and immunization have been reported as the core health topics of interest in the college population (6).

Although the levels of eHealth literacy among undergraduate students differ across cultures (7, 8) and fields of study (4), there is a gap in understanding potential differences in eHealth literacy among students who study health science using diverse perspectives, such as medicine and sports science. It is expected that both medical students and students of sports have the highest level of eHealth literacy in the University student population, because they will be the future leaders in health promotion. We hypothesized that students of sports and medicine do not differ in terms of eHealth literacy. The aim of this study was to evaluate eHealth literacy in students of sports and medical students and to assess the factors associated with better eHealth literacy.

METHODS

A cross-sectional study was carried out at the Faculty of Sports and Physical Education and the Faculty of Medicine, University of Belgrade. The study was conducted from April to October 2017. Students from the final year of their undergraduate studies (i.e. the 4th year at the Faculty of Sports and the 6th year at the Faculty of Medicine) were recruited.

The selection of a convenience sample of students from both faculties was performed in the following way: at the Faculty of Sports, students were divided into five groups, with each group having a compulsory classroom seminar once a week. Three out of five groups, with approximately 30 students, were randomly selected and invited to fill in the questionnaire. At the Faculty of Medicine, students were divided into five groups all five days of the week. Three classes were randomly selected each day, with approximately 20 students per class. The questionnaire was filled in at the beginning of those classes. All the students who were offered to fill in the questionnaire agreed to participate in the study, however, two students returned invalid questionnaires (response rate 99.3%). The approval for conducting the study was obtained from the Institutional Review Board of the Faculty of Medicine, University of Belgrade. The consent for participation was implied by filling in the questionnaire.

Instrument

A short anonymous questionnaire was administered to collect data. The first part of the questionnaire covered socio-demographic characteristics of the participants (gender, age, parental marital status, parental highest educational attainment, household monthly income, residence prior to entering University, grade point average-GPA, age at the time of the first use of internet).

In the next section, students were asked whether they used the Internet and how frequently as well as whether they used health-related websites (about fitness, diet etc) and smartphone apps (calorie counting, exercise and performance etc). Additionally, students were asked about the extent to which health-related information online influenced their decision-making regarding health (graded from "a little" to "a lot").

The e-health literacy was assessed by the eHEALS questionnaire (9). The eHEALS has 8 items that rank the level of confidence at finding, assessing, and using online health information in order to make informed health-related decisions (9). Answers are graded on a 5-point Likert scale from grade 1 (strong disagreement) to grade 5 (strong agreement). The total eHEALS score represents the sum of the scores for each item. This means that the total eHEALS score ranges from 8 to 40. A higher score represents a higher level of perceived eHealth literacy. The eHEALS was previously translated and validated in the Serbian language (10). The internal consistency of the Serbian version of eHEALS was 0.849 (10).

Data analysis

To assess differences between the categorical variables Pearson's Chi-square test (for variables with 2 categories such as gender, high school program) and Chi square linear-by-linear association (for variables with 3 or 4 categories, such as parental marital status, parental education level, household monthly income, frequency of internet use, extent to which online health-related information influences decision making). After determining that the dis-

tribution of eHEALS scores by means of the Kolmogorov Smirnov test was not normal, we applied non-parametric Mann-Whitney test to assess differences in scores between the two groups of students. The Spearman's test was used to investigate correlations between the selected variables.

To examine the effect measure for each eHEALS item relative to the type of Faculty, we performed the univariate logistic regression. In this model, we used the type of Faculty (sports vs. medicine) as the dependent variable. The independent variables were the perceptions of each eHEALS item categorized as positive (marked 4-agree or 5-strongly agree on Likert scale) or other (marked 1-strongly disagree, 2-disagree and 3-undecisive on Likert scale).

To determine the factors associated with a higher level of eHealth literacy, we performed the hierarchical multiple linear regression analysis. This analysis was performed separately for the subgroup of sport students and the subgroup of medical students, because it was found that the total eHEALS score significantly differed between the two groups of students. The independent variables were classified according to three models. The first model included basic demographic characteristics: gender, age and GPA. The second model included additional socio-demographic variables such as: household monthly income and residence before entering University. Finally, the third model took into account the patterns of Internet use: age at the time of the first internet use, the use of health-related websites and apps and the extent to which online health-related information influenced students' decision-making regarding health.

Table 1. Characteristics of the study sample according to the use of health-related websites (N=390)

Variable	Type of Faculty		p
	Sports N=89 Count (%)	Medicine N=301 Count (%)	
Gender			
Male	60 (67.4)	101 (33.6)	**0.001**
Female	29 (32.6)	200 (66.4)	
Age (years)*	22.9 (1.1)	24.1 (0.9)	**0.018**
Grade point average*	8.4 (0.5)	8.9 (0.7)	**0.003**
Household monthly income (Euros)			
< 405	32 (36.0)	68 (23.1)	**0.002**
405-810	36 (40.4)	110 (37.4)	
>810	21 (23.6)	116 (39.5)	
Missing answers	*0 (0.0)*	*7 (2.3)*	
Residence prior to studies			
Capital city	36 (40.4)	125 (41.5)	0.856
Outside of the capital	53 (59.6)	176 (58.5)	
Use of internet			
Yes	89 (100.0)	301 (100.0)	n/a
No	0 (0.0)	0 (0.0)	
Age at the time of the first internet use in years*	13.7 (2.4)	12.8 (3.0)	0.100
Frequency of internet use			0.327
Rarely	0 (0.0)	3 (1.0)	
Once a week	0 (0.0)	1 (0.3)	
Multiple times per week	2 (2.2)	8 (2.7)	
Multiple times per day	87 (97.8)	289 (96.0)	
Use of health-related websites			
Yes	71 (79.8)	234 (77.7)	0.771
No	18 (20.2)	67 (22.3)	
Use of health-related apps			
Yes	35 (39.3)	148 (49.2)	0.116
No	54 (60.7)	153 (50.8)	
Extent to which online health-related information influences decision making			
Not at all	7 (7.9)	28 (9.3)	
A little	20 (22.5)	94 (31.1)	
Partially	53 (59.6)	140 (46.4)	**0.001**
A lot	8 (9.0)	9 (3.0)	
Quite a lot	1 (1.1)	4 (1.3)	
Missing answers	*0*	*27 (9.0)*	

Legend: *Mean value with corresponding standard deviation in brackets; Grade point average range 6.0-10-0; Bold values denote statistically significant variables.

Overall, there were few missing answers. The missing answers were excluded from the analyses. Probability level of $p<0.05$ was considered statistically significant. Statistical analysis was performed in Statistical Package for Social Sciences 20.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

The study sample consisted of 390 University students: 89 from the Faculty of Sport and Physical Education and 301 from the Faculty of Medicine. Demographic characteristics as well as the patterns of digital behavior are presented in **Table 1**. Students differed in terms of demographic characteristics, but not in terms of the Internet use and digital behavior.

Median eHEALS score was 27 for sports students and 30 for medical students out of a maximum of 40 points (Mann Whitney 10906.00, p=0.008). Students' positive perception of their eHealth literacy is presented as proportions in **Table 2**. Also, Table 2 describes the measure of differences in eHEALS scores. Compared to sports students, medical students scored significantly higher in the majority of eHEALS items. When it comes to sports students, none of the investigated variables was correlated with the total eHEALS score. In the subgroup of medical students, eHEALS score was positively correlated with the use of health-related smartphone apps (ρ=0.154, p=0.007). A higher eHEALS score correlated with younger age at the time of the first Internet use (ρ=-0.168, p=0.004).

In the subgroup of sports students, the hierarchical multiple linear models showed that none of the investigated variables in the three models was associated with better eHealth literacy **(Table 3)**.

In the subgroup of medical students, the hierarchical multiple linear model no. 3 showed that being female, residing outside the capital before studying at the University, younger age at the time of the first Internet use, the use of health-related websites and smartphone apps as well as lower influence of online health-related information on decision making regarding heath were associated with better self-perceived eHealth literacy **(Table 4)**.

DISCUSSION

In this study we sought to examine eHealth literacy among students of sports and medical students. Given our initial hypothesis, the study findings indicate that perceived eHealth literacy differs between the students of sports and medical students. Thus, our hypothesis has been refuted. While a number of studies explored eHealth literacy in general undergraduate college populations (4, 11, 12), some studies were focused on more specific groups such as nursing students (7, 13-15) or students of health professions (8, 16, 17). Nevertheless, to date, sports students have not been included in the eHealth literacy assessment.

We found that medical students had higher levels of overall self-perceived eHealth literacy compared to

Table 2. Percentage of students who either agreed or strongly agreed with eHEALS items over total number of respondents according to type of Faculty

eHEALS items	Faculty		OR (95%CI)	p
	Sports	Medicine		
	N_p/N_{tot} (%)	N_p/N_{tot} (%)		
#1 I know what health resources are available on the Internet	17/89 (19.1)	61/301 (20.3)	1.08 (0.59-1.97)	0.799
#2 I know where to find helpful health resources on the Internet	47/89 (52.8)	210/301 (70.0)	2.08 (1.28-3.38)	**0.003**
#3 I know how to use the health information I find on the Internet to help me	53/89 (59.6)	225/301 (75.3)	2.06 (1.25-3.40)	**0.004**
#4 I know how to find helpful health resources on the Internet	56/89 (62.9)	223/301 (74.6)	1.73 (1.05-2.86)	**0.033**
#5 I have the skills I need to evaluate the health resources I find on the Internet	50/89 (56.2)	202/301 (67.6)	1.62 (1.01-2.63)	**0.049**
#6 I know how to use the Internet to answer my questions about health	50/89 (56.2)	213/301 (71.0)	1.91 (1.17-3.11)	**0.009**
#7 I can tell high quality health resources from low quality health resources on the Internet	58/89 (65.2)	227/301 (75.7)	1.66 (0.99-2.77)	0.051
#8 I feel confident in using information from the Internet to make health decisions	40/89 (44.9)	142/301 (47.3)	1.10 (0.68-1.77)	0.692

Legend: N_p - number of students who expressed agreement or strong agreement with a given item; N_{tot} - total number of respondents; OR - odds ratio; CI - confidence interval; Bold values denote statistically significant variables

Table 3. The hierarchical regression model with variables associated with a higher eHEALS score among sports students

Variable	Model 1			Model 2			Model 3		
	B	95% CI	p	B	95% CI	p	B	95% CI	p
Gender	1.10	-1.65, 3.86	0.427	0.820	-2.02, 3.66	0.568	0.742	-2.43, 3.92	0.643
Age	0.37	-0.82, 1.55	0.261	0.430	-76, 1.62	0.475	0.391	-0.88, 1.66	0.541
Grade point average	-0.48	-2.86, 1.90	0.691	-0.742	-3.18, 1.69	0.546	-0.862	-3.45, 1.72	0.508
Household monthly income				0.965	-0.78, 2.71	0.275	0.978	-0.87, 2.82	0.294
Residence prior to University				-0.308	-2.99, 2.38	0.820	-0.284	-3.11, 2.54	0.842
Age at the time of the first internet use							-0.126	-0.70, 0.45	0.664
Frequency of internet use							0.566	-3.89, 5.02	0.801
Use of health-related websites							0.852	-2.66, 4.36	0.630
Use of health-related apps							-0.034	-2.97, 2.90	0.982
Extent to which online health-related information influences decision making							-0.296	-2.09, 1.50	0.744
R^2		0.018			0.035			0.420	
Probability level of F for change in R^2		0.687			0.506			0.991	

Legend: B - unstandardized coefficient; CI - confidence interval; p - probability level

sports students. In terms of specific items, the largest difference (more than two-fold) was observed for confidence in locating helpful online health resources and using online health information to help them with various queries. Contrary to this, both sports and medical students were least confident with regards to being familiar with possible online health resources as well as regarding the use of online information to make health decisions. Pokharel et al. (8) reported a similar low confidence level among medical and dentistry students in relation with the influence of online health information on individual decision-making. However, this study reported a high level of confidence in knowing the available online resources of health information (8). One study that included female college students in health sciences suggested that students could have basic, intermediate or proficient level of eHealth literacy (16). The differences in the levels of eHealth literacy were based on the use of several sources of health information vs. the use of the Internet browsers only (16). Additionally, students who were labeled as proficient in eHealth literacy sought support from other people, such as librarians, whereas intermediate and basic eHealth literate students relied on the independent searches (16). Based on the results of this study, both sports and medical students could benefit from guidance and the instruction as to what available and reliable online health information sources are and how to implement health information to make conscious health decisions. Previous attempts to improve eHealth skills among college students have included stronger appreciation of digital technologies (18).

The hierarchical linear regression showed a significant model only in the subgroup of medical students and this was not the case with sports students. This finding

Table 4. The hierarchical regression model of variables associated with a higher eHEALS score among medical students

Variable	Model 1			Model 2			Model 3		
	B	95% CI	p	B	95% CI	p	B	95% CI	p
Gender	-1.42	-3.08, 0.23	0.090	-1.63	-3.29, 0.02	0.053	-2.08	-3.67, -0.49	**0.010**
Age	-0.47	-1.40, 0.45	0.312	-0.42	-1.34, 0.50	0.366	-0.09	-0.98, 0.81	0.850
Grade point average	-0.58	-1.79, 0.63	0.344	-0.29	-1.53, 0.94	0.639	-0.44	-1.63, 0.75	0.469
Household monthly income				0.42	-0.62, 1.45	0.426	-0.29	-1.33, 0.74	0.579
Residence prior to University				1.95	0.27, 3.62	0.023	1.98	0.38, 3.58	**0.015**
Age at the time of the first internet use							-0.52	-0.81, 0.23	**0.001**
Frequency of internet use							-0.41	-2.18, 1.37	0.651
Use of health-related websites							2.97	1.01, 4.93	**0.003**
Use of health-related apps							1.684	0.17, 3.19	**0.029**
Extent to which online health-related information influences decision making							-1.208	-2.17, 0.25	**0.014**
R^2		0.019			0.039			0.150	
Probability level of F for change in R^2		0.172			0.073			0.001	

Legend: B - unstandardized coefficient; CI - confidence interval; p - probability level; Bold values denote statistically significant variables

suggests that there may be other factors beyond socio-demographic characteristics and digital consumer behaviors that were not taken into account, which needs to be acknowledged as a study limitation. On the other hand, this analysis showed a wide spectrum of factors associated with a higher level of eHealth literacy among medical students, outlined only in the final, full model that included both socio-demographic variables and patterns of online behavior.

Of socio-demographic variables, being female and residing outside of the capital were associated with a higher level of eHealth literacy. Female gender has been consistently associated with better eHealth literacy across age-specific populations (9, 19), thus, our results support the previous literature data. This gender pattern can be linked to the gender gap in the use of health services (20). Specifically, women tend to use more primary and specialized care compared to men, except hospitalization (20). Similar issue likely applies to the use of digital technologies. Moreover, it is possible that this gender gap also stems from observations that women are more likely to seek health advice compared to men (21). Following gender, medical students who lived outside of the capital were more likely to have better eHealth literacy. Residence could be considered as proxy of students' current living arrangement, suggesting that these students live independently (either in student dormitories or in rented apartments) away from their immediate family, as they moved to the capital to study. Thus, it is reasonable to assume that such students need to rely more on their own capacity to support their health and well-being compared to their peers who continue living with their parents over the course of undergraduate schooling.

When it comes to digital behavior characteristics, younger age when starting to use the Internet and more frequent use of Internet were associated with better eHealth literacy of medical students. These results could be explained by the fact that people who have used the Internet for a longer time and more frequently tend to be more digitally versatile and resourceful when browsing the online health-related content. Moreover, medical students who used health-related websites and smartphone apps had a higher likelihood of having better eHealth literacy. This finding is well expected, given that exploration of digital health-related information enables users to be savvier on whether specific sources are credible and reliable. In fact, it has been noticed that the use of apps promotes a healthier lifestyle (such as an increased intake of fruits and vegetables) and motivates weight loss and engagement in physical activity (22). While the use of health-related websites and apps holds promising results in terms of health promotion, most students believe that these media outlets cannot substitute for conventional face-to-face consultations with a heath care provider (23). Finally, a lower influence of online health-related information on medical students' decision making was also a predictor of better health literacy in our hierarchical linear regression model. This finding was also expected in the subgroup of medical students, as they are seemingly critical towards the online health information and supportive of evidence-based data. It is possible that, on these occasions, students tend to refer to other sources (16) to make sure their health-related decisions are appropriate.

Several limitations of our study need to be recognized. The size of our sample of sports students is somewhat small compared to the sample of medical students. This, however, reflects the size of student population in the respective Faculties, as there are more medical than sports students. Also, the study sample comprised students from one University that is located in the capital and represents the largest urban area in Serbia. Perhaps a more diverse sample of students from other Universities would potentially offer a different insight in eHealth literacy. We have not included the aspects of health behavior such as a balanced diet (number of fruit and vegetable potions per day) and regularity of having breakfast or the level of physical activity that could have differed between sports students and medical students. The inclusion of these factors could have potentially outlined statistically significant variables in the hierarchical linear regression model in the subgroup of sports students. Additionally, because of the cross-sectional study design, we could not make definite inferences between the examined socio-demographic variables and the outcomes of interest.

To conclude, medical students report being more confidents in terms of their eHealth literacy skills compared to sports students. However, both groups of students report overall low confidence in knowing the available and reliable health-related sources on the Internet. Both socio-demographic features and digital behavior patterns influence eHealth literacy, but they are not consistent in the two groups of students and seem to depend on their field of study. Both sports and medical students would likely benefit from the enhancement of eHealth literacy skills in the undergraduate curricula. In the assessment of predictors contributing to better eHealth literacy, future studies should include a broad range of behavioral characteristics.

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Conflict of interest

The authors declare that they do not have conflict of interest.

Author contributions

TG contributed to study design, data collection, data analysis and interpretation and drafted the manuscript. JC, MC, RZ and AP contributed to study design, data collection, data analysis and interpretation and provided critical review of the intellectual content of the manuscript. AG contributed to study design, data analysis and interpretation and provided critical review of the intellectual content of the manuscript. All authors approved the final version of the manuscript before submission.

Ethical approval

Ethical approval for the study was obtained from the Institutional Review Board of the Institute of Epidemiology, Faculty of Medicine, University of Belgrade.

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ISPITIVANJE ELEKTRONSKE ZDRAVSTVENE PISMENOSTI MEDJU STUDENTIMA SPORTA I STUDENTIMA MEDICINE

Tatjana Gazibara[1], Jelena Cakić[1], Milica Cakić[1], Redžeb Zejnelagić[2], Aleksandra Popović[3], Anita Grgurević[1]

Sažetak

Uvod/cilj: Podaci o elektronskoj zdravstvenoj pismenosti (EZP) i mogućim razlikama u EZP među studentima nisu dovoljno poznati. Cilj ovog istraživanja bio je da se analizira EZP kod studenata sporta i medicine i procene prediktori bolje EZP.

Materijal i metode: Ova studija preseka je sprovedena od aprila do oktobra 2017. godine među studentima završnih godina Fakulteta sporta i fizičkog vaspitanja i Medicinskog fakulteta Univerziteta u Beogradu, Srbija. Uključeno je ukupno 89 studenata sporta i 301 student medicine. Studenti su popunjavali skalu za procenu elektronske zdravstvene pismenost - eHEALS.

Rezultati: U poređenju sa studentima sporta, studenti medicine su imali značajno viši skor na eHEALS-u (27 prema 30, redom p=0,008). Studenti medicine su bili dva puta sigurniji od studenata sporta u tome gde da pronađu korisne onlajn izvore informacija o zdravlju i kako da koriste onlajn zdravstvene informacije. Nije dobijen značajan hijerarhijski model linearne regresije za prediktore bolje EZP među studentima sporta. Kod studenata medicine zabeleženo je da su osobe ženskog pola, život van glavnog grada pre studija, mlađi uzrast pri prvom korišćenju interneta, korišćenje veb-sajtova u vezi sa zdravljem i aplikacija za pametne telefone, kao i slabiji uticaj onlajn informacija o zdravlju na donošenju odluka o zdravlju bili povezani sa boljom ocenom EZP.

Zaključak: Studenti medicine su bili sigurniji u svoju EZP u poređenju sa studentima sporta. Moguće je da faktori koji utiču na bolju EZP zavise od vrste studija.

Ključne reči: elektronska zdravstvena pismenosti, studenti, medicina, sport, fizičko vaspitanje.

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ORIGINAL ARTICLE

Physical activity decreases anxiety-related behavior in chronic prostatitis/chronic pelvic pain syndrome: functional behavioral study on the crossroad of experimental exercise physiology and andrology

Nikola Šutulović[1], Aleksa Zubelić[1], Djuro Macut[2], Milena Vesković[3], Dušan Mladenović[3], Aleksandra Rašić-Marković[1], Željko Grubač[1], Olivera Stanojlović[1], ✉Dragan Hrnčić[1]

[1]Institute of Medical Physiology "Richard Burian", Belgrade University Faculty of Medicine, 11000 Belgrade, Serbia

[2]Clinic of Endocrinology, Diabetes and Metabolic Disease, University Clinical Centre of Serbia, Belgrade University Faculty of Medicine, 11000 Belgrade, Serbia 11000 Belgrade, Serbia

[3]Institute of Pathophysiology "Ljubodrag Buba Mihailovic", Belgrade University Faculty of Medicine, 11000 Belgrade, Serbia

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✉ **Correspondence to:**
Prof. Dragan Hrnčić, MD, MSc, PhD
Institute of Medical Physiology "Richard Burian"
Faculty of Medicine, University of Belgrade
Visegradska 26/II, Belgrade 11000, Serbia
e-mail 1: dragan.hrncic@med.bg.ac.rs;
e-mail 2: drhrncic@yahoo.com

Summary

Introduction: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a inflammatory syndrome, manifested by pain, voiding symptoms, sexual dysfunction, and mental health issues including anxiety. Beneficial effects of exercise are known, but its influence on CP/CPPS has not been investigated. This study aimed to determine the effects of chronic aerobic physical activity on anxiety-related behavior and pain in rats with experimental CP/CPPS.

Material and Methods: Adult male *Wistar albino* rats (n=32) were randomly assigned to 4 groups (n=8 in each): **Sham-SED** (30-days sedentary-SED protocol on treadmill and intraprostatic injection of 0.9% NaCl); **Sham-PA** (30-days physically active-PA protocol on treadmill and intraprostatic injection of 0.9% NaCl); **CP/CPPS-SED** (30-days SED protocol on treadmill and intraprostatic injection of 3% λ-carrageenan); **CP/CPPS-PA** (30-days PA protocol on treadmill and intraprostatic injection of 3% λ-carrageenan). To establish pain dynamics, scrotal skin pain thresholds were measured by electronic von Frey aesthesiometer (evF) preoperatively: 2 and 1 day, and also postoperatively: 2nd, 3rd, and 7th day. Anxiety-like behavior was estimated by subjectiong the animals to the open field (OF), elevated plus maze (EPM) and light/dark (L/D) tests at the same postoperative days as evF.

Results: Rats that developed experimental CP/CPPS showed decreased mechanical pain threshold in the scrotal skin in all postoperative time points, in comparison to the Sham group. Also, in rats with prostatitis increased anxiety-like behavior was observed in OF, EMP and L/D test, compared to corresponding controls. Protocol of 30-day long exercise in rats with CP/CPPS led to reversion of anxiety-like behavior and increased scrotal pain threshold.

Conclusion: Results of the present study showed that exercise pretreatment on the treadmill for 30 consecutive days led to the amelioration of anxiety-related and pain-related behavior in rats with CP/CPPS.

Keywords: CP/CPPS, pain, anxiety, exercise, treadmill, rat

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) presents a urological entity with a growing prevalence of 35-50% among men of all ages. It is the most common type of non-infective prostatitis (1) manifested as a chronic painful condition in which a prominent symptom is spontaneous or provoked perineal pain in the absence of positive bacterial cultures in the prostate exprimate (2). This syndrome is followed by different urological signs and symptoms (erectile dysfunction, difficult and/or frequent urination, painful ejaculation), but it is also accompanied with plenty of psychiatric comorbidities (3). These comorbidities additionally lower the patient's quality of life (4). The CP/CPPS etiopathogenesis is complex and has been unelucidated by now. The most prevalent opinion is the one that chronic genitourinary pain is triggered by a neuropathic cause (5), which in addition induces pathological changes in various brain structures (6) followed by increased pro-inflammatory cytokines synthesis (7). A disbalance in the cytokine milieu ultimately results in the lowering of primary nociceptive neuronal activation threshold, peripheral sensitization, and development of neuropathic pain and prostatodynia(8).

Having in mind such a lack of understanding of the underlying mechanisms, therapeutic options are limited and success rates in these patients vary, especially when it comes to mental health-related comorbidities (9). Various studies indicated that chronic pain is associated with poorer quality of life, worse sleep quality, reduced physical activity, mood alterations and the development of anxiety disorder (10). Anxiety is defined as a psychobiological emotional state or reaction, consisting of an unpleasant feeling of tension, nervousness and worry followed by activation of the autonomic nervous system (11). The results of the research by Gureja et al. (12) suggest that the presence of chronic painful condition originating from different anatomical localization dramatically increases the likelihood of the development of psychiatric disorders. Therefore, there is an urgent need to find additional, preferably non-pharmacological, modes of treatment of CP/CPPS-related mental health issues including anxiety. Regular physical activity could be an option, but we still don't have direct evidence for its beneficial effects on CP/CPPS.

A sedentary lifestyle is a well-known risk factor for health impairment, and it is associated with a higher possibility for cardiovascular diseases, diabetes mellitus type 2, hypertension and osteoporosis, but also the development of different behavioral alterations (13). On the other hand, dosed and planned physical activity represents a proven mode of prevention of psychiatric diseases, such as anxiety disorders, and it is strongly associated with health improvement in general population (14). Epidemiological data suggest that more active people are less likely to develop a stress-related disorder, and also that exercise can reduce symptoms of anxiety (15). Also, it is well known that sedentary people have a higher risk of developing chronic pain (16). Other studies showed that exercise was an effective and potent non-pharmacological treatment for a variety of pain conditions and that it led to pain relief (17). Although positive effects of physical activity in patients with anxiety are known (18), the exact mechanisms of its influence on pain sensitivity and psychological comorbidities in patients with CP/CPPS have not been investigated yet. Animal exploratory behavior can be partially or completely inhibited by pain or anxiety, therefore reduced exploratory behavior may represent an indirect measure of anxiety (19). Chronic aerobic physical activity on a treadmill for small experimental animals enables appropriate modeling and dosing of physical activity in experimental conditions on animal subjects *in vivo*. These facts prompted us to consider physical activity as a suitable amelioration strategy for anxiety provoked by CP/CPPS.

The aim of this study was to investigate the effects of chronic aerobic physical activity on anxiety-related behavior and pain sensitivity in rats with experimentally induced CP/CPPS.

MATERIALS AND METHODS

Ethical statement

All experimental procedures were in full compliance with the Directive of the European Parliament and the Council (2010/63/EU) and approved by The Ethical Committee of the University of Belgrade (Permission No. 323-07-01339/2017-05/3).

Animals and housing

In our experiment, we used 32 adult male *Wistar albino* rats, obtained from the Military Medical Academy breeding laboratory (Belgrade, Serbia), which were three-month-old, and weighed 250–350g at the beginning of the experiment. Animals were kept under the controlled laboratory ambient conditions (22-24°C, 50±5% air humidity, 12/12h light: dark cycle with the light turned on from 08:00 a.m. to 08:00 p.m.) during the seven-day acclimation period, as well as, during the entire experiment. Animals were use in the experiment only once. During the experiment, animals were allowed to consume food and water *ad libitum*.

Experimental design and protocol

To examine the effects of chronic aerobic physical activity on experimental CP/CPPS development, we performed experiments **(Fig. 1.)** in accordance with our previous research (6,20) and literature data (21).

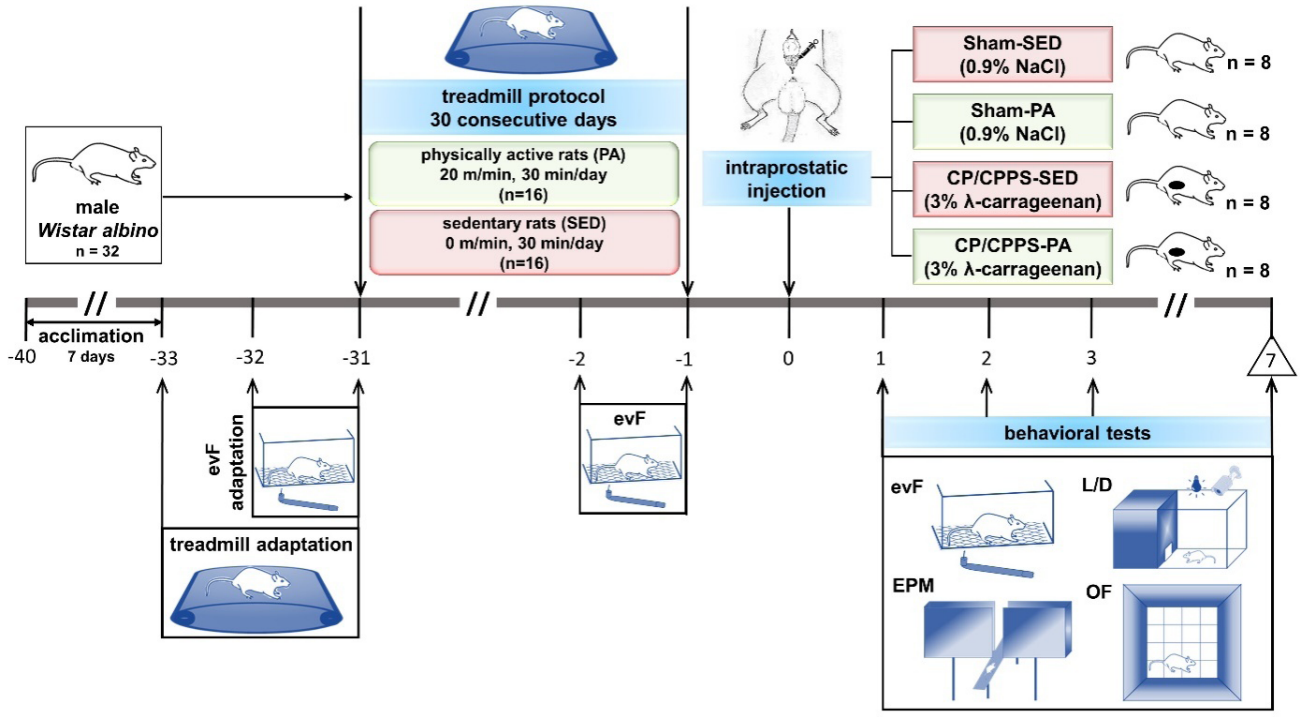

Figure 1. Experimental design. From the fortieth (-40) to the thirty-third (-33) preoperative day, male Wistar albino rats (n=32) acclimated within seven days to standard laboratory conditions. Afterward, from the thirty-third (-33) to the thirty-first (-31) preoperative day, the rats underwent three consecutive days of treadmill adaptation (10 min/day, belt speed: 10 m/min), as well as within the two consecutive days to scrotal pain threshold measurement adaptation by an electronic von Fray (evF) esthesiometer. In accordance with our previous research (22) and depending on the thirty consecutive days treadmill protocol which lasted from the thirty-first (-31) to the first (-1) preoperative day, the animals were divided into two groups. The animals that ran on a treadmill (30 min/day, belt speed: 20 m/min; n=16) were considered physically active (PA) rats, while the animals which spent the same amount of time on the treadmill off (30 min/day, belt speed: 0 m/min; n=16) were considered as sedentary (SED) rats. Further treatment which involved an intraprostatic injection during surgery (considered as day 0 of the experiment) led to an additional division of the rats into four groups: Sham-SED (intraprostatic injection of 0.9% NaCl and preoperative sedentary treadmill protocol; n=8); Sham-PA (intraprostatic injection of 0.9% NaCl and preoperative physically active treadmill protocol; n=8); CP/CPPS-SED (intraprostatic injection of 3% λ-carrageenan and preoperative sedentary treadmill protocol; n=8); CP/CPPS-PA (intraprostatic injection of 3% λ-carrageenan and preoperative physically active treadmill protocol; n=8).
To assess and monitor the development of experimental CP/CPPS, mechanical pain thresholds were measured in the scrotal skin by evF aesthesiometer in the pre-surgery period: 2 days and 1 day before intraprostatic injection, as well as, in post-surgery period: 2, 3, and 7 days upon intraprostatic injection. To assess anxiety-like behavior, the animals from all groups were subjected to a standard battery of three ethological tests (consisting of OF, EPM, and L/D tests in the order listed) at different post-surgery time points: 2, 3, and 7 days upon intraprostatic injection.

Forty days before surgery (-40), male *Wistar albino* rats (n=32) started a seven-day acclimation to laboratory conditions. Treadmill adaptation (3 consecutive days, 10 min/day, speed: 10 m/min), and scrotal pain threshold measurement using evF aesthesiometer (two consecutive days), were performed from the thirty-third (-33) to the thirty-first (-31) preoperative day. Depending on the treadmill protocol, which lasted from the thirty-first (-31) to the first (-1) preoperative day, the animals were divided into physically active rats (PA, 30 consecutive days, 30 min/day, speed: 20 m/min; n=16) and sedentary rats (SED, 30 consecutive days, 30 min/day, speed: 0 m/min; n=16). Further intraprostatic injection during surgery (0) has additionally divided the rats into four groups: Sham-SED (intraprostatic injection of 0.9% NaCl and preoperative sedentary treadmill protocol; n=8); Sham-PA (intraprostatic injection of 0.9% NaCl and preoperative physically active treadmill protocol; n=8); CP/CPPS-SED (intraprostatic injection of 3% λ-carrageenan and preoperative sedentary treadmill protocol; n=8); CP/CPPS-PA (intraprostatic injection of 3% λ-carrageenan and preoperative physically active treadmill protocol; n=8). Scrotal pain threshold measurement was performed on 2 (-2) and 1 (-1) days before, as well as 2, 3, and 7 days upon intraprostatic injection (0). Also, to determine anxiety-like behavior, 2, 3, and 7 days upon surgery (0), rats underwent the standard battery of three behavioral tests (EPM = elevated plus maze test, LD = light/dark test, OF = open field test). On the seventh (7) postoperative day, after the completion of behavioral tests, the rats were sacrificed, and prostates were sampled for histology hematoxylin-eosin (H&E) examination.

Chronic aerobic physical activity using treadmill apparatus

The treadmill apparatus for small experimental animals (NeuroSciLaBG-Treadmill, Elunit, Belgrade, Serbia), which was used in this study, consisted of one moving belt and four plexiglass-separated running compartments. For the purpose of stimulating the rats to run, each running compartment possessed an electrified metal grid with

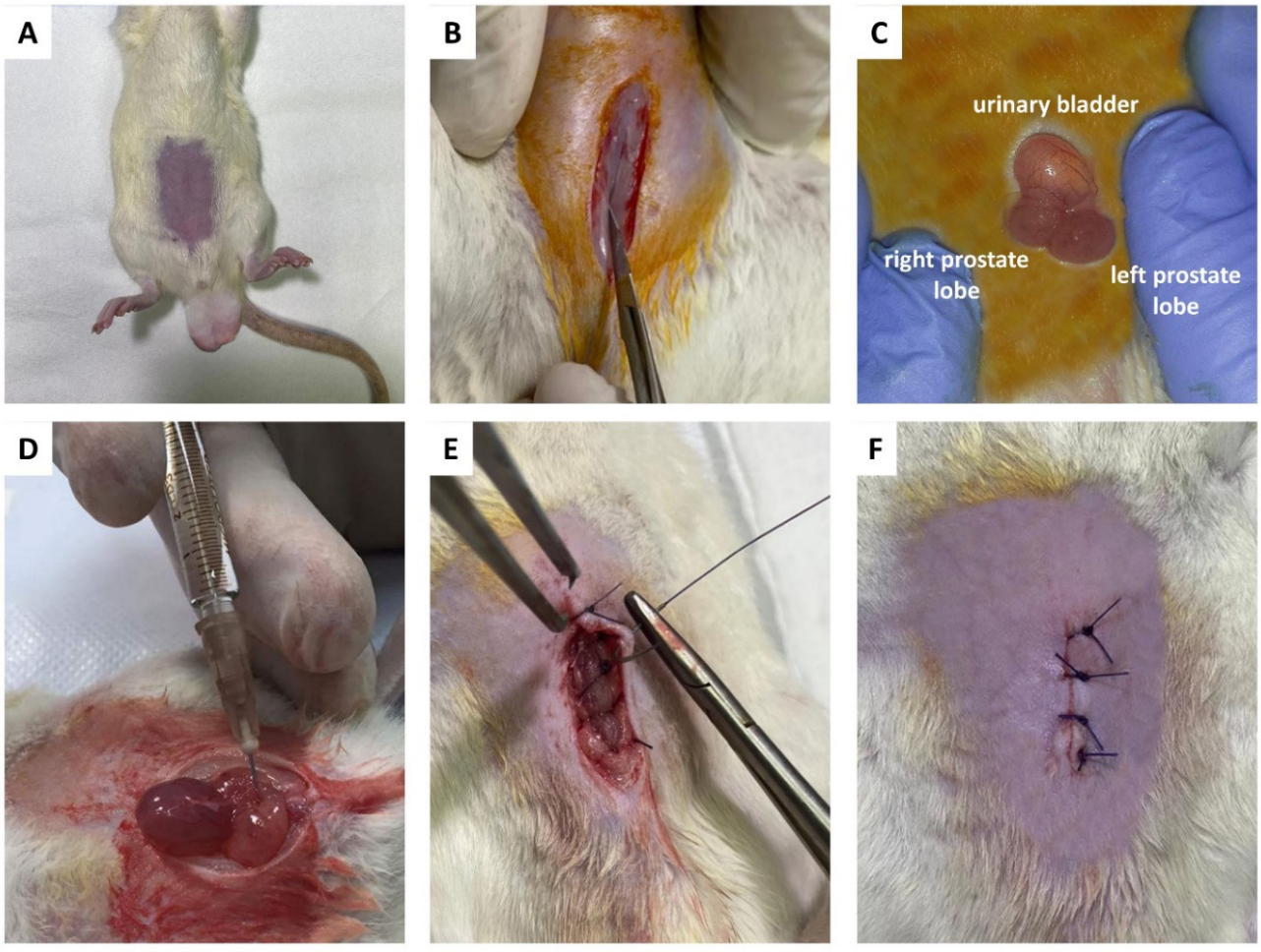

Figure 2. Experimental CP/CPPS induction by surgery and intraprostatic injection. Surgery was performed on a previously shaved and disinfected surgery field (A). A small midline incision of the lower front abdominal wall was done (B) and the urinary bladder with both(left and right) ventral prostate lobes were exposed (C). After the intraprostatic injection (D), the wound was closed in layers (E) using an absorbable suture (F).

the electric shock of low intensity (0.2 mA), as a negative stimulation on the starting edge, as well as a dark area as a positive stimulation on the ending edge. Rats were placed on the moving belt and ran in the direction opposite from the belt movement towards the positive stimulation and escaping the negative stimulation. Additionally, using the accompanied software, the protocol of belt moving (duration and speed), as well as the belt inclination were previously given. During the entire treadmill protocol, the belt was 0 ° incline.

Before starting the training protocol, the animals were adapted and familiarized with the treadmill apparatus over 3 consecutive days (10 min/day, belt speed: 10 m/min).

Physically active animals were made to run on the treadmill for 30 consecutive days (30 min/day, speed: 20 m/min). Exercise training using this protocol at this belt speed for treadmill running rats is considered aerobic in accordance with literature data which indicated that maximal lactate steady state (MLSS, i.e., the highest running intensity with constant exercise load at which blood lactate level does not reach up beyond the initial transient increase) was established (22-24). Corresponding sedentary animals were also kept in the treadmill off the apparatus for the same amount of time over 30 consecutive days (30 min/day, belt speed: 0 m/min).

Induction of experimental CP/CPPS by surgery and intraprostatic injection

Experimental CP/CPPS was induced in rats by surgical application of intraprostatic injection through a standard protocol described in detail in our previous papers (6,20). Briefly, in anesthetized rats **(Fig. 2A)** middle incision in the lower abdominal area **(Fig. 2B)** was done and left and right ventral prostate lobes with urinary bladder were exposed **(Fig. 2C)**. After this, the intraprostatic injection was applied **(Fig. 2D)**. Sterile suspension of 3% λ-carrageenan (Sigma Aldrich, St. Louis, MO, USA) in a total volume of 50 µl was injected in both ventral prostate lobes of the CP/CPPS group, while Sham animals were treated in the same way with intraprostatic injection of the equal volume of sterile 0.9% saline. The wound was closed in layers **(Fig. 2E)** using an absorbable suture **(Fig. 2F)**.

Scrotal pain threshold to mechanical stimuli

To assess scrotal skin pain thresholds to mechanical stimuli, we used an electronic von Frey aesthesiometer (IITC Life Sciences, CA) with polypropylene rigid filaments. The rats were situated in plexiglass-separated boxes with metal grid floors to adapt to the conditions in the measurement platform for 30 min. Perpendicular application of stimulus started on the restful rat when the rat remained quiet with the scrotum brought down on the platform bottom. A gradual increase of the pressure lasted until a reflex response (moving of the rat from resting position) was observed. An average value of three consecutively repeated measurements was used as the scrotal pain threshold. The rats were returned to their home cages immediately after the measurement was over.

Open field test

In the assessment of anxiety-like behavior, we used an automated and infrared sensor-equipped apparatus (Experimetria Ltd., Budapest, Hungary) with its accompanying software package (Conducta 1.0), as we previously described (20,25). At the beginning of the testing, to freely explore the new environment for 15 minutes, rats were placed individually in the central part of the sound-isolated, red-illuminated arena surrounded by black-colored walls. The system automatically registered, through infrared sensors, the parameters of horizontal locomotor activity, the total distance and time of ambulatory movements, as well as the number of rearings, as a parameter of vertical locomotor activity. Additionally, using an accompanying software, the open field area was divided into16 squares of which 4 middles were marked as the central zone, while the remaining 12 were marked as a peripheral zone. The time that the animal spent in the central zone was calculated and used as the reliable parameter of the anxiety-related behavior. In addition, to express the ratio between the rat's ambulation in the peripheral zone and the total ambulatory distance, we calculated thigmotaxis index which was expressed in percentages (%).

Elevated plus maze test

The elevated plus maze platform (Elunit, Belgrade, Serbia), 0.5 m-raised from the ground, consisted of two pairs of identical open arms and identical enclosed arms, merging on the central platform at an angle of 90 degrees. The rats were placed individually on a central platform and allowed to explore the maze for 5 min, while their behavior was recorded with the computer-attached infrared camera (HikVision Bullet 2612, China) placed above the platform. To reduce olfactory stimuli, after each rat finished testing, the maze was carefully cleaned with alcohol solution. This test is based on the animal's conflict between the innate need to explore and the innate fear of a new, unfamiliar environment, represented by raised, bright and unprotected open arms. Avoiding such an environment and sticking to a closed, sheltered environment, represented by closed arms, is a characteristic of anxiety-related behavior (26). The output parameters of this test included the total number of transitions between closed and open arms and the time spent in the open arms, as a trustworthy measure of the anxiety level. These variables inversely reflect the anxiety level. Video records are analyzed offline by an investigator blinded to the treatment.

Light/dark test

For this test, the light-dark test arena (Elunit, Belgrade, Serbia) consisted of a bigger, white-colored opened light compartment which is connected by a small squared aperture with a smaller one, black-colored closed dark compartment. The rats were individually placed in the center of the light compartment and allowed to explore the test area, while their behavior was monitored with camera (Logitech C210, Switzerland) mounted above the light compartment. The output parameters of this test were: the time that an animal spent in the light compartment of the light-dark test, as well as the number of transitions from the light to the dark compartment. Captured video sequences were analyzed after test completion by an investigator blinded to the experimental protocol.

Statistical analysis

To assess the normality of variables distribution, *Kolmogorov-Smirnov* test was used. The output data of pain and anxiety-like behavioral tests showed normal distribution. Hence, the results were expressed as means ± standard deviation (SD) for all variables. The statistical significance of the differences between the groups, as well as in-group differences were estimated by One-way ANOVA with *Tukey-Kramer LSD post hoc* test. The values of $p<0.05$, $p<0.01$, or $p<0.001$ were considered to be significant.

RESULTS

Chronic aerobic physical activity increased scrotal pain thresholds in rats with experimentally induced CP/CPPS

There were no significant differences between control and experimental animals in scrotal pain thresholds for mechanical stimuli in basal conditions, i.e. 2 days and 1 day before the surgery (Sham-SED vs. CP/CPPS-SED, $p>0.05$; Sham-PA vs. CP/CPPS-PA, $p>0.05$, **Fig. 3**). Also, there were no differences within the Sham-SED and Sham-PA groups in all postoperative measurements in

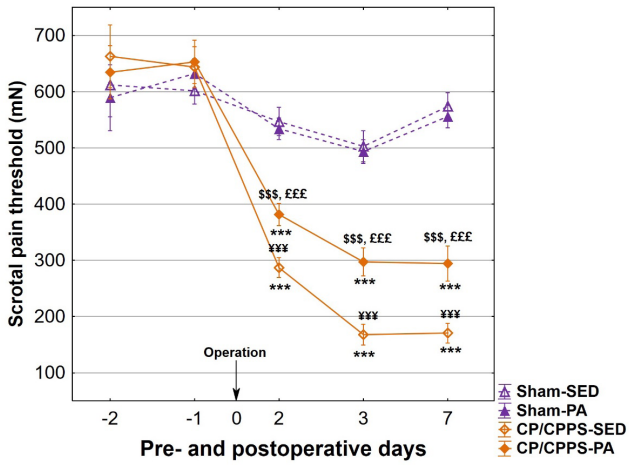

Figure 3. Scrotal pain thresholds in control (Sham-SED, Sham-PA) and experimental (CP/CPPS-SED, CP/CPPS-PA) rats.
Scrotal pain threshold measurements were performed by evF 2 and 1 day before, as well as 2, 3, and 7 days upon the operation (0). Values are mean± SD. Statistical significances of between-group differences in the scrotal pain threshold (¥¥¥p<0,001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $$$p<0.001 vs. CP/CPPS-SED), as well as within-group differences (***p<0.001 vs. -1) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption to **Fig. 1**.

comparison with the basal values (p>0.05, **Fig. 3**). Scrotal pain thresholds in rats with CP/CPPS (groups CP/CPPS-SED and CP/CPPS-PA) were highly significantly reduced (p<0.001), when compared to the thresholds in Sham operated rats (groups Sham-SED and Sham-PA) on the 2nd, 3rd, as well as 7th day upon surgery (**Fig. 3**). Also, pain thresholds were highly significantly reduced within the CP/CPPS-SED and CP/CPPS-PA rats in all postoperative days, compared to their basal pain thresholds (p<0.001, **Fig. 3**).

On the other hand, 30-day lasting chronic aerobic exercise on a treadmill led to a high statistically significant increase of postoperative scrotal pain thresholds in CP/CPPS-PA rats, in comparison to the corresponding sedentary rats from CP/CPPS-SED group (CP/CPPS-PA vs. CP/CPPS-SED, p<0.001, **Fig. 3**).

Chronic aerobic physical activity beneficially modified anxiety-like behavior in rats with experimentally induced CP/CPPS

Open field test

Analysis of the exploratory locomotor activity of control, Sham operated rats (Sham-SED and Sham-PA groups), and experimental rats with CP/CPPS(CP/CPPS-SED and CP/CPPS-PA groups) in the OF showed different behavioral patterns, which indicated the occurrence of anxiety-like behavior in rats with CP/CPPS (CP/CPPS-SED and CP/CPPS-PA rats), as shown in representative traces of ambulatory movements in the OF arena **(Fig. 4A-D)**.

Quantitative analysis of output variables of OF test showed that physically active Sham-PA rats had statistically significant higher ambulatory distance **(Fig. 5A)** on the 2nd (p<0.001), 3rd (p<0.05), and 7th postoperative day (p<0.05), in comparison with the Sham-SED rats. The same holds for the time of the ambulatory movements **(Fig. 5B)** on2nd (p<0.001), 3rd (p<0.01), and 7th postoperative day (p<0.05). Also, Sham-PA animals, in comparison to the Sham-SED animals, spent statistically significantly more time in the center of the OF **(Fig. 6A)** in 2nd (p<0.01), 3rd (p<0.001), and 7th postoperative day (p<0.001). A similar observation was made regarding the number of rearings **(Fig. 6B)** on the 2nd (p<0.001), 3rd (p<0.001), and 7th postoperative day (p<0.01). Index of thigmotaxis **(Fig. 7)** was statistically significantly lower in Sham-PA rats on the 2nd (p<0.001), 3rd (p<0.05), and 7th postoperative day (p<0.05), in comparison with the Sham-SED rats. Within-group differences of all OF the test parameters among the Sham-SE D and Sham-PA rats were not significantly changed in the 3rd and 7th, in comparison with the 2nd postoperative day.

Further analysis showed that the total ambulatory distance **(Fig. 5A)** and time **(Fig. 5B)** were significantly decreased in CP/CPPS-SED and CP/CPPS-PA rats, compared to the corresponding control Sham-SED and Sham-PA rats in 3rd (p<0.001) and 7th postoperative day (p<0.001). On the 2nd postoperative day, a statistically significant difference (p<0.001) in mentioned parameters was observed only between CP/CPPS-PA and Sham-PA rats, while the difference between CP/CPPS-SED and Sham-SED rats was not statistically significant (p>0.05). Also, CP/CPPS-PA animals, in comparison to the Sham-PA animals, spent statistically significantly less time in the center of the OF **(Fig. 6A)** in 2nd (p<0.01), 3rd (p<0.001), and 7th postoperative day (p<0.01), also had a statistically significant lower number of rearings **(Fig. 6B)** in 2nd (p<0.001), 3rd (p<0.001), and 7th postoperative day (p<0.01), and additionally revealed a higher index of thigmotaxis **(Fig. 7)** in 3rd (p<0.001), and 7th postoperative day (p<0.001). A similar observation was in the comparison of CP/CPPS-SED and Sham-SED rats onthe 3rd and 7th postoperative day in all test parameters **(Fig. 5-7)** in the 3rd (p<0.001), and 7th postoperative day (p<0.001). The difference between mentioned groups in all test parameters was not statistically significant onthe 2nd day ofthe surgery (p>0.05, **Fig. 5-7**). Within-group differences of all OF the test parameters among the CP/CPPS-SED rats were not significantly changed in the 3rd (p<0.001) and 7th (p<0.001), in comparison to the 2nd postoperative day. Physically active CP/CPPS-PA rats had statistically significant lower ambulatory distance **(Fig. 5A)** and time **(Fig. 5B)**, as well as a higher index of thigmotaxis **(Fig. 7)** in 3rd (p<0.05) and 7th (p<0.05), in comparison to the 2nd postoperative day. On the other hand, the difference was not statistically significant regarding time in the center of the open field **(Fig. 6A)** and

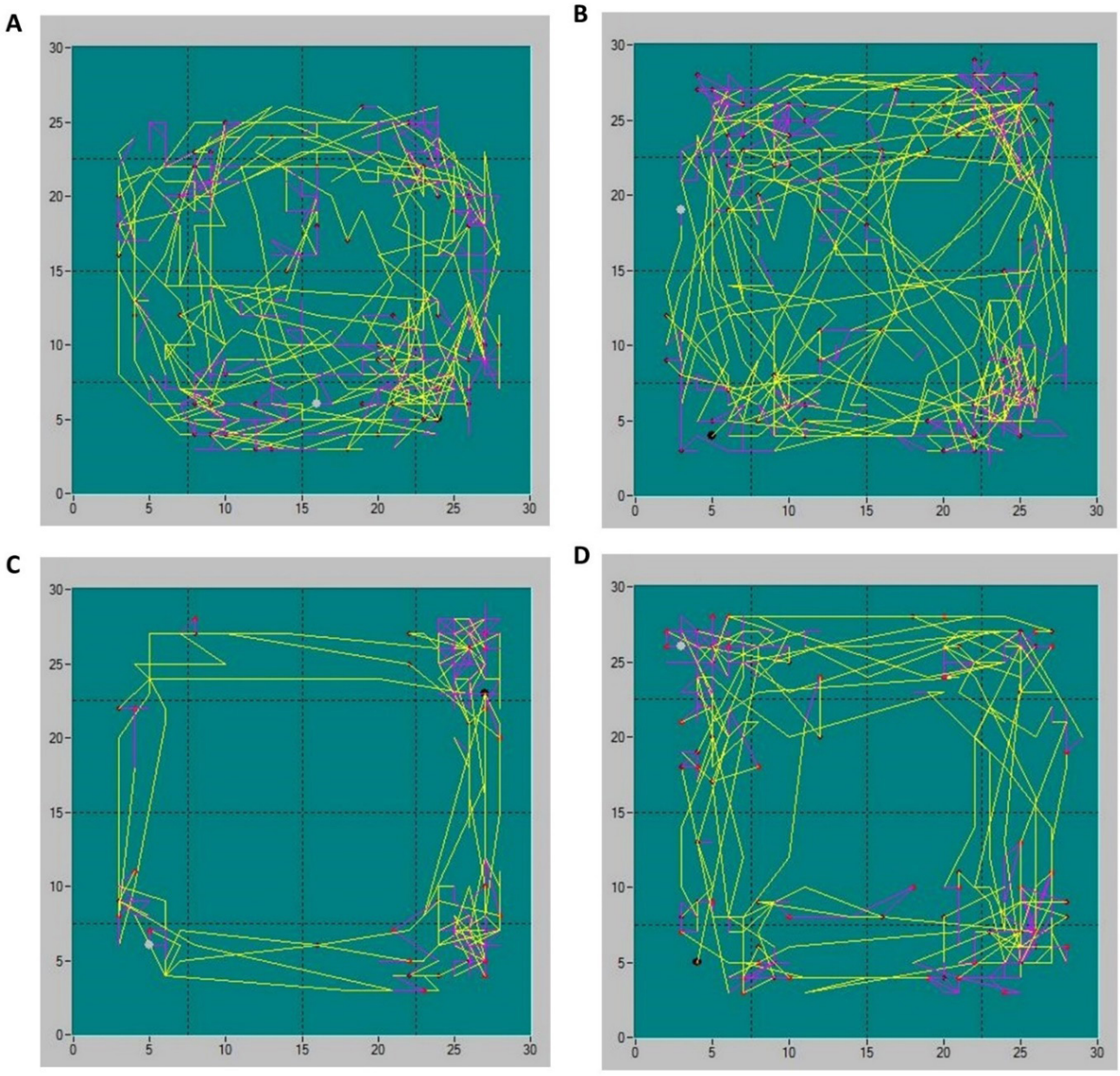

Figure 4. Representative open field traces of horizontal and vertical locomotor activity of control: Sham-SED (A), Sham-PA (B), and experimental: CP/CPPS-SED (C) and CP/CPPS-PA (D) animals.
Each animal was individually tested in the open field for 15 minutes. Horizontal and vertical spontaneous locomotor activity was automatically recorded by an infrared sensor system, and then additionally analyzed using the accompanying software package (Conducta 1.0). For details see the caption in **Fig. 1**.

a number of transitions **(Fig. 6B)** on3rd (vs. 2, p>0.05) and 7th postoperative day (vs. 2, p>0.05).

The partial anxiolytic effect of the exercise pretreatment was observed through a comparison of physically active CP/CPPS-PA and sedentary CP/CPPS-SED animals with prostatitis. There were no statistically significant differences in all OF the test parameters **(Fig. 5-7)** on the 2nd postoperative day between the mentioned groups (CP/CPPS-PA vs. CP/CPPS-SED, p>0.05). On the 3rd postoperative day, the differences between CP/CPPS-SED and CP/CPPS-PA rats were highly statistically significant (p<0.001) in all parameters, except the ambulatory time (p>0.05, **Fig. 5A**). Physically active CP/CPPS-PA rats, compared to the sedentary CP/CPPS-SED rats on the 7th day upon surgery had statistically significant higher ambulatory distance (p<0.001, **Fig. 5A**) and time (p<0.01, **Fig. 5B**), they spent more time in the center of the open field (p<0.01, **Fig. 6A**) and made more rearings (p<0.05, **Fig. 6B**), and also had a lower index of thigmotaxis (p< 0.05, **Fig. 7**).

Elevated plus maze test

Quantitative analysis of the output data derived from the EPM test showed that exercise treatment in Sham-PA rats lead to a statistically significant increase in a number of open/closed arms transitions **(Fig. 8A)** in the 2nd (p<0.001), 3rd (p<0.01), and 7th postoperative day (p<0.001), in comparison with the Sham-SED rats. The same holds true for the time that animal spent in the open

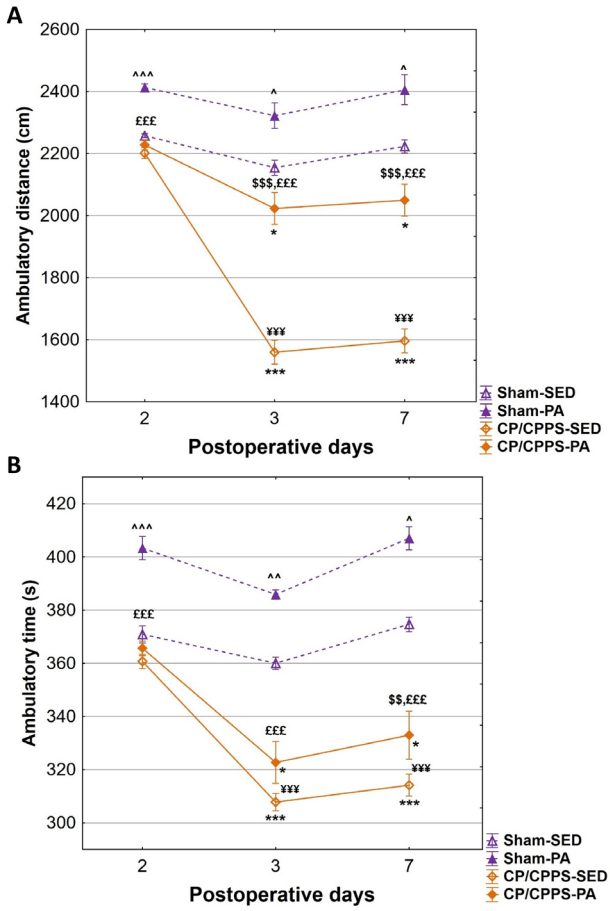

Figure 5. Ambulatory distance (A) and time (B) during open field testing in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD. Statistical significances of between-group differences in the ambulatory distance and time (^p<0.05, ^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, **p<0.01, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

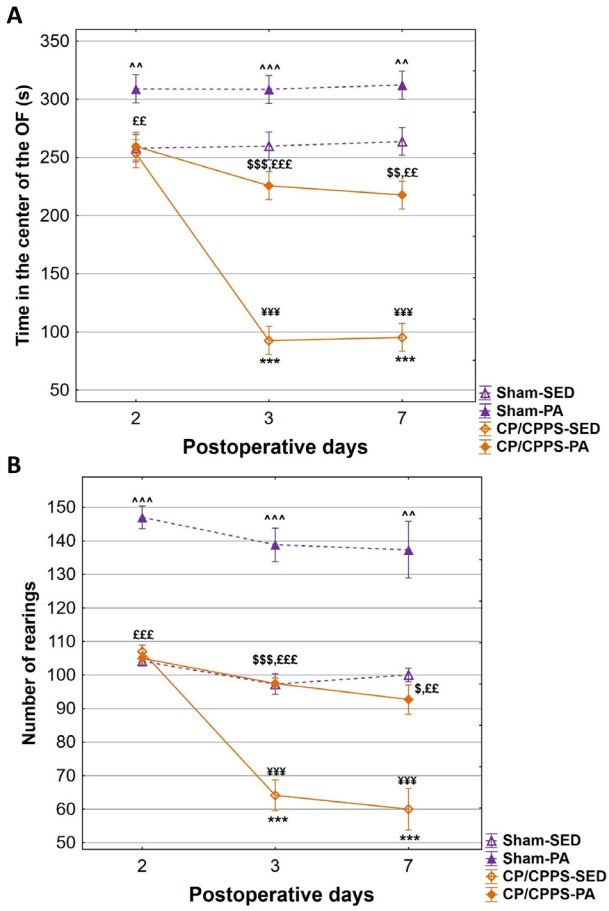

Figure 6. Time spent in the center of the open field (A) and a number of rearing (B) in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
The number of rearings was presented as the number of the rat's hind legs propping up. Values are mean±SD. Statistical significances of between-group differences in time spent in the center of the open field and number of rearings (^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥p<0.05, ¥¥¥p<0.001 vs. Sham-SED; ££p<0,01, £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig 1**.

arms **(Fig. 8B)** on the 2nd (p<0.05), 3rd (p<0.01), and 7th postoperative day (p<0.01). Within-group differences of all EPM test parameters among the Sham-SED and Sham-PA rats were not significantly changed on the 3rd and 7th, in comparison with the 2nd postoperative day.

No differences in EPM test variables were detected between the rats with prostatitis and the control rats on the 2nd postoperative day (Sham-SED vs. CP/CPPS-SED, p>0.05; Sham-PA vs. CP/CPPS-PA, p>0.05, **Fig. 8A, B**). On the other hand, sedentary CP/CPPS-SED, and physically active CP/CPPS-PA rats with prostatitis, compared to the corresponding Sham-SED and Sham-PA controls had a lower number of open/closed arms transitions **(Fig. 8A)** and spent less time in the open arms **(Fig. 8B)** in 3rd (p<0.001) and 7th postoperative day (p<0.001). Also, there was a highly significant reduction of the number of open/closed arms transitions **(Fig. 8A)**, as well as the time spent in the open arms **(Fig. 8B)** within the CP/CPPS-SED and CP/CPPS-PA rats on the 3rd (p<0.001) and 7th postoperative day (p<0.001).

However, exercise (CP/CPPS-PA group) significantly increased the number of open/closed arms transitions **(Fig. 8A)** on the 3rd (p<0.05), as well as 7th day upon the surgery (p<0.05), in comparison to the sedentary CP/CPPS-PA animals. Also, there is a highly significant increase in the time animals spent in the open arms **(Fig. 8B)** in CP/CPPS-PA rats on the 3rd (p<0.01) and 7th day (p<0.001) upon surgery, in comparison with the CP/CPPS-SED rats.

Light/dark test

Sham-PA animals spent statistically significantly more time in the light compartment on all postoperative days (p<0.05, **Fig. 9A**), in comparison with the Sham-SED rats. The same observation concerning the number of L/D transitions **(Fig. 9B)** on the 2nd (p<0.05), 3rd (p<0.01), and 7th postoperative day (p<0.01). Within-group differ-

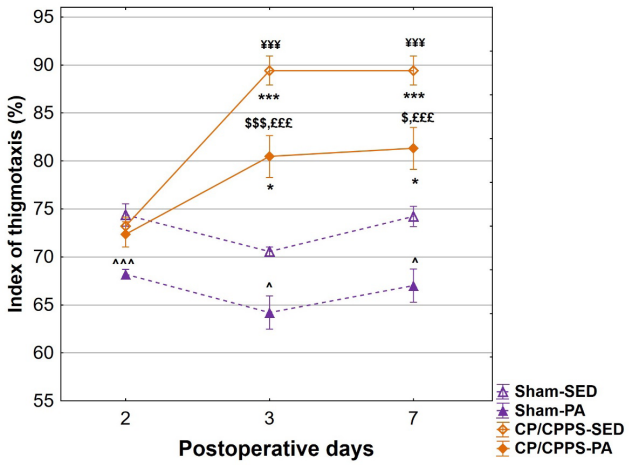

Figure 7. Index of thigmotaxis in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
The index of thigmotaxis was calculated as a ratio between the distance of rat ambulatory distance in the peripheral zones and the total ambulatory distance and expressed in percentages (%). Values are mean±SD. Statistical significances of between-group differences in the index of thigmotaxis (^p<0.05, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01 vs. CP/CPPS-SED), as well as within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption to **Fig. 1.**

ences of L/D test parameters among the Sham-SED and Sham-PA rats were not significantly changed on the 3rd (vs. 2, p>0.05), and 7th postoperative day (vs. 2, p>0.05).

The time that CP/CPPS-SED and CP/CPPS-PA animals spent in the light compartment **(Fig. 9A)** was significantly shorter, compared to Sham-SED and Sham-PA groups on the 3rd (p<0.001), as well as the 7th day upon the surgery (p<0.001). The same holds for the number of L/D compartment transitions **(Fig. 9B)** on the 3rd(p<0.001), as well as, on the 7th day upon surgery (p<0.001). Within-group differences among the CP/CPPS-SED rats were statistically significant regarding the time in the light compartment of the L/D test **(Fig. 9A)**, as well as the number of L/D transitions **(Fig. 9B)** on the 3rd (vs. 2, p<0.001) and 7th postoperative day (vs. 2, p<0.001). A similar observation was made in CP/CPPS-PA group on the 3rd (vs. 2), and the 7th (vs. 2) postoperative day, regarding the time that the animal spent in the light compartment of the L/D test (p<0.001, **Fig. 9A**), as well as the number of L/D transitions (p<0.05, **Fig. 9B**). There was no statistically significant difference in these parameters in 2nd day between the mentioned groups (p>0.05, **Fig. 9A, B**).

Additionally, chronic aerobic exercise in CP/CPPS-PA rats, compared to the sedentary CP/CPPS-SED rats, on the 3rd (p<0.05), as well as on the 7th day upon intraprostatic injection (p<0.05), led to a statistically significant increase in the time spent in the light compartment of the L/D test **(Fig. 9A)**, and also in the number of the L/D transitions **(Fig. 9B)**. There was no statistically significant difference in the parameters derived from the L/D test on the 2nd day between these groups (CP/CPPS-PA vs. CP/CPPS-SED, p>0.05, **Fig. 9A, B**).

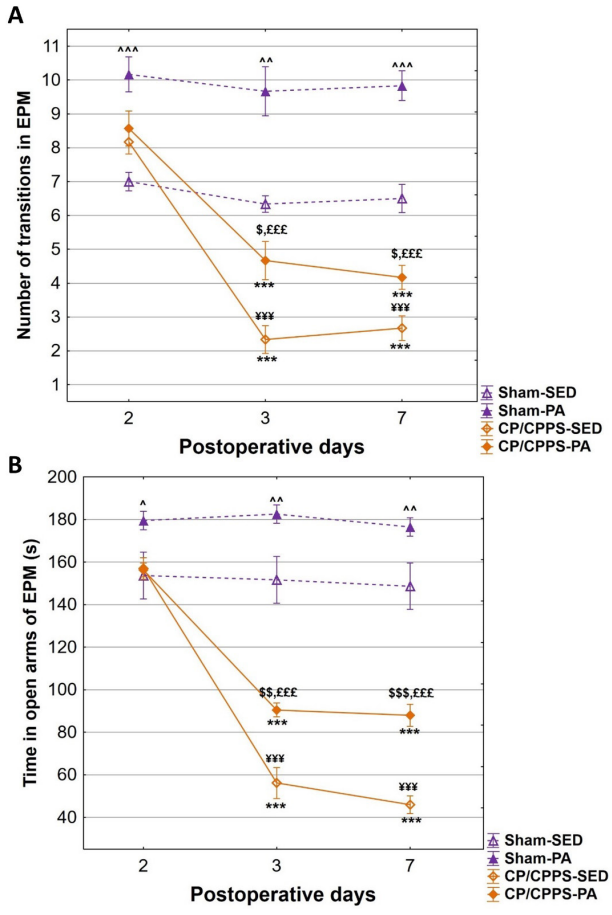

Figure 8. A number of transitions between the opened and closed arm (A) and the time spent in the open arms (B) of elevated plus maze test (EPM) in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD.Statistical significances of between-group differences in time spent in the light compartment and the number of transitions between the light and dark compartment of the L/D test (^p<0.05, ^^p<0.01 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05 vs. CP/CPPS-SED), as well as, within-group differences (*p<0.05, ***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

DISCUSSION

Considering that chronic pelvic pain and discomfort are the most prominent symptoms among the patients suffering from CP/CPPS (Krieger et al., 1999), the occurrence and dynamics of experimental CP/CPPS development in our study are confirmed by functional test, i.e. pain threshold measurement. Namely, intraprostatic injection of 3% λ-carrageenan significantly reduced scrotal mechanical pain thresholds in rats with CP/CPPS (both SED and PA group) on the 3rd and the 7th day upon surgery, in comparison with the respective control Sham operated rats (receiving 0.9% saline). The rats with developed experimental CP/CPPS showed increased anxiety-like behavior, compared to the corresponding sham operated controls.

Results of the present study showed that 30-day long exercise on the treadmill led to amelioration of anxiety-re-

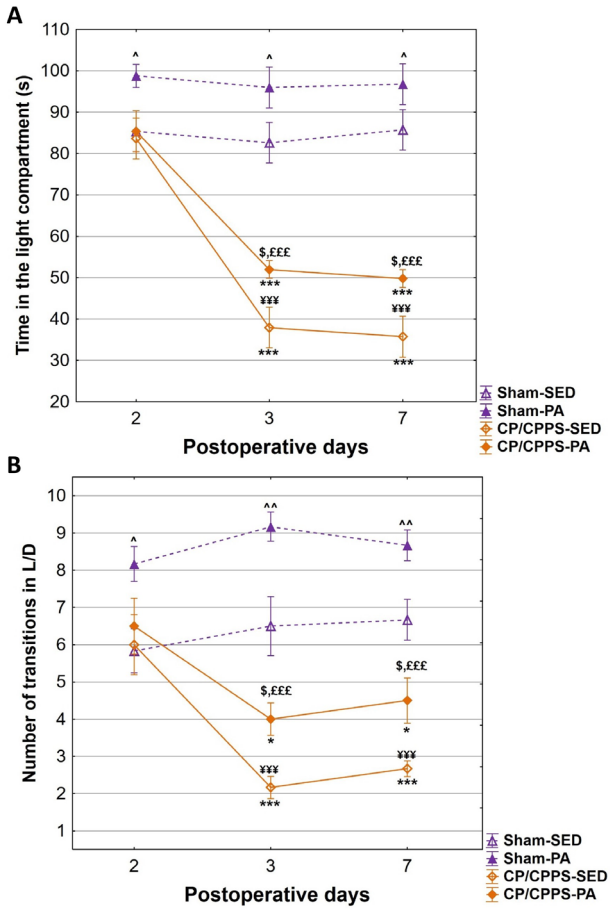

Figure 9. The time spent in the light compartment (A) and the number of transitions between the light and the dark compartment (B) of light/dark (L/D) test in control: Sham-SED, Sham-PA, and experimental: CP/CPPS-SED, CP/CPPS-PA animals.
Values are mean±SD. Statistical significances of between-group differences in number of transitions and time spent in the opens arms of EPM (^p<0.05, ^^p<0.01, ^^^p<0.001 vs. Sham-SED; ¥¥¥p<0.001 vs. Sham-SED; £££p<0.001 vs. Sham-PA; $p<0.05, $$p<0.01, $$$p<0.001 vs. CP/CPPS-SED), as well as, within-group differences (***p<0.001 vs. 2) were estimated by one-way ANOVA with Tukey-Kramer LSD post hoc test. For details see the caption in **Fig. 1**.

lated and pain-related behavior in rats with CP/CPPS, as it was evident by favorable modulation of all parameters in the applied battery of ethological tests for the assessment of anxiety-like behavior. Thus, chronic aerobic physical activity on the treadmill is a potent non-pharmacological therapeutic option for anxiety in CP/CPPS.

Results obtained in our study by the functional behavioral testing could be explained by several potential mechanisms. The heterogeneous group of symptoms that characterize CP/CPPS is the reason for the still unknown and unclear etiopathogenesis, although numerous risk factors are identified, including intraprostatic urinary reflux, endocrine disbalance, inflammation through the CNS, psychological and hereditary factors, immunological disbalance and muscle-skeletal dysfunctions (27). Statistically significant changes in serum cortisol levels have been found in patients with CP/CPPS (28), while the hypothalamic-pituitary-adrenal (HPA) axis dysfunction is hypothesized to be one of the main mechanisms that links CP/CPPS with anxiety (29). We also previously found that elevated levels of corticosterone in the rat's serum have a positive correlation with lipid peroxidation and oxidative stress in the cortex, thalamus and hippocampus (20). Therefore, corticosterone, by increasing the level of available glucose in the brain, and via the impaired signaling pathways on the other hand, promotes the spontaneous generation of free oxygen radicals, increases pro-oxidant genes transcription and reduces antioxidant defense mechanisms. Impaired redox balance, on the other hand, could mediate the development of anxiety–related behavior, as it has been previously linked in basic and clinical studies (30).

Antinociceptive effect of physical activity observed in our study by mechanical pain threshold tests, could be explained by the increased concentration of endogenous cannabinoids in the serum, which has been observed in humans and animals after running and cycling (31). Cannabinoids are known for their analgesic effects (32). Physical activity reduces pain sensitivity through changes in neuroendocrine and autonomic nervous functions, especially through increasing levels of endogenous endorphins and modifying neurotransmitter systems including dopaminergic, noradrenergic and serotonergic systems (33). Additionally, there is an increase in the plasma nitrogen oxide (NO) concentration instantly after physical activity (34) and the antinociceptive effect of NO has been demonstrated (35).

In a study performed by Dybowski et al. (36), it has been shown that the symptoms of anxiety can worsen the pain severity, the degree of voiding problems, as well as quality of life in patients with prostatodynia. These data explain the potential mechanisms of pelvic pain development, but also indicate that anxiety is not only a consequence of chronic pain in CP/CPPS, but that it can also be one of the etiological factors for CP/CPPS. Although the effects of physical activity on numerous different physiological and psychological factors are proven, the precise mechanism of the anxiolytic effect is still unclear. This effect can be partially explained by the favorable influence of physical activity in the regulation of stress response, through the HPA axis stabilization (37) or glucocorticoid concentration reduction, but also through the stimulation of neurogenesis and angiogenesis by upregulated brain-derived neurotrophic factors (BDNF) synthesis, which is important for proper brain functioning and anxiety reduction (15). Given that CP/CPPS is characterized by an increased ROS generation and intense oxidative stress damage of neurons which negatively affect behavioral performances (20), physical activity with proven antioxidant effect can lower the lipid peroxidation level, reduce ROS generation, and ameliorate behavioral performances (38).

There is a wide range of therapeutic modalities for treating CP/CPPS, acting on the different pathophysio-

logical mechanism or directly on the manifested symptom, which reflects the complexity of this syndrome. Giubilei et al. (39) performed a randomized prospective trial to investigate the effects of physical activity on patients with CP/CPPS, and participants in the aerobic exercise group showed reduced pain and anxiety levels in comparison to subjects in the placebo/stretching group. These results are by our findings derived in an experimental setting. Planned and dosed physical activity is often recommended to reduce the harmful effect of chronic inflammation and chronic painful conditions in the body (40).

Conclusions

The results of the present study showed that regular exercise on the treadmill for 30 consecutive days led to the amelioration of anxiety-related and pain-related behavior in rats with CP/CPPS. Thus, chronic aerobic physical activity should be considered a non-pharmacological therapeutic option for treating anxiety in CP/CPPS patients. These experimental findings should be confirmed in further clinical studies in the field of sports medicine and andrology.

Acknowledgments

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

NŠ, AZ, MV, DM, ARM and DH designed the experiment, performed the experiments and drafted the manuscript. DjM and OS contributed to the experimental studies and drafted the manuscript. All authors reviewed and approved the final manuscript.

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FIZIČKA AKTIVNOST MENJA PONAŠANJE POVEZANO SA ANKSIOZNOŠĆU U HRONIČNOM PROSTATITISU/SINDROMU HRONIČNOG PELVIČNOG BOLA: FUNKCIONALNA I BIHEJVIORALNA STUDIJA NA RASKRSNICI EKSPERIMENTALNE FIZIOLOGIJE VEŽBANJA I ANDROLOGIJE

Nikola Šutulović[1], Aleksa Zubelić[1], Djuro Macut[2], Milena Vesković[3], Dušan Mladenović[3], Aleksandra Rašić-Marković[1], Željko Grubač[1], Olivera Stanojlović[1], Dragan Hrnčić[1]*

Sažetak

Uvod: Hronični prostatitis/sindrom hroničnog pelvičnog bola (eng. *Chronic prostatitis/chronicpelvicpainsyndrome*, CP/CPPS) je neinfektivni inflamatorni sindrom, manifestovan brojnim urološkim simptomima, ali često praćen seksualnom disfunkcijom i problemima sa mentalnim zdravljem, uključujući i anksioznost. Studije su pokazale povoljne efekte hroničnog vežbanja u tretmanu anksioznosti i hroničnog bola, ali njen uticaj na bol i anksioznost u CP/CPPS još uvek nije ispitan. Cilj ovog istraživanja je bio da se utvrde efekti hronične aerobne fizičke aktivnosti na ponašanje povezano sa anksioznošću kod pacova sa eksperimentalno izazvanim CP/CPPS.

Materijali i metode: Odrasli mužjaci pacova soja *Wistar albino* (n=32) su nasumično podeljeni u grupu fizički aktivnih koji su trčali na tredmilu 30 uzastopnih dana (PA, 30 min/dn, brzina: 20 m/min; n=16) i grupu sedentarnih koji su proveli isto vreme u isključenom tredmilu (SED, 30 min/dn, brzina: 0 m/min; n=16). Nakon protokola na tredmilu, u zavisnosti od intraprostatične injekcije tokom operacije (0.9% NaClili 3% λ-karagenin), pacovi su nasumično podeljeni u sledeće grupe (n=8 u svakoj): **Sham-SED** (sedentarni protokol i 0,9% NaCl); **Sham-PA** (protokol vežbanja i 0,9% NaCl); CP/CPPS-SED (sedentarni protokoli 3% λ-karagenin); **CP/CPPS-PA** (protokol vežbanja i 3% λ-karagenin). U cilju praćenja razvoja CP/CPPS i dinamike bola, skrotalni prag bola na mehaničku draž je meren upotrebom elektronskog von Freyestezi-ometra(evF), i to: 2. i 1. preoperativnog dana, kao i 2., 3., i 7. postoperativnog dana. Kako bi se ispitalo postojanje ponašanja povezanog sa anksioznošću, životinje iz svih grupa su podvrgnute bateriji tri etološka testa (test otvorenog polja, test uzdignutog krstastog lavirinta i test svetlo/tama) u 2., 3. i 7. postoperativnom danu.

Rezultati: Pacovi koji su razvili eksperimentalni CP/CPPS, u poređenju sa Sham pacovima, su imali snižen skrotalni prag bola na mehaničku draž u svim ispitivanim postoperativnim danima, a takođe su ispoljavali i ponašanje povezano sa anksioznošću u sva tri etološka testa. Protokol vežbanja na tredmilu, u trajanju od 30 uzastopnih dana je kod pacova sa CP/CPPS doveo do smanjenja ponašanja povezanog sa anksioznošću i do povećanja skrotalnog praga bola.

Zaključak: Rezultati ovog istraživanja su pokazali da je dozirano i planirano vežbanje na tredmilu u trajanju od 30 uzastopnih dana dovelo do smanjenja anksioznosti i bola kod pacova sa eksperimentalnim CP/CPPS.

Ključne reči: CP/CPPS, bol, anksioznost, trening, tredmil, pacov.

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REVIEW

Application of fractal and textural analysis in medical physiology, pathophysiology and pathology

Igor Pantić[1-4], Jovana Paunović Pantić[5], Sanja Radojević-Škodrić[6]

[1] University of Belgrade, Faculty of Medicine, Department of Medical Physiology, Belgrade, Serbia.

[2] University of Haifa, Israel

[3] Ben-Gurion University of the Negev, Faculty of Health Sciences, Department of Physiology and Cell Biology, Israel

[4] Khalifa University of Science and Technology, College of Medicine and Health Sciences, Department of Pharmacology, Abu Dhabi, United Arab Emirates

[5] University of Belgrade, Faculty of Medicine, Department of Pathological Physiology, Belgrade, Serbia.

[6] University of Belgrade, Faculty of Medicine, Department of Pathology, Belgrade, Serbia.

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Correspondence to:

Prof. Igor Pantic, MD, PhD

University of Belgrade, Faculty of Medicine,

Department of Medical Physiology

Visegradska 26/II, RS-11129, Belgrade, Serbia

E-mail: igorpantic@gmail.com; igor.pantic@med.bg.ac.rs

Tel.: +381113607102; Fax: +381113611261

Summary

Fractal and textural analyses represent a rapidly developing class of computational and mathematical methods with potential wide applications in medicine and biology. In recent years, they have been successfully used for the evaluation of subtle alterations in cell and tissue morphology associated with various physiological and pathological processes. It has been shown that cells in early stages of apoptosis exhibit changes in chromatin fractal and textural features. Cellular senescence is also sometimes associated with changes in textural patterns in some cell populations. So far, artificial intelligence approaches based on co-occurrence matrix textural data were successfully implemented in predicting cell damage in in vitro conditions, with artificial neural networks achieving the best performance. In the future, several methodological issues and challenges related to the use of fractal and textural methods will have to be resolved before their introduction into contemporary clinical practice. This concise review focuses on the recent research on the application of fractal and textural methods in experimental physiology and related fields.

Key words: fractal, texture, signal, artificial intelligence.

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INTRODUCTION

Fractal and textural analyses represent a rapidly developing class of computational and mathematical methods with potential wide application in medicine and biology. Since their introduction in the second half of the 20th century, they have been implemented in both fundamental and clinical medical fields and they have contributed to the better understanding of various physiological and pathological processes. The examples include the utilization of fractal computations to describe self-similarity nature of nuclear chromatin, as well as the use of textural features to detect changes of tissue structural entropy during the process of physiological aging. These methods also have a potentially significant diagnostic value in medicine since they may be used to enhance objectivity and the level of automation of various protocols and techniques during pathohistological analysis of tissues and cells (1-5).

Both fractal and textural methods can be used for analyzing various signals in medicine (3-5). These mostly include two-dimensional data such as the ones associated with digital micrographs. One-dimensional signals such as the ones obtained during electroencephalography and electromyography can also be evaluated. Some fractal features of three-dimensional computer models can also be successfully quantified in order to better understand different levels of structural organization related to complex biological systems. In essence, there are very few methodological constraints that limit the use of these techniques in both fundamental and applied medical sciences, and it is estimated that these methods will become important additions to many conventional research protocols in future (1-3).

In recent years, there have been many attempts to integrate these methods with machine learning algorithms in order to develop artificial intelligence systems capable of classification and prediction of biological processes (6, 7). Quantifications of cell textural features can be used to train various machine learning models such as the ones based on a binomial logistic regression, decision trees and random forests. Support vector machines as a supervised machine learning approach also use fractal input data during the model training and testing for classification and prediction accuracy. Finally, numerous artificial neural networks can be created to use these types of data. The examples include relatively simple multilayer perceptron networks, but also complex Bayesian and convolutional neural networks for computer vision in pathology and other medical fields (7-10).

This concise review focuses on recent research on the application of fractal and textural methods to experimental physiology and related fields. We primarily focus on fractal box counting algorithm and textural gray level co-occurrence matrix (GLCM) algorithm since they are probably most frequently used in medical research. We also cover the use of discrete wavelet transform mathematical analysis as a common addition to GLCM. Finally, we discuss our recent results on the potential use of these methods in the development of artificial intelligence models in fundamental and clinical medicine.

FRACTAL AND TEXTURAL INDICATORS

The most important fractal indicators are fractal dimension and lacunarity (11-15). There are numerous ways to calculate fractal dimension from a signal, but today, standard box counting method is most widely implemented. When evaluating a two-dimensional signal, the structure, which is usually binarized, is covered by a series of boxes on different scales, after which the partially or fully filled boxes are counted (15). Subsequently, the software forms a log-log regression line based on these numbers and respective scales, and the value of fractal dimension is computed from the slope of the line. This value for the binarized 2D structure is usually between 1 and 2 and it represents an indirect quantification of complexity and the level of detail. Lacunarity, on the other hand, represents the degree of "gappiness" in the fractal architecture, and it is computed from a variation coefficient of the number of resolution units per box. The values of fractal dimension and lacunarity may be in a strong statistical association for some signals but this is not always the case (13-15).

Textural indicators are computed based on higher mathematical operations and the second order statistical analysis is often required (16-19). Gray level co-occurrence matrix approach is often used for this although today there are many different alternatives. In two-dimensional signals, gray intensity values are allocated to the resolution units after which the value pairs are analyzed taking into account the distance between the units and the orientation (i.e. horizontal, vertical, diagonal). Probably most important textural features that are subsequently calculated are angular second moment, inverse difference moment, entropy, and contrast (16, 17). Angular second moment is often a representation of textural uniformity, whereas inverse difference moment greatly depends on the local homogeneity of resolution units. Entropy depends on the level of chaos and disorder of texture, while the contrast is an indirect quantification of textural heterogeneity. Most textural features are mathematically interrelated although the strength of correlation may vary due to many contributing factors (16-19).

Today, in medicine and biology, as an addition to the traditional GLCM analysis, mathematical wavelet analysis is also sometimes performed. This analysis is based on the mathematical concept of wavelet signals and, among numerous different approaches, Harr discrete wavelet transform probably has the biggest potential in medical research (20, 21). Wavelet coefficient energies computed using this technique are often indirect indicators of textural

heterogeneity and can be used to provide a more detailed insight and explanations on the nature of GLCM changes.

FRACTAL DIMENSION AND TEXTURAL FEATURES OF NUCLEAR CHROMATIN

Nuclear chromatin is a complex macromolecule and many aspects of its structural organization and biophysical principles that govern it are not entirely understood (22-26). The most fundamental level of chromatin organization is based on nucleosomes, a complex of DNA and histone proteins, where the DNA is wrapped around a protein octamer, and forms the so-called beads-on-a-string structure. The nucleosomes with the help of other histones and nonhistone proteins then coil into a filamentous helical system, 30 nm in diameter, designated as chromatin fiber. Chromatin fibers can form large swaths of transcriptionally inactive heterochromatin, but they can also uncoil to the basic beads-on-a-string form and become more active as euchromatin. Higher levels of coiling are also possible and may occur during cell division or other processes (22-26).

When looking at monomer attraction forces within a polymer such as chromatin and their interaction with repulsion forces, traditional models assumed the creation of an equilibrium state, or equilibrium globule as a transition from an initial coil-globule condition (27-29). This equilibrium model of chromatin architecture has long been a dominant view in some scientific circles. At the beginning of the 21st century, an alternative model, based on the fractal globule, has been proposed, and some evidence point to it as being the correct interpretation. Fractal globule possesses some characteristics of self-similarity, a hallmark trait of fractals. In the fractal globule, a distinct territorial organization is observed (unlike mixed structure in equilibrium), and many similar globules can be observed on different scales. Fractal dimension of euchromatin and heterochromatin differ, with euchromatin usually having a higher level of fractal complexity (29). Probably the most important works that in detail explain arguments for the equilibrium and fractal models of chromatin architecture are the ones by Mirny, Kwon and Sung (27, 28).

Textural features of chromatin can be successfully quantified using the above-mentioned gray level co-occurrence matrix method. This technique can be applied both in conventional light microscopy and transmission electron microcopy evaluation of chromatin architecture. So far three most frequently quantified chromatin GLCM indicators have been angular second moment, inverse difference moment and entropy. They are potentially capable of detecting subtle alterations in chromatin distribution during various physiological and pathological processes even if these changes cannot be visualized by an experienced histologist or pathologist (30-32).

Programmed cell death may be followed by pronounced changes in chromatin fractal and textural indicators. One of the first studies describing these changes was published by Losa and Castelli (2005) in human breast cancer cells, where apoptosis was induced by the chemical agent calcimycin (33). It was shown that during the early stages of cell death, a significant loss of chromatin complexity occurs demonstrated by reduction in the fractal dimension. Furthermore, this is followed by a significant increase of GLCM sum entropy and some other textural features. Both fractal and GLCM methods seem to be more sensitive than conventional cytofluorometric techniques in detection of early apoptosis (33).

Some other proapoptotic substances can also change chromatin distribution inside the nucleus which then reflects on GLCM features. The example is oxidopamine, a potent neurotoxin that in certain conditions induces cell death in many different cell populations. In some previous works, it was demonstrated that this compound even in small, sublethal concentrations leads to the reduction of nuclear angular second moment and inverse difference moment (30, 31). These changes are probably related to DNA and chromatin damage that takes place due to the effects of reactive oxygen species and oxidative stress as it has been hypothesized recently (34).

There are three potential explanations for the changes of GLCM and fractal parameters of chromatin in different experimental settings. First, condensation of chromatin that usually occurs during the early stages of cell death may influence both chromatin complexity and texture (33, 34). Condensed, inactive chromatin can probably have lower values of fractal dimension and high values of uniformity and local homogeneity quantified by angular second moment and inverse difference moment, respectively. Second, chromatin marginalization, that is also sometimes present during cell damage and death, may also change chromatin fractality and entropy (35). Finally, subtle changes in euchromatin/heterochromatin ratio that are independent of chromatin condensation and marginalization may also affect fractal dimension of the nucleus particularly knowing that these two forms of chromatin, when considered separately, have different values of complexity (36, 37). Previously, it was demonstrated that within a single cell population such as the hepatocytes, the cells that have very discrete differences in gene expression (periportal versus perivenous hepatocytes) have significantly different values of GLCM chromatin indicators, even though these differences are not visible during conventional microscopy (32). In future, it remains to be seen if fractal and GLCM methods will have a practical application in terms of being used as a part of sensing systems to detect cell damage and death.

FRACTAL AND TEXTURAL ANALYSIS IN AGING RESEARCH

One of the first works to introduce the chaos theory and fractality in aging and senescence research was by Lipsitz and Goldberger (1992), which suggested that the reduction of fractal complexity during aging contributes to the decreased ability of the organism to adapt to physiological stress (38). Since then, there have been numerous studies confirming such loss of complexity in various tissues and cell populations. In many tissues, the reduction of fractal dimension is sometimes followed by an increase in structural degradation and deterioration, which can be indirectly quantified with some textural features such as GLCM entropy. Nowadays fractal and textural methods are frequently used to demonstrate age-related changes in tissue cytoarchitecture, intercellular communication and even individual cells and their organelles (39, 40).

One of the examples where fractal analysis method was used to describe complexity loss of cytoarchitecture during aging is our study on spleen hematopoietic tissue in mice (41). Here we obtained spleen tissue from 64 male Swiss albino mice and divided them into 8 separate age groups. The hematopoietic tissue was stained with nucleic acid specific toluidine blue dye and the results indicated that during aging the fractal dimension of the tissue decreased while the lacunarity increased. Another study which used toluidine blue technique was done with liver tissue, however, here instead of quantifying tissue fractal parameters, we opted for calculation of fractal descriptors of chromatin organization (42). As expected, we showed that there was an age-dependent reduction of the fractal dimension. Age-related changes in tissue and cell fractal parameters are not necessarily present solely in old animals. Postnatal development is also sometimes characterized by a similar reduction of complexity as it was shown in the previous work on Giemsa-stained chromatin in mice spleen follicular cells (43).

Regarding the textural indicators, to the best of our knowledge, the first study in the field of aging research to use the GLCM approach was done by Shamir et al. (2009) on the animal model of Caenorhabditis elegans (44). Here the authors analyzed age-associated changes in muscle tissue and demonstrated changes in entropy and directionality, probably due to structural degradation. The particularly interesting observation of this study was the agreement of the detected changes with gene expression findings, demonstrating the ability of GLCM method to indirectly predict epigenetic processes in cells. This work also discussed two different theories of aging, one focused on stochastic accumulation of damage and the other focused on changes in developmental pathways, as well as the ability of textural analysis to provide indirect evidence supporting the latter (44).

Similarly to the work of Shamir and associates, in 2012, textural entropy increase due to aging was quantified in mice spleen hematopoietic tissue (45). However, in this case, the focus of the study was on cell nuclei rather than on tissue cytoarchitecture. Apart from changes in textural entropy, it was shown that local textural homogeneity of the nuclei (quantified as inverse difference) significantly decreased. Two potential explanations of the changes were provided: one focused on DNA damage accumulation, and the other on epigenetic dysregulation.

Regarding more recent works on the use of GLCM analysis in aging research, one must mention the work of Imakubo et al. (2021) done on Caenorhabditis elegans oocytes. Age related changes of oocyte appearance were evaluated by quantifying various textural features and GLCM correlation feature proved to be a sensitive indicator. This study showed the potential of GLCM algorithm to be used as a part of future biosensors capable of objectively assessing oocyte quality and potentially reducing errors in fertilization (46).

Future applications of fractal and textural analyses in experimental gerontology will mainly be focused on testing the ability of these methods to detect and quantify age-associated accumulation of DNA damage and changes in gene expression. Also, we will need to evaluate the effects of numerous chemical mediators related to aging on fractal and textural characteristics of cells and tissues. Finally, future work will need to include the standardization, validity testing and other aspects of quality assurance of these methods. Both fractal and GLCM algorithms will have to be implemented in different experimental settings, and inter-observer and intra-observer reliability will have to be assessed. Only then will we be able to draw definite conclusions on the scientific value of these methods in aging research.

ARTIFICIAL INTELLIGENCE BASED ON FRACTAL AND TEXTURAL DATA

Artificial intelligence (AI) in essence represents a large group of computation methods, models and algorithms where a machine learns or acquires the ability to perform cognitive functions that at least partially resemble those of a human. There are various types of machine learning (ML) some of which are supervised while others are unsupervised (48, 49). Machine learning in medicine and biology offers new and exciting possibilities of automation and autonomy of numerous diagnostic and research protocols and methods. Even today, various ML-based computer automated diagnostic systems are implemented in both fundamental and clinical medicine, and it is estimated that in future, artificial intelligence will become an important part of decision making in almost every medical discipline (48, 49).

Fractal and textural analyses offer an abundance of data and most of them can be used to train and test AI models. These models can be developed with the aim of

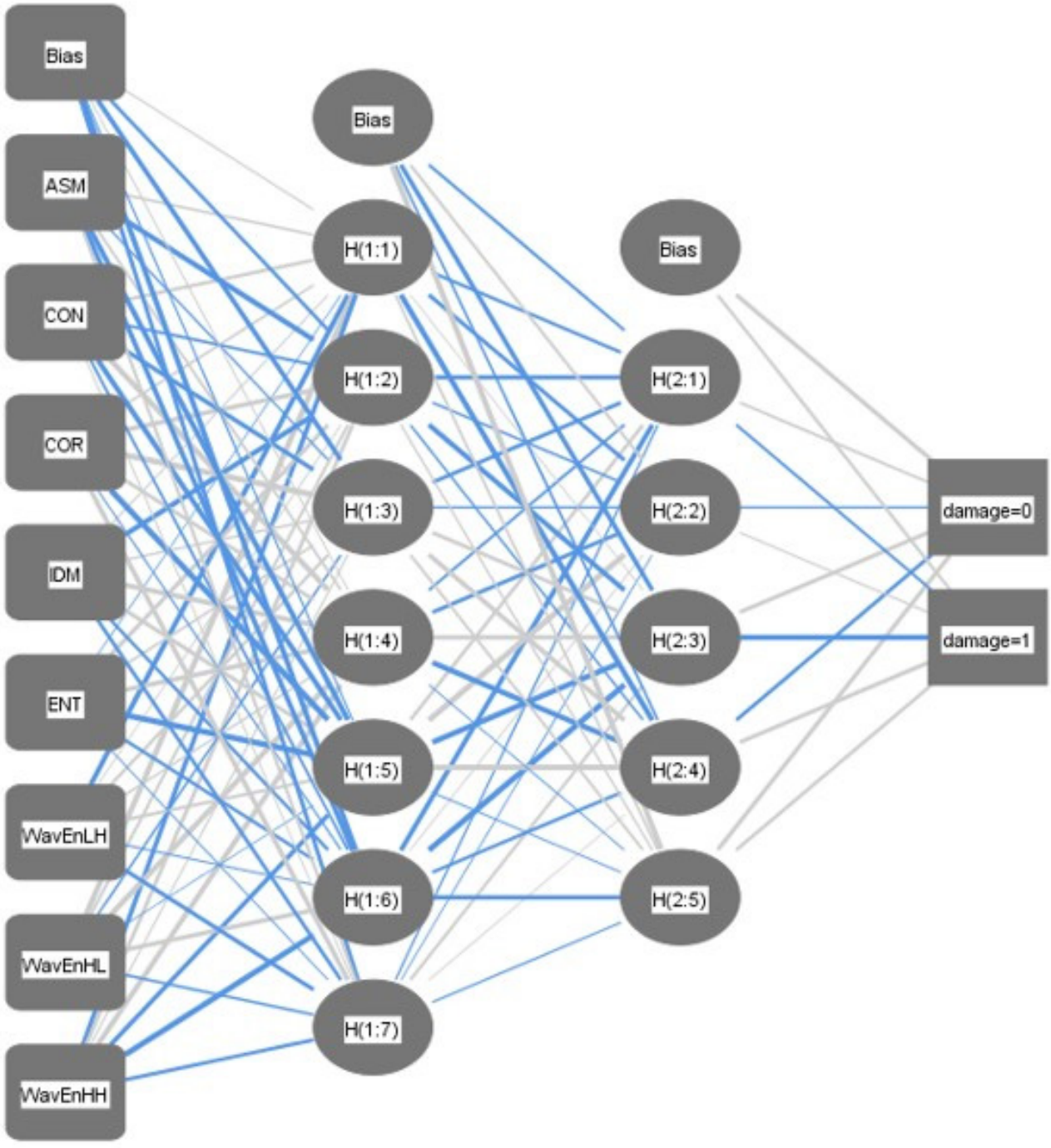

Figure 1. Example of an artificial neural network architecture with 2 hidden layers of neurons that uses GLCM (ASM as angular second moment, CON as contrast, COR as correlation, IDM as inverse difference moment, ENT as entropy) and wavelet coefficient energies (WavEnLH, WavEnHL, WavEnHH) as input data. The network is used to classify damaged (damage=0 as output) and intact cells (damage=1 as output).

classifying biological systems (i.e. cells) based on their physiological properties. They can be also created with the ability of prediction of physiological or pathological phenomena. The common approach would be to use fractal indicators such as fractal dimension and GLCM indicators such as angular second and inverse moments as input data during training. The output data can be a class of cells or tissues formed based on a hallmark trait, or a biochemical parameter as a variable (6-8).

Probably the most feasible AI application of fractal and textural data is their use in training supervised machine learning algorithms. During this type of training, the machine is exposed to the series of input data (i.e. fractal dimension, inverse difference moment etc.) and the resulting output data which is usually binary (6, 7). After many repetitions, the machine learns to associate certain values from the input with the result. In artificial neural networks this learning is done by weight adjustment in hidden layers of neurons **(figure 1)**. Neural networks to this date probably remain the most efficient supervised learning approach to GLCM data. These include simple multilayer perceptrons which, are relatively

```
from sklearn.ensemble import RandomForestClassifier
from sklearn.svm import SVC
from sklearn.linear_model import LogisticRegression
from sklearn.neural_network import MLPClassifier
from sklearn.datasets import make_classification
from sklearn.model_selection import train_test_split
from sklearn import metrics
from sklearn.metrics import RocCurveDisplay

X= df[ [ 'S10AngScMom', 'S10Contrast', 'S10Correlat', 'S10InvDfMom' ] ]
y = df['damage']
X_train, X_test, y_train, y_test = train_test_split(X, y, test_size=0.2)
my_model = clf = MLPClassifier(solver='lbfgs', alpha=1e-5, hidden_layer_sizes=(5, 3), random_state=1)
my_model.fit(X_train, y_train)
y_predict = my_model.predict(X_test)
accuracy = metrics.accuracy_score(y_test, y_predict)
print('Estimated accuracy of the MLP model is', accuracy)
ax = plt.gca()
rfc_disp = RocCurveDisplay.from_estimator(my_model, X_test, y_test, ax=ax, alpha=0.8)
rfc_disp.plot(ax=ax, alpha=0.8)
plt.show()
```

```
Estimated accuracy of the MLP model is 0.835
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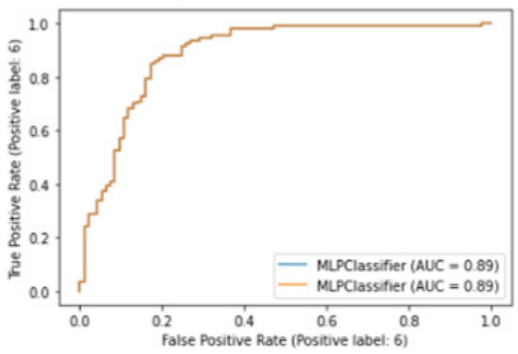

Figure 2. Example of the programming code for the multilayer perceptron AI model that uses GLCM angular second moment, inverse difference moment, correlation and contrast features as input data. The model has the classification accuracy of 83% in separating damaged from intact cells and area under the ROC curve of 0.89. The code was written in Python programming language and Scikit-learn library.

easy to develop in contemporary programming languages **(figure 2)**, and also convolutional neural networks frequently used form computer vision. Other possible supervised learning algorithms include the ones based on decision trees **(figure 3)**, random forest, support vector machines, principal component analysis or binomial logistic regression (6, 7).

Our recent publication on the application of artificial intelligence methods focused on the ability of GLCM-trained machine learning models to identify cell damage caused by sublethal doses of ethanol (7). As input data, we used GLCM contrast, GLCM correlation, angular second moment, inverse difference moment and GLCM variance. Three AI approaches were evaluated: multilayer perceptron neural network, binomial logistic regression, and random trees. The results indicated that the multilayer perceptron had the highest classification accuracy and the area under the receiver operating characteristic curve suggesting that this approach had the highest discriminatory power when separating damaged from intact cells (7).

In future, before using AI algorithms based on fractal and GLCM data in practice, one will have to resolve several limitations related to training, testing and validity of these methods. Many AI algorithms are essentially "black box" models meaning that it is difficult, if not impossible to interpret the inner mechanisms that govern the model (apart from input and output data). This may especially be true of artificial neural networks, but it may also be applied to support vector machines and random forests. Second, rigorous quality assurance of both fractal and GLCM method, as well as the future biosensors based on AI must be performed. Finally, issues regarding data validity and sample size must be resolved particularly knowing that in some medical scientific areas it may be difficult to obtain data large enough form training a machine learning model. Only after these challenges are adequately resolved, we will be able to include GLCM and fractal-based AI algorithms in clinical practice.

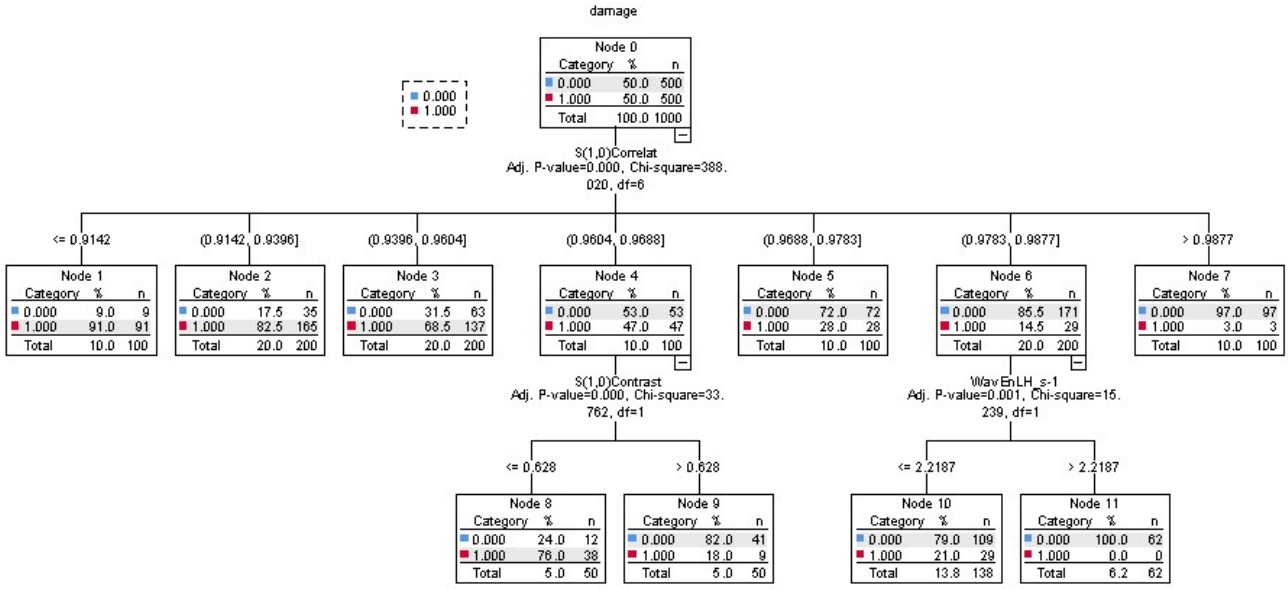

Figure 3. Machine learning model based on decision tree that uses chi-square automatic interaction detection to make decisions from GLCM and wavelet data.

CONCLUSION

Fractal and textural analyses are contemporary and innovative computational approaches with potentially wide application in signal analysis. Previously, they have been successfully applied in detecting subtle changes in cell morphology and intercellular communication associated with aging and apoptosis. Data obtained from fractal and textural analyses can be used for training and evaluation of various machine learning models. So far, artificial intelligence approaches based on co-occurrence matrix data were successfully implemented in predicting cell damage in *in vitro* conditions, with artificial neural networks achieving the best performance. In future, several methodological issues and challenges related to the use of fractal and textural methods will have to be resolved before their introduction to contemporary clinical practice.

Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

IP conceptualized the manuscript, JPP and SRŠ did literature screening. All authors participated in manuscript writing and provided critical intellectual input.

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PRIMENA FRAKTALNE I TEKSTURALNE ANALIZE U MEDICINSKOJ FIZIOLOGIJI, PATOFIZIOLOGIJI I PATOLOGIJI

Igor V. Pantić[1,2,3,4], Jovana D. Paunović Pantić[5], Sanja M. Radojević-Škodrić[6]

Sažetak

Fraktalna i teksturalna analiza predstavljaju klasu računarskih i matematičkih metoda koje se brzo razvijaju, i koje se odlikuju potencijalno širokom primenom u medicini i biologiji. Poslednjih godina se uspešno koriste za procenu diskretnih promena u morfologiji ćelija i tkiva povezanih sa različitim fiziološkim i patološkim procesima. Prethodno je pokazano da se pojedine ćelije u ranim fazama apoptoze odlikuju promenama u fraktalnim i teksturalnim karakteristikama jedarnog hromatina. Ćelijsko starenje je takođe ponekad povezano sa promenama teksturalnih obrazaca u nekim ćelijskim populacijama. Do sada su algoritmi veštačke inteligencije zasnovani na teksturalnim podacima dobijenim iz matriksa simultanog pojavljivanja sivih intenziteta rezolucionih jedinica, uspešno primenjeni za predviđanje oštećenja ćelija u in vitro uslovima, pri čemu su neuronske mreže postigle najbolje performanse. U budućnosti će morati da se reši nekoliko metodoloških pitanja i izazova u vezi sa upotrebom fraktalnih i teksturalnih metoda pre njihovog uvođenja u savremenu kliničku praksu. Ovaj kratki pregledni rad se fokusira na nedavna istraživanja o primeni fraktalnih i teksturalnih metoda u eksperimentalnoj fiziologiji i srodnim oblastima.

Zaključak: Studenti medicine su bili sigurniji u svoju EZP u poređenju sa studentima sporta. Moguće je da faktori koji utiču na bolju EZP zavise od vrste studija.

Ključne reči: fraktal, tekstura, signal, veštačka inteligencija.

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REVIEW

Preoperative anxiety: an important, but neglected issue

Ksenija Jovanović[1, 2], Nevena Kalezić,[1, 2] Sandra Šipetić Grujičić[3]

[1] Center for Anesthesiology and Resuscitation, University Clinical Center of Serbia, Belgrade, Serbia
[2] Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[3]Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

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Correspondence to:
Ksenija Jovanović, Center for Anesthesiology and Resuscitation, University Clinical Center of Serbia, Pasterova 2 St., 11000 Belgrade;
Email: ksenia.stevanovic@gmail.com
tel: +381668300966

Summary

Preoperative anxiety refers to a state of discomfort caused by an upcoming operation, anesthesia, the disease itself, or hospitalization. Although the reported incidence of preoperative anxiety varies in a wide range, the majority of surgical patients experience at least some degree of anxiety preoperatively and it can be frequently seen in the preoperative setting. The specific factor that contributes most to the emergence of perioperative anxiety has not been identified yet. Still, older age and female gender have been consistently marked as independent predictors of preoperative anxiety. Several different scales have been proposed in recent decades for the measurement of preoperative anxiety. Since high-level preoperative anxiety is associated with severe postoperative complications and can significantly alter surgical treatment outcomes, this issue should not be neglected. Timely identification of anxious patients may reduce the incidence of preoperative anxiety and its possible consequences.

Keywords: preoperative anxiety; postoperative complications; incidence; measurement.

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INTRODUCTION

The term anxiety is derived from the Latin word *anxietas*, meaning concern, i.e., from Greek ανησυχία – worry, restlessness. Anxiety disorders have been known for thousands of years but were acknowledged as a separate diagnostic entity within psychiatric diseases only in the late 20th century. (1) Nowadays, those mental disorders are defined as: *"non-psychotic mental disorders in which anxiety is the only one or the leading symptom and is not caused by organic brain diseases or other psychiatric diseases"*, (2) i.e. mental disorders in which anxiety represents the most prominent symptom. (3)

The preoperative period is a stressful time, characterized by the emergence of specific emotional, cognitive and psychological responses to the anticipation of the upcoming surgery. (4) Since the feeling of anxiety arises due to the anticipation of a potentially unfavorable, risky, or unpleasant event or outcome, preoperative anxiety refers to a state of discomfort caused by an upcoming operation, anesthesia, the disease itself, or hospitalization. (5) It has been shown that preoperative anxiety can significantly alter surgical treatment outcomes. (6) Thus, the present review aims to briefly summarize the current knowledge of the basic characteristics and importance of preoperative anxiety.

THE INCIDENCE OF PREOPERATIVE ANXIETY

In a study by Kuzminskaitė et al. (7) that included 149 patients scheduled for elective non-cardiac surgery only 12.6% of patients felt anxious preoperatively. On the other hand, several recent studies revealed thatpreoperative anxiety could be seen in over 70% of surgical patients. (8-11) Furthermore, a cross-sectional study conducted by Aust et al. in 2018 that included over 3000 adult surgical patients showed that only 8% of patients did not feel anxious at all during the preoperative period. (12) Thus, based on the available literature data, the reported incidence of preoperative anxiety varies to a large degree, depending on several factors, such as the type of the study, the population in question, the geographical region where the study was conducted, the measurement scale and the type of the surgery. Still, most authors agree that the majority of surgical patients experience at least some degree of anxiety preoperatively.

THE RISK FACTORS FOR PREOPERATIVE ANXIETY

When it comes to the factors that contribute to the development of preoperative anxiety, the literature data are inconsistent. Many patients' characteristics have been associated with the occurrence of preoperative anxiety, such as demographic factors, socio-economic factors, psychosocial factors, as well as the type of surgery/anesthesia. Among these factors, age, female gender, worse socio-economic status, lower level of education, more extensive surgery, and previous bad experiences with surgery and anesthesia were most often associated with the onset of preoperative anxiety. (8, 13-17) Although older age and female gender were consistently marked as independent predictors of preoperative anxiety in several studies, (18-20), the specific factor that contributes most to the emergence of preoperative anxiety has not been identified yet. This suggests that additional studies are required to further clarify which patients' characteristics and surgical factors are responsible for the development of preoperative anxiety so that an individual approach to the assessment and/or therapy of preoperative anxiety in those subgroups of patients can be applied to reduce the incidence of preoperative anxiety. (21)

MEASUREMENT OF PREOPERATIVE ANXIETY

Basically, preoperative anxiety can be measured using two different approaches: objectivelyand by subjective scales. Objective methods include indirect assessment of anxiety levels through the estimation of the degree of sympathoadrenal system activation, and, more directly, by measuring stress hormones. An increase in heart rate, blood pressure,plasma cortisol andcatecholamines values, as well as a decrease in heart rate variability and oxygensaturation, were described as consequencesof higher levels of preoperative anxiety. (22-24) For instance, a study by Balasubramaniyan N. et al. from 2016 investigated the association of cardiovascular alterations and anxiety in 80 hypertensive patients undergoing dental procedures. The authors demonstrated that high-level preoperative anxiety is associated with significant increases in heart rate and systolic blood pressure. (25) Furthermore, newer studies suggest that the measurement of catechol-o-methyltransferase may be useful inidentification of patients with preoperative anxiety. Namely, it has been shown that anxious patients have lower levels of this enzyme (and thus higher levels of circulating catecholamines) compared to the patients who are not anxious during the preoperative period. (26) The main disadvantage of objective techniques for anxiety measurement is that they are time-consuming and not easy to apply in a busy daily practice, which is why they are rarely used nowadays. Recently described positive correlation between subjective and objective methods of anxiety measurement, (27) along with the development of a variety of reliable subjective (and easy-to-use) scales limit the routineapplication of objective anxiety measurements even further.

On the other hand, the level of preoperative anxiety can also be assessed using the subjective (self-descriptive) scales. The most commonly usedarethe Hospital Anxiety and Depression scale (HAD), (28) Visual Ana-

logue Scale for Anxiety (VAS-A), the State-trait anxiety inventory (STAI), (29) the Amsterdam Preoperative Anxiety and Information Scale (APAIS), (30) Linear Analog Anxiety Scale (LAAS) (31) and Multiple Affect Adjective Check List (MAACL), (32), and each one of them has its specific advantages and flaws.

The VAS-A is certainly the simplest one to use. Created in 1976, the scale consists of a 100 mm horizontal line, which is marked with zero at its left end (meaning: "I am not anxious at all") and with 100 at its right end (meaning: "I am extremely anxious"). The subjects are asked to indicate the level of anxiety they feel at the moment by drawing a vertical line on the scale, with the line drawn closer to the right end indicating a higher degree of anxiety. The main disadvantage of this scale is reflected in the fact that it doesn't have a precisely established cut-off point. Still, according to Facco et al., (33) a score over 46 mm represents a clinically significant level of anxiety, while a score of ≥ 70 mm correlates with very high levels of anxiety. (34)

The original Dutch version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS), developed in 1996 by Moerman et al., (30) nowadays represents a valuable and widely accepted instrument for the measurement of preoperative anxiety. As a matter of fact, some experts even consider the APAIS scale as a "gold standard" for the identification of anxious patients preoperatively. (12, 35) The scale consists of six questions, grouped into two components: the first one measures anxiety (related to anesthesia and surgery, four questions) and the second assesses the need for information (the two remaining questions). The questions are scored from 1 to 5 based on the Likert method, where 1 means "not at all" and 5 means "extremely". The total score ranges from 4 to 20 points for the part of the scale related to anxiety and from 2 to 10 points for the part of the scale related to the need for information. A higher score indicates a higher level of anxiety and a greater need for information. The scale has been translated and validated into several languages - French, Malay, Spanish, and Chinese, (36-39) and, since recently, the scale has even been adapted and validated among the Serbian population. (40) The main limitation of the APAIS scale, as stated by the authors of the original scale, is its inability to distinguish anxiety related to anesthesia from anxiety related to surgery. Due to its different and specific structure, the Serbian APAIS version has overcome this disadvantage: anesthesia- and surgery-related anxieties can be separately assessed.

The selection of the most appropriate scale remains difficult. This process should be guided by the time available for the assessment of preoperative anxiety, patients' characteristics and comorbidities, physicians' preferences, and the reliability of a specific scale. Still, it should be emphasized that the choice of the scale is not as important as the timely identification of anxious patients and the application of measures to lower the level of preoperative anxiety.

THE CONCEQUENCES AND SIGNIFICANCE OF PREOPERATIVE ANXIETY

The significance of preoperative anxiety is clearly reflected in the fact that it has been designated as by far the worst aspect of preoperative care by the majority of surgical patients (worse even than the pain), as evidenced by the results of a large observational study by Walker et al. from 2016, which included over 15,000 patients. (41)The importance of preoperative anxiety is also emphasized by the fact that the latest guidelines of the European Society of Anesthesiology (ESA) from 2018 included the assessment of preoperative anxiety as an unavoidable step and a part of the routine preoperative preparation and evaluation of surgical patients. (42) Furthermore, it has been shown thatif the level of preoperative anxiety exceeds normal ranges, it can lead to numerous consequences. First of all, anxiety can significantly affect the patient's psychological status, leading to psychological alterations, from nervousness to agitation. Moreover, mediated through sympathetic, parasympathetic, and endocrine stimulation, preoperative anxiety may contribute to the development of numerous complications, starting from minor ones - in the form of inability to cannulate peripheral veins due to sympathetic vasoconstriction, through delayed relaxation of the masticatory muscles and increased cough reflex during the induction of anesthesia, hemodynamic fluctuations and an increased need for anesthetic agents intraoperatively, up to the more frequent occurrence of nausea and vomiting, an increased need for analgesics, prolonged mechanical ventilation and hospitalization in the postoperative period, as well as an increased risk of infections. (43-46) In addition, it has been shown that preoperative anxiety is an independent predictor of increased in-hospital mortality and morbidity from cardiovascular diseases in patients undergoing cardio-surgical operations. (44) Also, a strong correlation was found between preoperative anxiety and subsequent dissatisfaction with surgical treatment. (47) Finally, our previous study (6) demonstrated that high-level preoperative anxiety is associated with severe postoperative complications (postoperative mental disorders, pulmonary complications, and postoperative nausea).

MANAGEMENT OF PATIENTS WITH PREOPERATIVE ANXIETY

Although a lot is known about preoperative anxiety, the best way for managingthose patients is still unknown and this issue represents a matter of debate inperioperative medicine. This is further emphasized by the fact that currently there are no guidelines that provide clear guidance on the prevention and/or treatment of patients with preoperative anxiety. (21) So, the question remains: *"What can we do?".*

Nowadays, a variety of measures and interventions can be applied to reduce the incidence of preoperative anxietyand alleviate its symptoms. Those include patient counseling and education, pharmacotherapy, and, recently more popular alternative methods. Patient education mainly represents the primary and the most commonly applied method to reduce the incidence of preoperative anxiety. Even though the effectiveness of these measures has been demonstrated by numerous studies, (48-50) there are dilemmas related to the choice of patient education methods. Specifically, while some authors advocate education by means of phone, written (typed) or video materials, (51, 52) results of other studies have shown that personal contact with patients and verbal means significantly relieve anxiety symptoms. (53, 54) Furthermore, modern-day techniques, such as mobile applications, (55)internet content, (56) and even virtual reality, (57) have been shown to be effective in the management of anxious patients. Still, in some patients, educational efforts will not bring good results, whether due to the patient's characteristics, time limits, or the complexity of anxiety causes. In such cases, conventional pharmacological approach may be useful: benzodiazepines,sympatholytics, gabapentinoids, and antidepressants. Recently it has been shown that even melatonin can have a beneficial effect on reducing the degree of preoperative anxiety. (58) Besides the fact that some authors evenrefute the anxiolytic effects of frequently used medications, it should be emphasized thatpharmacotherapy has its limitations and increases treatment costs. This is the reason why alternative and less expensive methods for the management of anxious patients have lately gained a lot of interest. Beneficial effects of aromatherapy, (59, 60) music therapy, (61) acupuncture, (62) and even therapeutic inhaled essential oils (63) have been described. Still, to the best of our knowledge, currently, there are no studies that have compared the effects of all available measures. Thus, the best and the most effective method for the reduction of anxiety in patients during the preoperative period is yet to be found. Until further research is conducted, clinical evaluation is of greatest importance and interventions should be tailored according to the patient's individual needs.

Conclusion

Preoperative anxiety can greatly affect the outcome of surgical patients' treatment. The present review briefly summarizes the current knowledge on the topic and emphasizes the importance of preoperative anxiety. It also suggests that this issue should not be neglected. Given that anxiety is a frequent problem during the preoperative period, both for patients and for medical professionals, it is necessary to perform timely identification of anxious patients and to apply the appropriate measures in order to reduce the incidence of preoperative anxiety and its possible consequences.

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Author Contributions

1) the conception or design of the work: K.J., N.K., S.S.G.; 2) the acquisition: K.J., N.K., S.S.G.; 3) analysis, or interpretation of data: K.J., S.S.G.; 4) preparing the draft of the manuscript: K.J., N.K.; 4) interpretation of revised version of manuscript: K.J., S.S.G.

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PREOPERATIVNA ANKSIOZNOST: VAŽAN, ALI ZAPOSTAVLJEN PROBLEM

Ksenija Jovanović[1, 2], Nevena Kalezić[1, 2,] Sandra Šipetić Grujičić[3]

Sažetak

Preoperativna anksioznost se odnosi na stanje nelagodnosti uzrokovano predstojećom operacijom, anestezijom, samom bolešću ili hospitalizacijom. Iako incidencija preoperativne anksioznosti varira u širokom rasponu, većina hirurških pacijenata iskusi barem mali stepen anksioznosti pre operacije, te je anksioznost česta u preoperativnom periodu. Specifičan faktor koji najviše doprinosi nastanku perioperativne anksioznosti do sada nije identifikovan. Ipak, uznapredovale godine starosti i ženski pol su dosledno označeni kao nezavisni prediktori nastanka preoperativne anksioznosti. Za procenu i merenje nivoa preoperativne anksioznosti, u poslednjih nekoliko decenija predložen je veliki broj različitih skala. S obzirom da je pokazano da je visok nivo preoperativne anksioznosti povezan sa značajnim postoperativnim komplikacijama i da može značajno uticati na ishode hirurškog lečenja, ovaj problem svakako ne bi trebalo zanemariti. Pravovremena identifikacija anksioznih bolesnika i primena odgovarajućih terapijskih mera preoperativno, značajno može smanjiti incidenciju preoperativne anksioznosti i komplikacija do kojih ona može dovesti.

Ključne reči: preoperativna anksioznost; postoperativne komplikacije; incidencija; merenje.

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REVIEW

A practical approach to high-altitude illness

Suzana Bojić [1,2]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia;

[2]Department of Anesthesiology and Intensive Care, University Clinical Hospital Center "Dr. Dragisa Misovic – Dedinje", Belgrade, Serbia

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Correspondence to:
Suzana Bojić
Department of Anesthesiology and Intensive Care
University Clinical Hospital Center "Dr. Dragisa Misovic – Dedinje"
Heroja Milana Tepića 1, 11 000 Belgrade, Serbia
Phone: +381 60 5287435
E-mail: subojic@yahoo.com

Summary

At high altitudes, the human body is exposed to low partial pressure of inhaled oxygen, the condition known as hypobaric hypoxia. When the ability of the human body to adapt to these conditions is exceeded, Acute Altitude Illness (AAI) develops. In the AAI spectrum, Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE) and High-Altitude Cerebral Edema (HACE) are usually described. Due to the high incidence of AAI and potentially high mortality in HAPE and HACE patients, a series of prophylactic and therapeutic measures are introduced as proposed by the current guidelines. The most important prevention of AAI is the low speed of ascent. The treatment of choice for HAPE and HACE is quick descent, supplemental oxygen if available, and medications such as acetazolamide, dexamethasone, nifedipine, and phosphodiesterase inhibitors.

Keywords: Acute Altitude Illness, Acute Mountain Sickness, High Altitude Cerebral Edema, High Altitude Pulmonary Edema, hypoxia.

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INTRODUCTION

A vast majority of the global human population resides at altitudes close to the sea level. Only about 1% is permanently settled above 2500 m. (1)However, every year tens of millions of people travel to high-altitude areas of the Alps, the Rockies, the Himalayas or the Andes for work or leisure. Areas that only world-class professional mountaineers visited a few decades ago are nowadays sites of blooming mass tourism and the supporting industry. The importance of better education of medical professionals on altitude-related medical conditions cannot be more emphasized in the current climate of rapidly developing high-altitude tourism. Even so, formal medical education still fails to address this subject adequately. (2)

The most important feature of a high-altitude environment is low barometric pressure. With ascending altitude, barometric pressure drops exponentially. However, the composition of the lower atmospheric layers is surprisingly uniform, up to 100 km above the sea level, with approximately 21% oxygen content. Therefore, although the inspired air always contains 21% oxygen, the partial pressure of oxygen in the inspired air *will decrease* with ascending altitude. Such a condition is called *hypobaric hypoxia*. In contrast, almost all cases of hypoxia at the sea level are classified as *normobaric hypoxia*. Low partial pressure of inhaled oxygen results in low partial pressure throughout the oxygen cascade, thus impeding all oxygen-dependent cellular processes.

Luckily, the human body can adapt to altitude and hypobaric hypoxia in the process called acclimatization. When these adaptation mechanisms are overwhelmed, Acute Altitude Illness (AAI) develops. Acute Altitude Illness is didactically and clinically divided into Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE). However, the effects of high altitude expand beyond these three manifestations.

ACUTE MOUNTAIN SICKNESS

Acute Mountain Sickness is the mildest form of AAI. It affects an increasing number of people with ascending altitude, with the reported incidence of up to 75% at altitudes over 5 000 m. (3) It is generally accepted that AMS occurs at altitudes of ≥ 2500 m in unacclimatized individuals with the usual delay of 4–12 h upon the arrival at the new altitude. However, in susceptive individuals, symptoms of AMS can manifest at lower altitudes as well. (4)

The clinical diagnosis of AMS is made per exclusion, but in real-world conditions scoring systems (otherwise developed for research purposes) are used to identify individuals with AMS. The most frequently used one is Lake Louise AMS Score **(Table1)**. It should be emphasized that the assessment of symptoms should be performed at least 6 h after the ascent has been completed to allow enough time for AMS to present and avoid misinterpretation of the symptoms of exhaustion, dehydration or environmental exposure. (5) Based on the latest revision of the Lake Louise criteria, a score of 3 or more points with at least one point for headache suggests AMS. (6) However, some authors have challenged headache as a mandatory criterion for AMS diagnosis, arguing that some cases of AMS could be overlooked because patients were not presenting with headache. (7)

Table 1. Lake Louise Acute Mountain Sickness Score.

Headache	0—None at all 1—A mild headache 2—Moderate headache 3—Severe headache, incapacitating
Gastrointestinal symptoms	0—Good appetite 1 - Poor appetite or nausea 2 - Moderate nausea or vomiting 3 - Severe nausea and vomiting, incapacitating
Fatigue and/or weakness	0 - Not tired or weak 1 - Mild fatigue/weakness 2 - Moderate fatigue/weakness 3 - Severe fatigue/weakness, incapacitating
Dizziness/ light-headedness	0 - No dizziness/light-headedness 1 - Mild dizziness/light-headedness 2 - Moderate dizziness/light-headedness 3 - Severe dizziness/light-headedness, incapacitating

(Modified from: Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, et al. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol. 2018;19(1):4-6.)

Several risk factors for developing AMS have been proposed, with conflicting evidence for some of them. They include a history of previous AMS, younger age, obesity, preexisting lung disease, increased exertion, rapid ascent, ascent >400 m per day, altitude attained, preacclimatisation, altitude of residence and a more controversial gender and resting SpO2. (8-11)There is no evidence that chronic underlying medical problems such as asthma, coronary artery disease, or diabetes mellitus increase the risk of becoming ill following an ascent. (4) Current guidelines of the Wilderness Medical Society differentiate three risk categories of altitude ascents based on the speed of ascent and the individual's suspected or known susceptibility to AAI **(Table 2)**. (12)

Prophylactic measures include both non-pharmacological and pharmacological interventions. Non-pharmacological actions are far more beneficial to patients than pharmacological ones. They include preacclimatization and an adjusted speed of ascent. Decision on the speed of ascent depends on multiple environmental and personal factors, including terrain, weather, logistical issues, but also the fitness and competence of the expedition members. For ascents to altitudes over 3000 m, most guidelines recommend the daily increase of sleeping el-

Table 2. Risk categories for Acute Altitude Illness.

Risk category	Description
Low	• Individuals with no history of altitude illness and ascending to ≤ 2800 m • Individuals taking ≥ 2 days to arrive at 2500 - 3000 m with subsequent increases in sleeping elevation < 500 m/day and an extra day for acclimatization every 1000 m
Moderate	• Individuals with a history of AMS and ascending to 2500 - 2800 m in 1 day • No history of AMS and ascending to >2800 m in 1 day • All individuals ascending >500 m/day (increase in sleeping elevation) at altitudes above 3000 m but with an extra day for acclimatization every 1000 m
High	• Individuals with a history of AMS and ascending to >2800 m in 1 day • All individuals with a history of HACE or HAPE • All individuals ascending to > 3500 m in 1 day • All individuals ascending > 500 m/day (increase in sleeping elevation) above >3000 m without extra days for acclimatization • Very rapid ascents (e.g., < 7 days ascents of Mt. Kilimanjaro)

AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema. The altitudes listed in the table refer to the altitude at which the person sleeps. Ascent is assumed to start from elevations < 1200 m. The risk categories described pertain to unacclimatized individuals.
(Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s):S3-s18.)

evation should not exceed 300-600 m, with at least one day for rest after every 1000 m of altitude gained. Sleeping altitude is considered more significant than maximal altitude achieved during waking hours. (12) So far, there is only one actual randomized controlled trial to evaluate the influence of the speed of ascent on AMS, and this study provided strong evidence for the fact that slower ascent is associated with lower incidence and severity of AMS as well as a higher ascent success rate. (13)

Preacclimatization refers to repeated exposure to hypobaric or normobaric hypoxia in the days and weeks before the high-altitude travel. Although recommended and employed by many experienced high-altitude mountaineers, current guidelines do not endorse particular protocols of preacclimatization. Still, they only suggest that some preacclimatization should be considered due to a lack of evidence to support a specific practice. (12) However, it is recognized that exposure to hypobaric hypoxia is more effective than exposure to normobaric hypoxia and more prolonged exposure to hypoxic conditions compared to shorter ones. (14)

Table 3. Recommended medications used for prevention of AMS, HAPE and HACE in adults.

Medication	Indication	Dosage
Acetazolamide	AMS, HACE	125 mg every 12 h
Dexamethasone	AMS, HACE	2 mg every 6 h or 4 mg every 12 h
Ibuprofen	AMS	600 mg every 8 h
Nifedipine	HAPE	30 mg ER every 12 h or 20 mg ER every 8 h
Tadalafil	HAPE	10 mg every 12 h
Sildenafil	HAPE	50 mg every 8 h

All medications are taken via the oral route. AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema; ER - extended-release.
(Modified from: Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s)S3-s18.)

Adequate hydration is mandatory at high altitudes to avoid dehydration which can mimic the symptoms of AMS. It is important to note that overhydration can be as dangerous as AMS due to dilutional hyponatremia. (15) Coca plant is traditionally used in the Andes to alleviate or prevent symptoms of AMS, but current evidence does not support its use. (16) Short-term oxygen therapy from small volume canisters (2 – 10 L/canister) does not bring any benefit to AMS prevention or treatment. (12)

Prophylactic medications **(Table 3)** are recommended in moderate and high-risk situations **(Table 2)**. (12) Acetazolamide and dexamethasone are the most frequently used prophylactic drugs. Due to fewer side effects, acetazolamide is preferred to dexamethasone, but dexamethasone should be used in cases of severe adverse effects to acetazolamide. The concurrent use of these drugs for prophylactic purposes is not advised except in emergencies that mandate very rapid ascent, such as search & rescue or military missions. The timing of prevention is essential. Both medications should be started on the day before the ascent, but they still have beneficial effects if started on the first day of the ascent. For individuals ascending to and staying at the same elevation for more than several days, prophylaxis may be stopped after two days spent at the highest altitude. For individuals ascending to a mountain top and then descending significantly on the same day, medications should be stopped in the absence of AMS/HACE symptoms. (12) There are indications that ibuprofen (17-19), metoclopramide (20) or budesonide (21, 22) could be used to prevent AMS, but more robust evidence is still needed (23). Weak recommendation exists, however, for ibuprofen to be used for AMS prevention in individuals who do not wish to take acetazolamide or dexamethasone or who have ad-

verse reactions to these medications. (12) Paracetamol, Gingko Biloba and inhaled budesonide are not currently recommended for AMS prophylaxis. (12)

By far the most effective treatment option for AMS is descent. Descent is indicated in severe AMS and treatment-resistant AMS. (12) Symptoms usually resolve after 300 to 1000 m of descent, but the descent is not always necessary, and it sometimes is not possible either.

Using supplemental oxygen therapy is highly recommended for treating AMS. However, oxygen supplementation should be reserved for severe AMS or high-altitude medical facilities since bottled oxygen or oxygen concentrators are scarce. The way of oxygen administration and inspired fractional concentration of oxygen (FiO2) should be targeted to raise SpO2to >90% to relieve symptoms or if descent is not possible. (12)

Recommended medications for the treatment of AMS are listed in Table 4. Both acetazolamide and dexamethasone should be considered for the treatment of AMS. Acetazolamide is the preferred prophylactic option that is seldom sufficient in treating severe AMS. At the same time, dexamethasone is the preferred treatment option used for prophylaxis in high-risk situations. Paracetamol and ibuprofen are recommended for treating high-altitude headaches but not for AMS treatment. (12)

If AMS symptoms do not progress to HAPE or HACE, they usually resolve spontaneously or after pharmacological or non-pharmacological treatment. Most frequently, the patients who no longer have AMS symptoms will decide to undertake further ascent. However, if symptoms do not fully resolve after the descent, the ascent to previously attained altitude is not advised. (12)

More severe forms of AAI are HAPE and HACE. The mortality rate from HAPE and HACE is approaching 50% without adequate medical care. (24) Patients can develop HAPE and HACE simultaneously in up to 10 % of cases. (25)

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema (HAPE) is non-cardiogenic pulmonary edema associated with the exposure to hypobaric hypoxia. The incidence of HAPE rises with altitude to 6% at 4500 m and up to 15% at 5500 m. Sporadic cases have been described at altitudes as low as 2000 m. In individuals with a history of HAPE, the recurrence rate is as high as 60%. It is likely fatal if left untreated. The mortality rate depends on multiple factors, including early recognition and treatment, but it is still very high, approximately 50% in untreated patients. Although AMS and HAPE are considered parts of the AAI spectrum, only half of the patients with HAPE have predeceasing or concomitant AMS. (26)

Risk factors are similar to those for AMS but also include individual susceptibility due to low hypoxic ventilatory response, the use of sleep medication, excessive salt ingestion, pulmonary hypertension, increased pulmonary vascular reactivity, and genetic susceptibility. (27-30)

The current understanding of HAPE pathophysiology suggests hypoxia is a primary cause. Hypoxia causes widespread hypoxic pulmonary arterial vasoconstriction, leading to increased pressure in pulmonary circulation. That, in addition tohypoxia-induced increase in capillary permeability, causes fluid to move into the alveoli resulting in noncardiogenic pulmonary edema. (31)

Typically, the initial presentation of HAPE is unspecific with a decreased exercise tolerance, exertional dyspnea, chest pain and non-productive cough. It can quickly progress to dyspnea at rest and productive cough with frothy pink sputum of pure blood. Objectively, SpO2 is at least 10% lower than expected for a particular altitude, usually between 40% and 70%. Patients are typically tachypneic, tachycardiac, sometimes with central cyanosis, rales and wheezes. (26, 32) Chest X-ray patterns of HAPE are also non-specific and encompass bilateral symmetrical perihilar opacities, bilateral symmetrical diffuse opacities, unilateral diffuse opacities, bilateral asymmetrical focal opacities, and even lobar consolidation with lower zone or, less commonly, upper zonal predilection but with the normal-sized heart and mediastinum. (33) EKG sometimes shows a right axis deviation and/or myocardial ischemia. Laboratory investigations are of limited use. In a patient with pulmonary infiltrates on chest radiography, rapid correction of clini-

Table 4. Recommended doses of the medications used for treating AMS, HAPE and HACE in adults.

Medication	Indication	Route	Dosage
Acetazolamide	AMS, HACE	PO	250 mg every 12 h
Dexamethasone	AMS,	PO, IV, IM	4 mg every 6 h
Dexamethasone	HACE	PO, IV, IM	8 mg once, then 4 mg every 6 h
Nifedipine	HAPE	PO	30 mg ER every 12 h or 20 mg ER every 8 h

AMS - Acute Mountain Sickness; HACE - High Altitude Cerebral Edema; HAPE - High Altitude Pulmonary Edema; ER - extended release; PO - oral route; IV - intravenous route; IM - intramuscular route.
(Modified from: Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med. 2019;30(4s):S3-s18.)

cal status and SpO2 with supplemental oxygen is pathognomonic of HAPE. (26)

Crucial prophylactic measure for HAPE includes gradual ascent since there is a clear relationship between the rate of ascent and disease incidence. Preacclimatisation should also be considered. Pharmacological prophylaxis (Table 3) should be used only in individuals with a history of HAPE. Nifedipine is the medication of choice and should be started on the day before the ascent and continued either until descent is initiated or the individual has spent four days at the highest elevation, perhaps up to 7 days if the individual's rate of ascent was faster than recommended. Acetazolamide can be considered to prevent the reentry HAPE in people with a history of this disorder. Phosphodiesterase inhibitors should be considered in HAPE-susceptible individuals who are not candidates for nifedipine and dexamethasone in individuals who are not candidates for either nifedipine or phosphodiesterase inhibitors. Salmeterol is not recommended for HAPE prevention. (12)

Given the life-threatening nature of HAPE, the primary therapeutic option is descent. The patient should descend at least 1000 m with the least possible effort. If available, supplemental oxygen should be provided to target SpO2 >90% or to relieve symptoms. A portable hypobaric chamber could be used if descent is not feasible,is delayed or supplemental oxygen is not available. Continuous positive airway pressure (CPAP) devices should be considered when another therapeutic approach is unavailable or as an adjunct therapy in patients not responding to supplemental oxygen. (12)

Recommended pharmacological treatment is listed in Table 4. Nifedipine is the medication of choice. Tadalafil or sildenafil can be used if nifedipine is not available, but concomitant use with nifedipine should be avoided due to possible hypotension. Acetazolamide and diuretics should not be used to treat HAPE. Due to insufficient evidence, no recommendation can be made regarding dexamethasone. (12)

HIGH-ALTITUDE CEREBRAL EDEMA (HACE)

HACE is the rearrest but the most severe and the most dangerous form of AAI. If not recognized and managed correctly, it can lead to death within 24 h due to brain herniation. It is generally considered an extreme or end-stage form of AMS. Incidence if HACE is up to 12% at altitudes of 6000 m. (34, 35) The risk factors for HACE are identical to those for AMS.

Two prevailing theories identify hypoxia as the primary etiological factor of HACE. Hypoxia evokes hemodynamic responses leading to cerebral overperfusion of microvascular cerebral blood vessels. This translates to elevated capillary pressure and capillary leakage resulting in vasogenic edema. (36)However, cytotoxic edema, also observed in HACE, is likely a consequence of Na+/K+ ATPase dysfunction due to diminished oxygen supply. (37) Both vasogenic and cytotoxic components are likely to contribute to intracranial hypertension.

Unlike HAPE, most HACE cases present a clear progression of AMS symptoms to decline in cognitive functions, the level of consciousness, slurred speech, papilledema and truncal ataxia. (38) Truncal ataxia, often described as "drunken sailor gait," can be frequently overlooked or misinterpreted as muscle fatigue. One must keep a full vigilance of truncal ataxia since it is the earliest sign of HACE (4). Other symptoms can also overlap with dehydration, hypothermia, hypoglycemia or hyponatremia, so laboratory testing is essential for differential diagnosis. Imaging techniques are usually not readily available in remote areas but, just like lumbar punction (39), only show elevated intracranial pressure with cerebral edema. There is no correlation between the severity of edema with HACE clinical presentation or the outcome (34, 40), and neither imaging nor lumbar punction are necessary for diagnosis.

Prevention of HACE should be prioritized over treatment. Appropriate acclimatization by gradual ascent as described in AMS prevention and/or repeated preacclimatisation will likely prevent this illness. (25) Medications can and should be used in moderate and high-risk situations (Table 2) to prevent HACE (Table 3). Dexamethasone is most frequently used. As for AMS prevention, medication should be started on the day before the ascent. For individuals ascending to and remaining at a given elevation, upon the arrival at the target elevation, the medication should be continued for four days in individuals adhering to the recommended ascent rate and 4 to 7 days in individuals ascending faster than recommended rates. Individuals who ascend to a target elevation and immediately descend can stop the medication once the descent is initiated (12)

HACE is, by definition, a true medical emergency with a very high mortality rate. It is essential to initiate the treatment as soon as possible, which can be challenging, if not impossible, in remote areas without endangering the lives of other expedition members. Descent and supplemental oxygen are recommended non-pharmacological treatment options for HACE. A portable hyperbaric chamber should be used if they are not feasible or available. There is no recommendation concerning CPAP use due to a lack of evidence. Pharmacological treatment should be initiated immediately (Table 4), especially if descent is not possible at the time or other non-pharmacological treatment options are unavailable. Dexamethasone is the primary treatment of choice for HACE, but acetazolamide can be used as an adjunct. (12) To our knowledge, studies on diuretic use in treating HACE were not published to date.

Conclusion

When the ability of the human body to adapt to high altitude is exceeded, an AAI develops. In the AAI spectrum, AMS, HAPE and HACE are usually described. Due to the high incidence of AAI and potentially high mortality in HAPE and HACE patients, a series of prophylactic and therapeutic measures are introduced. The most important prevention of AAI includes acclimatization and low speed of ascent, but pharmacological prophylaxis is available and recommended in some cases. The treatment of choice for HAPE and HACE is quick descent with oxygen and a portable hyperbaric bag if available, as well as the use of supplemental oxygen, acetazolamide, nifedipine, dexamethasone, and phosphodiesterase inhibitors.

Conflict of interest

None to declare.

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PRAKTIČAN UVOD U AKUTNU VISINSKU BOLEST

Suzana Bojić[1,2]

Sažetak

Ljudsko telo je na velikim nadmorskim visinama izloženo niskom parcijalnom pritisku kiseonika. Ovo stanje je poznato kao hipobarna hipoksija. Kada je sposobnost organizma da se prilagodi ovim uslovima prekoračena, dolazi do razvoja akutne visinske bolesti (AVB). U okviru spektra ABV opisuju se tri entiteta: akutna planinska bolest, visinski edem pluća i visinski edem mozga. Zbog velike učestalosti AVB i potencijalno visokog mortaliteta kod pacijenata sa visinskim edemom pluća ili mozga, preporučuje se niz profilaktičkih i terapijskih mera u skladu sa aktuelnim smernicama. Najvažnija mera prevencije AVB je malabrzina uspona i lekovi acetazolamid, deksametazon i ibuprofen. Terapija izbora za visinski edem pluća i mozga je brzo spuštanje na značajno nižu nadmorsku visinu, oksigenoterapija i lekovi acetazolamid, deksametazon, nifedipin i inhibitori fosfodiesteraze.

Ključne reči: akutna visinska bolest, akutna planinska bolest, edem mozga, edem pluća, hipoksija.

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CASE REPORT

An unusual case of combined laryngocele presenting as cervical swelling

Jovanović Anđelina[1], Valjarević Svetlana[1,2], Jovanović Milan[1,2]

[1]Department of Otorhinolaryngology with Maxillofacial Surgery, Clinical Hospital Center "Zemun", Belgrade, Serbia
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Jovanovic Andjelina, KBC Zemun, Vukova 9,
Mob. 062/22 00 32,
andjelinakjosevski@yahoo.com

Summary

Laryngocele is a sac-like, pathological enlargement of the Morgagni's ventricle, which occurs between the true and false vocal cords. This change is filled with air and is continuous with the lumen of the larynx. It is usually asymptomatic and is accidentally detected during radiological diagnostics. We present the case of a 54-year-old patient who came for examination due to a painless swelling in her neck on the left side, which lasted for 8 months and increased upon Valsalva's maneuver. Occasionally the patient was hoarse. By clinical otorhinolaryngological examination and computed tomography of the neck and larynx, we found a cystic formation, filled with air, which extended above the larynx and spread to the side of the neck.The laryngocele was surgically removed using an external cervical approach. The neck of the laryngocele is sent through the thyroid membrane, while preserving the upper laryngeal nerve and the accompanying vascular stalk. Pathohistological examination revealed that the laryngocele consisted of respiratory layered cylindrical epithelium. Laryngocele should be taken into account in differential diagnosis of neck swelling.

Keywords: combined laryngocele, neck swelling, cervical surgical approach.

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INTRODUCTION

Laryngocele is a marked expansion of Morgagni's ventricle, a part of the laryngeal duct between the true and the false vocal folds; it is filled with air and communicates with the lumen of the larynx. Laryngocele can be internal or combined (1). Most often, it is asymptomatic, but in some patients, due to its size, very difficult breathing occurs, and a tracheotomy may be required (2). The etiology is still unclear, but obstruction, increased pressure in the larynx and congenital defects are possible risk factors for its occurrence (3). The frequency of laryngocele is 1 in 2.5 million people per year. Laryngocele is 5-6 times more common in men, mostly in the sixth decade of life (4). No side bias was noted (3). Bilateral laryngoceles are extremely rare, with 6 cases published in literature so far. Laryngopyocele is also a rare clinical entity. It makes up 8% of all laryngocele cases (4).

CASE REPORT

A fifty-four-year-old woman was admitted to ENT office for examination with an eight-month-old, painless swelling on the left side of the neck, which enlrged with the Valsalva maneuver. She did not have difficulties with breathing or swallowing, but she complained of occasional hoarseness. She was not an active smoker and did not drink alcoholic beverages. Fiberoptic laryngoscopy showed floating edema of the vocal cords that were mobile during phonation and respiration, as well as a marked edema of the left ventricular fold. CT of the neck and larynx with I.V. contrast confirmed an air-filled sac-like formation extending from the supralaryngeal region to the lateral side of the neck **(Figure A)**.

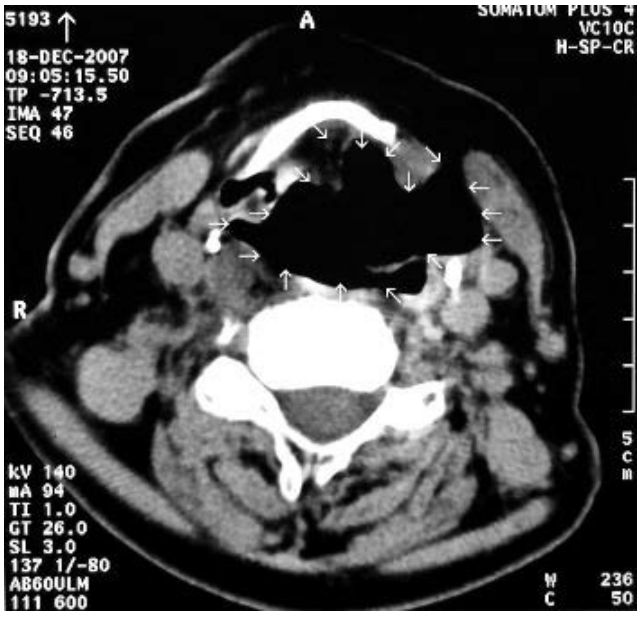

Figure A. CT of the neck and the larynx with i.v. contrast - saccular formation, filled with air, which extended from the supralaryngeal region to the side of the neck

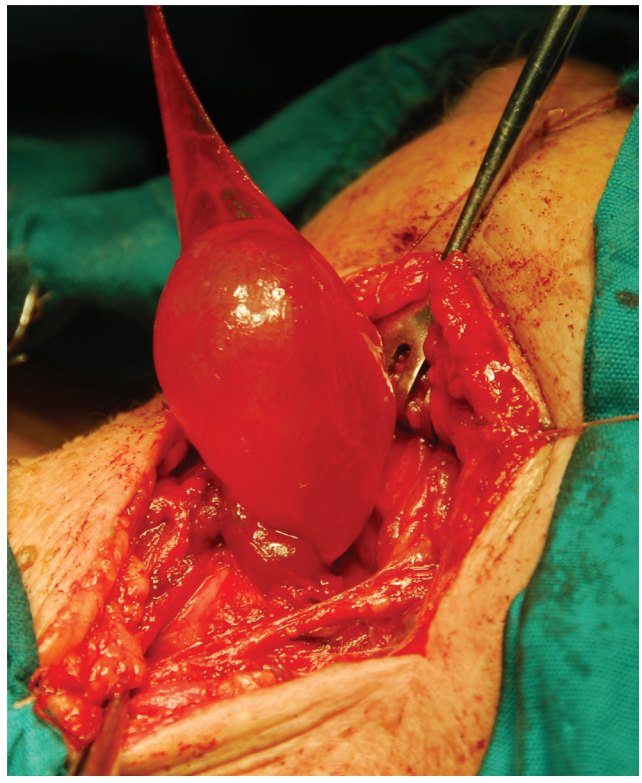

Figure B. External surgical approach

The laryngocele was approached through a horizontal cervical incision of 8 cm, from the medial edge of the sternocleidomastoid muscle (mSCM) to the medial line of the neck at the height of the upper edge of the thyroid cartilage, with lifting of the subplatysmal skin flaps. The neck of the laryngocele was followed down the thyroid membrane (figure B), with preservation of the superior laryngeal nerve and associated vascular pedicle.

When we approached the mucous membrane of the larynx, the neck of the laryngocele was ligated and the bag formation was separated. The cyst was resected, prepared and separated up to the thyrohyoid membrane and the supraglottis. Microscopic examination revealed that the laryngocele consisted of respiratory layered cylindrical epithelium.

DISCUSSION

Laryngocele is an air sac that arises from the larynx and spreads into the neck through the membrane of the thyroid gland or remains inside the larynx. It extends superiorly into the paralaryngeal space, limited medially by the ventricular fold, and laterally by the thyroid cartilage and thyrohyoid membrane. A simple laryngocele contains only air. In some cases, it may contain mucus, which is caused by the presence of mucinous glands;in that case it is calledlaryngomucocele. If the laryngocele becomes infected with bacterial or fungal agents, it contains pus and becomes a laryngopyocele (2,5,6).

Laryngoceles can be congenital or acquired. The etiology is not fully elucidated, but it is believed that they arise due to congenital weakness of the laryngeal wall caused by strain during coughing (6,7). Congenital defects are described as the most common cause in newborns. Despite various anatomical variations and birth defects seen in adults, it is difficult to explain all cases on these grounds. A constant increase in pressure in the lumen of the larynx can cause laryngocele even in people with a normal larynx (5). This leads to an increase in intra-abdominal pressure and a consequent increase in intraglottic pressure. Prolonged periods of increased pressure within the lumen of the larynx can cause dilatation of the laryngeal sac. This is associated with certain professions as described: weightlifters, glassblowers, singers, brass players. Chronic cough, excessive and forced cough due to chronic respiratory disorders, can also cause dilatation of the laryngeal tube and become a predisposing factor for the development of laryngocele (6,7).

Patient history, clinical otorhinolaryngological examination, endoscopic examination of the larynx and imaging of the larynx and the neck are necessary and important diagnostic steps in patients with laryngocele (2,5,6).

Laryngoceles generally have non-specific symptoms. When they are symptomatic, patients often complain of dysphonia or painless neck swelling, which increases during the Valsalva maneuver and decreases with pressure (4). Other clinical symptoms are cough, dyspnea, dysphagia, dull neck pain; globus feeling in the throat and inspiratory stridor are most often present in internal and large combined laryngoceles. In extreme cases, laryngoceles lead to upper airway obstruction and may require emergency tracheotomy. Laryngopioceles are infected laryngoceles, which, consequently, more often cause respiratory complications and even paralysis of the vocal cords and emphysema (6,7).

Radiological diagnostics, especially computed tomography (CT), is of great importance in arriving at diagnosis, in determining the size of a laryngocele, but also in detecting associated malignancies and in treatment planning. It has been noted that laryngocele can especially develop in association with supraglottic carcinoma of the larynx (3). Direct laryngoscopy is a sovereign diagnostic procedure in every case of laryngocele. Newer publications categorize laryngocele as internal or combined. The previously used classification of internal, external and combined laryngocele is being slowly abandoned. External laryngoceles cannot exist because laryngoceles originate from the laryngeal tube. The internal laryngocele is limited within the false vocal fold, medial to the thyrohyoid membrane, and the combined one extends upwards and protrudes through the thyrohyoid membrane to the neck (8,9). In CT,laryngoceleis seen as a cyst filled with air or liquid. CT clearly differentiates a laryngocele from a saccular cyst and removes the suspicion of an occult tumor (2,5,6).

Differential diagnoses include: thyroglossal cyst, brachial cyst, saccular cyst, cystic hygroma, lymphangioma, hemangioma, ductal cyst of the submandibular gland, pharyngeal diverticulum, teratoma, dermoid cyst, lymphoma, parotid tumor, ectopic thyroid tissue, neurofibroma, lymphadenopathy or cancer. (10,11).

As laryngocele is a rare condition, there is no consensus on its surgical treatment. The operation is performed when there are symptoms. Asymptomatic cases can be monitored (11). Numerous surgical techniques are available - external, internal or combined approach and the traditional non-external one (5).

Endoscopic microsurgery and CO2 laser application have become popular in the last two decades for internal laryngoceles (1,12). The surgical approach is related to the type and size of the formation. Most patients with combined laryngoceles are treated with an external approach (5), and that is how we operated on our patient. This approach allowed us good exposure and precision. In literature, a lower recurrence rate is registered in such cases (2). Disadvantages can be skin scars, higher morbidity, a longer duration of surgery, a longer period of hospital treatment and higher costs (2,10). Postoperative complications can be wound infections, seroma, fistula, scar, hematoma, injury to the upper laryngeal artery and nerve(13). We had no postoperative complications. Combined laryngoceles can also be treated with an endolaryngeal approach (12). We did not choose the endoscopic approach because of the size of the lesion.

Conclusion

Laryngoceles should be taken into account in differential diagnosis of neck swelling. Even with the best diagnostic and radiographic examination techniques, this differentiation cannot be clearly performed, so a direct examination of the larynx is necessary. The chosen external surgical approach provided reliable preparation and removal of the combined laryngocele, while preserving the superior laryngeal nerve and its vascular pedicle.

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KOMBINOVANA LARINGOKELA KAO REDAK UZROK OTOKA NA VRATU

Jovanovic Anđelina[1], Valjarević Svetlana[1,2], Jovanović Milan[1,2]

Sažetak

Laringokela je vrećasto, patološko proširenje Morganjijevog ventrikulusa, koje nastaje između pravih i lažnih glasnica. Ova promena je ispunjena vazduhom i u kontinuitetu je sa lumenom larinksa. Obično je bez simptoma i slučajno se otkriva u toku radiološke dijagnostike. Prikazujemo slučaj pacijentkinje stare 54 godine koja se javila na pregled zbog bezbolnog otoka na vratu sa leve strane, koji je trajao 8 meseci i povećavao se naValsalvin manevar. Povremeno je pacijentkinja bila promukla. Kliničkim otorinolaringološkim pregledom i kompjuterizovanom tomografijom vrata i larinksa našli smo cističnu formaciju, ispunjenu vazduhom, koja se pružala iznad larinksa i širila u bočnu stranu vrata.Laringokelu smo u celini hirurški odstranili spoljašnjim cervikalnim pristupom. Vrat laringokele je ispraćen niz tiroidnu membranu, uz očuvanje gornjeg laringealnog nerva i prateće vaskularne peteljke. Patohistološkim pregledom, utvrđeno je da se laringokela sastoji od respiratornog slojevitog cilindričnog epitela. Laringokele treba uzeti u obzir u diferencijalnoj dijagnozi otoka vrata.

Ključne reči: kombinovana laringokela, otok na vratu, spoljašnji hirurški pristup

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ORIGINAL ARTICLE

Organizational commitment of healthcare employees in a private sector

Stefan Dugalić[1], Milena Šantrić-Milićević[2], Dejana Stanisavljević[3], Bojana Gutić Vukobrat[4], Miroslava Gojnić[1], Maja Macura[1], Dragana Božić[1], Tamara Stanisavljević[5], Miloš Petronijević[1], Svetlana Vrzić-Petronijević[1], Milica Petronijević[5], Jovana Todorović[2]

[1]University of Belgrade, Faculty of Medicine, University Clinical Centre of Serbia- Clinic for Gynecology and Obstetrics, Belgrade, Serbia

[2]University of Belgrade, Faculty of Medicine, Institute of Social Medicine, Belgrade, Serbia

[3]University of Belgrade, Faculty of Medicine, Institute for Medical Statistics and Informatics, Belgrade, Serbia

[4]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

[5]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Jovana Todorovic
University of Belgrade, Faculty of Medicine,
Institute of Social Medicine, Belgrade, Serbia
Dr Subotica 15, 11000 Belgrade, Serbia
Phone: +381112643830
Email: jovana.todorovic@med.bg.ac.rs

Summary

Introduction: Organizational commitment is defined as 'psychological relationship of an individual with an organization'. The aims of this study were to analyze organizational affective and normative commitment of young healthcare providers, factors that determine their perception of organizational support, as well as to identify possibilities to promote employee dedication to the healthcare organization they worked for.

Method: The research was conducted as a cross-sectional study in a private healthcare institution 'Fizio Vracar' in Belgrade. Meyer-Allen questionnaire (with 24 questions) was distributed during the third week of May 2018, and 30 physical therapists of both sexes and with median age 29.9 completed it, voluntarily and anonymously.

Results: The organizational normative commitment declined with the increase of organizational support (r=-0.526; p<0.001), while organizational affective commitment increased with the increase of organizational support (r=0.756; p<0.001). On the scale from 1 to 5, all the employees had the average score above 3 for affective and normative commitment (3.72±0.56 and 3.19±0.75), while the score for organizational support was above 4 (4.11±0.54). The model of multiple linear regression showed that affective and normative commitment were factors that determined the perception of organizational support (B=0.66; 95% CI: 0.41-0.91; and B=-0.20; 95% CI: -0.38; -0.02).

Conclusion: Even though organizational support had better score than affective and normative commitment, there is certainly room for their improvement. Managers and employees should consider the employee requests together, care more about employee general satisfaction, empower team spirit, while the organization should implement mechanisms to retain work force.

Key words: healthcare employees, work environment, perception, organizational support, affective commitment, normative commitment, work psychology, human resources management

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INTRODUCTION

Organizational commitment is defined as 'psychological relationship of an individual with an organization'. This type of research is rare within healthcare area, making it additionally valuable for HR management which aims to provide the clients with continuous quality healthcare.

Numerous research provide evidence that the building organizational commitment may contribute to better functioning and creating of desirable outcomes both on systemic and organizational level within the system, which are most frequently observed by high performance, low brain drain level and less absence time (1-6). Besides these effects on macro (systemic) and mezzo (organizational) level, there is evidence on the relevancy of investment into organizational commitment in order to achieve more quality relationships on a micro (individual) level, such as relationships between employees and users (7, 8). The significance of organizational commitment in sustainability of a healthcare system is well recognized (9), while increased mobility of healthcare employees in recent years emphasizes the need for healthcare systems to prepare to preserve their self-sustainability (9-11).

Numerous studies were focused on determining the perception of organizational commitment (12). Organizational commitment of employees is considered a performance determinant (13-15). Meyer and Allen (16) have defined organizational commitment as a psychological connection between employees and their organization which influences the probability for employees to stay with the organization. They have described organizational commitment as 'emotional attachment to organization, identifying with the organization and engaging within the organization'. Meyer and Allen developed three-component model of organizational commitment and designed a questionnaire to examine each component separately (16, 17). According to them, three types of commitment that relate the employees with their organizations are: Affective component - "I want to stay"; Normative component – "I have to stay"; Continuous dedication – "I should stay". Affective commitment is the first domain which includes the intensity of person's identification with the organization and participation in the organization. Affective commitment leads to the perception of normative commitment. Normative commitment describes the employee's intent to stay with the company because he/she feels obliged to. The construction of normative commitment is formulated as the sense of obligation which could be derived from numerous factors. Meyer and Allen identified two complex mechanisms which could contribute to normative commitment (16). The first one is a strong relationship between the individual's values and values of organization. The second mechanism is of more instrumental nature related to the reward system. Continuous commitment is observed from the point of view of costs the employee believes he/she would have if organization is left – if the cost of leaving exceeds the cost of staying, the employee tends to stay with the organization in order to avoid unplanned cost of leaving. The employees with continuous commitment stay with the organization because they have to, meaning that being their only option (18).

Most frequently, the literature observes the commitment from the aspect of organizational support which implies management investment in the working conditions and employee development (for example, the functioning of system for evaluation and reward) (19). A recent research in academic community in Serbia has shown that the success in education is positively correlated to organizational fairness (20).

There is no sufficient research to provide conclusions on organizational commitment of healthcare employees in Serbia.

The aims of this study were to analyze organizational affective and normative commitment of young healthcare providers, factors that determine their perception of organizational support, as well as to identify possibilities to promote employee dedication to the healthcare organization they worked for. The starting hypothesis was that the perception of organizational support was associated with employee normative commitment, and thus influenced affective commitment of young healthcare professionals.

METHODS

The research was conducted as a cross-sectional study in a private healthcare institution 'Fizio Vracar' in Belgrade. Meyer-Allen questionnaire (with 24 questions) was distributed during the third week of May 2018, and 30 physical therapists of both sexes and with median age 29.9 completed it, voluntarily and anonymously.

As an instrument, the research used Mayer-Allen questionnaire (19) on affective commitment and normative commitment and perception of support to organization. The original questionnaire is available on-line. This questionnaire has been translated from English and customized for research in a healthcare organization by being tested, before its distribution, on five persons and all necessary changes have been entered in the questionnaire (Appendix 1). The participation was anonymous and voluntary. The questionnaire had 24 questions. Seven questions are related to subject's general data. Questions on affective commitment (AC, five in total), normative commitment (NC, five in total) and experience on organizational support (EOS, seven in total), had five-level Likert scale answers. Internal consistency of questions for AC, NC and EOS was validated by Cronbach alpha coefficient.

DATA ANALYSIS

Statistical analysis included the methods of descriptive statistics (measures of central tendency and variability measures) and analytical statistics (correlation and linear regression). Correlation was examined using the Spearman correlation test. Linear regression analysis has been used to determine separate correlation between four individual factors (sex, age, AC, NC – independent variables) with organizational support as dependent variable (single regression model), as well as to determine the model of organizational support improvement (multiple regression model) based on statistically significantly correlated independent variables with outcome variable. The values of single and multiple linear regression analysis were presented by non-standard regression coefficients (B) and 95% confidence interval (*CI*). All the values at $p<0.05$ level were taken as statistically significant. SPSS 21 was used for data processing. The results were presented in tables (7 tables in total).

RESULTS

The study included 30 subjects employed with private healthcare institution FIZIO VRACAR in Belgrade. Employee gender structure is as follows, with both genders included: 14 male subjects (47 %) and 16 female subjects (53%). Subject's average age was 29.90 ± 2.11, with age range 26-34. Marital status of the largest number of subjects was out-of-wedlock (70%).

The values of Cronbach alpha coefficient point to adequate level of internal questionnaire consistency **(Table 1)**. All examined domains have values of 70% or above.

Table 1. Internal questionnaire consistency

Domain	Cronbach alpha coefficient
Affective commitment	0.66
Normative commitment	0.70
Experience on organizational support	0.78

The range of replies from Affective commitment domain (AC) was from 1 to 5. The highest obtained value was for the question 'I enjoy talking about my organization with people outside of it" (4.10±0.61). The average values of all replies were higher than neutral score (3). Normative commitment (NC) domain of the subjects included five questions with the range of replies from 1 to 5. Average values of all replies were approximately neutral score (3). The highest average value of replies was obtained for the question 'I would continue working for this organization in the future since it deserves this' (3.77±0.82). The lowest average value of replies was obtained for the question 'I would feel guilty if I left the organization at this moment' (2.67±1.03). The third examined domain Experience on organizational support (EOS) included seven questions in the range between 2 and 5. The average values of replies to the questions from the first domain are higher than neutral score (3) pointing to employees' satisfaction in relation to total support provided by the organization. The highest average score was obtained for the question 'Our organization cares about our opinion' (4.37±0.67). Average values higher than 4 were obtained for questions: 'Our organization regularly supports its employees who are experiencing problems' (4.33±0.61), 'Organization cares about general satisfaction of employees at work' (4.10±1.06) and 'Each employee is treated with honest respect' (4.30±0.75). The lowest average value was obtained for the question 'Our organization does not ignore employees' complaints' (3.77±0.90).

Table 2 presents the average values of scores according to questionnaire domains. The highest score was obtained for domain Experience of organizational support (4.11±0.54), while the lowest one was for Normative commitment (3.19±0.75).

Table 2. Description of domain scores

Min		Max	x	SD	Skjunis	Kurtosis
Affective commitment, AC	2.80	4.60	**3.72**	0.56	0.271	-1.069
Normative commitment, NC	2.20	4.60	**3.19**	0.75	0.845	-0.061
Experience of organizational support, EOS	3.14	5.00	**4.11**	0.54	-0.244	-0.864

Correlation coefficient matrix for the observed criteria has shown statistically significant correlation between variables **(Table 3)**. There is a highly statistically significant correlation between variables EOS and AC ($p<0.01$) and highly statistically significant negative correlation between variables EOS and NC ($p<0.01$).

Table 4 shows the relation of 4 factors with organizational support by single and multiple regression model.

Table 3. Correlation coefficient matrix (r)

	Affective commitment, AC	Normative commitment, NC	Experience of organizational support EOS
Affective commitment, AC			
Normative commitment, NC	-0.359		
Experience of organizational support, EOS	0.756**	-0.526**	

Table 4. Variables associated with Experience of organizational support domain

Variables	Univariable		Multivariable	
	B (95% CI)	p	B (95% CI)	p
Gender	0.22 (-0.18-0.63)	0.264		
Age	0.02 (-0.08-0.11)	0.745		
Affective commitment, AC	0.73 (0.48-0.97)	**<0.001**	0.66 (0.41-0.91)	**<0.001**
Normative commitment, NC	-0.38 (-0.62; -0.14)	**0.003**	-0.20 (-0.38; -0.02)	**0.033**

In a multiple regression model, statistically significant independent predictors of EOS domain score are variables AC (p<0.001) and NC (p=0.033). Statistically significant inverse correlation between variables NC and EOS has been shown. The subjects with higher scores in NC variable have lower scores in EOS. Variable AC has a positive correlation with EOS. Subjects with higher AC scores have higher score in EOS. Subjects' gender and age are not correlated to the experience of organizational support, while normative and affective commitment are.

DISCUSSION

Primary aim of this study was to describe components of affective and normative commitment of employees in a private healthcare organization 'Fizio Vračar'. Specific aim was to determine if there was a correlation of affective and normative commitment with organizational support. Data was collected by using a questionnaire designed to measure commitment and provide score that could be analyzed. Statistical tests demonstrated that the questionnaire had gathered reliable subject data.

The study main results showed that there was an affective commitment and normative commitment, as well as organizational support within the organization. The analysis of affective commitment has established that in the given organization all employees have average score in affective commitment while higher score was given only for one out of five examined components of this commitment. Analysis if normative commitment has established that, in the given organization, all employees have average score in normative commitment while lower score was given for one out of five examined components of this commitment.

The factors that determine experience of support for young healthcare employees are affective and normative commitment in individual models of single logistic regression, as well as in multiple logistic regression model. Having in mind that the organization needs higher affective commitment, organization management may, most probably, improve affective and normative commitment if retention mechanisms are applied, organizational problems solved together with the employees, reputation elevated as well as respect to employees and organization, and team spirit empowered. Organizational support may be stronger if the management and employees consider employees' complaints together and care more of general employee satisfaction.

Similar to obtained results, other studies suggest that managers should strive to improve their capacities for organizational support (work processes, equipment, staff, beds, space) in order to encourage affective commitment and improve performance (21). According to new theory model of quality studied in hospitals in Ontario (*Ontario Hospital Association Quality Healthcare Workplace model*), there are three performance motivators – work environment, work characteristics and organizational support. The motivators influence individual outcomes (higher employee engagement and commitment) and consequently affect the organizational outcomes, including the quality and patient safety and operative efficiency (when patients are treated in the most efficient and effective way), recruiting and staff retention, employer's reputation, and productivity and costs (22). This study also emphasizes the importance for managers to understand that employees' commitment is a precondition for high performance and to focus on factors that contribute to improving of employee engagement. Engaged employees are especially important due to their commitment to achieving organizational goals and proven positive correlation between employee engagement and other desirable goals of human resources, including retention, individual performance and absence. Engaged employees are devoted to their employers, satisfied with their work and willing to provide additional efforts in order to achieve goals of their organization (22).

As healthcare organizations are faced with increasing demand, while at the same time it is expected to retain the high level of service to their patients with less resources (23), greater engagement is desirable from both the aspect of employee and organization. Firstly, from the point of view of an individual employee, the theory of social identity states that individuals seek to identify with relevant social groups and thus their identification with, engagement in, and/or commitment to organization present a part of their self-concept and self-valuation. This element is especially emphasized by the results of the study conducted in Fizio Vračar, where item 'I do not feel like a member of the family in my organization' of the affective commitment component had high score. Namely, identification with or commitment to is something that employees seek for. Secondly, from the point of view of the organization, greater engagement is desirable because of positive correlation between employee engagement and achieving other favorable goals connected to human resources.

Managers are the ones to provide sufficient resources in order to enable greater engagement because there is evidence that providing of appropriate resources is an important factor in better business outcomes (24),

Many authors wrote on positive influence of affective commitment to individual and organizational performance (25). Alternatively, it is expected that the lack of commitment results in poorer performance (26). Committed employees are satisfied with their work and willing to provide additional efforts to achieve organizational goals, while such engagement is a request for higher performance (22, 27).

It should be emphasized that even though Allen and Mayer scale does not allow the participant to state the reason for commitment (for example 'I owe my organization a lot' or 'I would feel guilty if I left the organization now') the level of normative commitment influences organizational support. For example, the pediatricians in Taiwan are not happy with their work and have low commitment, which consequently may be the reason why young doctors leave this field and leave the country (28).

Research on organizational commitment of 162 doctors and 43 managers in Spain state hospitals ER (29), showed that the doctors committed averagely to the problems of the hospital where they worked (average 3.8 on a scale from 1 to 5), feel medium affection (3.4) and had high score in intention to keep working in that place (4.0). Similar to Fizio Vračar, the affective commitment of doctors in Spain had lower score than the normative commitment. Doctors' capabilities had influence on their affective commitment; specific training for emergency procedures and seniority influenced their continuous commitment while the opinion they had on the organization influenced their affective commitment. The resources of the hospital had no influence on work commitment, while training and perception of the services did. (29)

Even though the research did not show that gender and age influenced the organizational support, it is considered that some personal variables influence the employee's commitment to the organization. Different generations have different preferences and needs while differences (in gender, age, race, family status or origin, social and cultural connections) may have an impact on the fact how employee in each group commits to organization as it contributes to different value system, obvious and unique in each of the observed groups (30-33).

Numminen et al. (34) established that affective commitment of freshly graduated nurses had medium score. Multiple variant analyses detected significant associations between commitment and competence, turnover intentions, work satisfaction, previous professional education and work area. Specifically, the affective dimension with connotation of identifying with nurse work and preparedness to stay in that field implied positive organizational support for engagement (35) and positive career development (36). A strong correlation between commitment and intention to stay is detected (37), while work satisfaction appeared as an important factor influencing the commitment (36, 38).

According to Jamaluddin et al. (39), healthcare organizations should strive to sustainability. New and effective strategies and practices which proved to be able to provide benefits to the organizations still are not able to survive in a long run (40, 41), being called 'improvement evaporation effect' (40, 42), because a successful change and strategy application in any organization may not happen and survive in a long run without the good support of human capital (43). The same authors also discovered that internal organizational factors such as management support, HR management, training and empowering of employees, as well as team work, were the areas to be focused to in order to achieve corporate sustainability. This study on organizational support in a private organization obtained similar results.

The attempts in recent decades in work psychology to explain the variation in individual productivity were frustrating as they did not consider organizational commitment, professional quality of life and organizational empowering. These positions describe the connection to work tasks, sense of competence and belief in capability to perform the task, self-determination related to the control and choice of work behaviour, supervisor support, especially the support of inspiring leaders who provide the purpose and efficiency to employees, existence of trainings for leaders as well as further development, and present a promising aid to influence employees' commitment (44, 45).

Gambino (46) emphasized that managers who were interested to retain employees should have understood which aspects of commitment and support contribute most to a typical decision of the employee to stay in the field of works, and more specifically with the same employer. A better understanding of their influence to staff retention may assist the managers to allocate resource in a better way so as to keep the experienced employees and provide more quality service to the patients. Unfortunately, there are few of these research and the results of this private organization research may be observed only as a beginning of a long journey towards identification of correlations between work characteristics, organizational commitment, support and productivity.

An empirical study which identified the relations between work characteristics, organizational commitment, work satisfaction, work engagement and organizational policy and procedures in transitional economy in Serbia included 566 persons employed with 8 companies (47). Similar to Fizio Vračar, the results of this large study showed that the existing models of work motivation which include all elements of organizational support need to adjust to partly increase work satisfaction and partly increase organizational commitment. Employees

in private companies scored higher on all variables except for work characteristics and the author explained that reason might be found in economic situation in Serbia and high rate of unemployment (over 20%), causing the fact that young people are satisfied by finding a job and not by the job itself (47).

The levels of organizational commitment and support may be improved even though it is suggested that employee commitment must be provoked by the organization and not assumed, implying that the organizations should try to be proactive in influencing the level of organizational commitment in their organizations (48). The organizations that want to be leaders in the market need to recognize the importance of focusing to organizational commitment of employees and work engagement for the benefit of both the organization and employees.

Other researchers suggest strategies for improvement such as salary increase, work load decrease, modification of task structure, growing passion for work and creating more professional opportunities for personal development of nurses as well as promotion. (49).

It is needed to have managerial initiatives which may consider including the employees in discussions on their aspirations and interests and introducing policies which may help them balance their financial and family needs with their own health and safety (45). Managers should try to improve the provision of adequate resources of beds, technology and work equipment (50).

The questionnaire on organizational commitment developed by Meyer and Allen (51) may be used to continue research in the area. For example, variable such as performance, work satisfaction and probability to leave the organization as well as occupational commitment may be analyzed (52-54).

Specifically, as suggested by Gregory (55), the organizations should identify and implement the policies and interventions with the aim to create work environment which provides more support and to implement policies and programs to retain employees (56).

This research has numerous limitations so the results need to be observed in that sense. This is a cross-sectional study which shows no effect of an intervention or causal correlation. Moreover, the subjects were evaluated only in a specific period of life. Namely, the study shows only current time correlation between the examined factors but does not describe which factor is the cause and which one is the consequence. Furthermore, the research was conducted on 30 subjects; although this number is high for a private sector in Serbia, the results may not be generalized. Also, there is a bias in subject selection. Namely, the convenient choice of subjects may be the reason why certain possible irregularities were not identifies, such as the relation of the gender, age, marital status, education and income with the affective and normative commitment and organizational support. The method based on self-reporting made the results biased under the assumption that those employees have a more positive perception of the organizational climate. It is equally important to say that the goals of the research focused on examining the perception so there were no objective productivity indicators, which would be the next step in this research. Considering the fact that we investigated in the private sector, even though privacy and anonymity were guaranteed, a certain degree of subjectivity in subjects' replies is possible; it is possible the subject provided the replies which would be favorable in case the employer had insight into their questionnaires. Although the study fulfills its purpose to provide the preliminary insight into a model, it is recommended for future studies to use more objective measures, larger sample and more variables related to healthcare employees. An empirical study should be conducted in order to understand, in more detail, the role of organizational commitment in relation to sustainability of state-owned organizations within healthcare system. As employees from different areas may have different approaches to corporate sustainability (57), it is more appropriate to conduct a study based on employees' area of work. Further studies may possibly investigate different types of commitment of employees in a hospital, such as nurses, administrative staff and medical workers separately. Therefore, even though there is an obvious similarity to other studies, the results obtained by this study may be interpreted as correct only for the above-mentioned organization and its staff, and cannot be generalized. The advantage of this study is in providing concrete insight, enabling the development of specific organization due to its implications on policy and management practice, and it provides suggestion of specific steps and investigation in the area.

Conclusion

Even though organizational support had better score than affective and normative commitment, there is certainly room for their improvement. Managers and employees should consider the employee requests together, care more about employee general satisfaction, empower team spirit, while the organization should implement mechanisms to retain work force.

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ORGANIZACIONA POSVEĆENOST ZDRAVSTVENIH RADNIKA U PRIVATNOM SEKTORU

Stefan Dugalić[1], Milena Šantrić-Milićević[2], Dejana Stanisavljević[3], Bojana Gutić Vukobrat[4], Miroslava Gojnić[1], Maja Macura[1], Dragana Božić[1], Tamara Stanisavljević[5], Miloš Petronijević[1], Svetlana Vrzić-Petronijević[1], Milica Petronijević[5], Jovana Todorović

Sažetak

Uvod: Organizaciona posvećenost se definiše kao „psihološki odnos pojedinca sa organizacijom". Ciljevi ove studije bili su da se analizira organizaciona afektivna i normativna posvećenost mladih zdravstvenih radnika, faktori koji određuju njihovu percepciju organizacione podrške, kao i da se identifikuju mogućnosti za unapređenje posvećenosti zaposlenih zdravstvenoj organizaciji u kojoj su radili.

Metod: Istraživanje je sprovedeno kao studija preseka u privatnoj zdravstvenoj ustanovi „Fizio Vračar" u Beogradu. Meier-Allen upitnik (sa 24 pitanja) podeljen je tokom treće nedelje maja 2018. godine, a dobrovoljno i anonimno ga je popunilo 30 fizioterapeuta oba pola i srednje starosti 29,9 godina.

Rezultati: Organizaciona normativna posvećenost je opadala sa povećanjem organizacione podrške (r=-0,526; p<0,001), dok je organizaciona afektivna posvećenost porasla sa povećanjem organizacione podrške (r=0,756; p<0,001). Na skali od 1 do 5 svi zaposleni su imali prosečnu ocenu iznad 3 za afektivnu i normativnu posvećenost (3,72±0,56 i 3,19±0,75), dok je ocena za organizacionu podršku bila iznad 4 (4,11±0,54). Model višestruke linearne regresije pokazao je da su afektivna i normativna posvećenost faktori koji određuju percepciju organizacione podrške (B=0,66; 95% CI: 0,41-0,91; i B=-0,20; 95% CI: -0,38; -0,02) .

Zaključak: Iako je organizaciona podrška imala bolji rezultat od afektivnog i normativnog zalaganja, svakako ima prostora za njihovo unapređenje. Menadžeri i zaposleni treba da zajedno razmatraju zahteve zaposlenih, više brinu o opštem zadovoljstvu zaposlenih, osnažuju timski duh, dok organizacija treba da implementira mehanizme za zaposlenih.

Ključne reči: kombinovana laringokela, otok na vratu, spoljašnji hirurški pristup

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Appendix sa apstraktima

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Specijalni broj časopisa “Medicinska istraživanja“ prati simpozijum u obliku Knjige sažetaka.

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Članovi Organizacionog **odbora simpozijuma„Stremljenja i novine u medicini“**

Prof. dr Ivana Novaković, predsednik
Prof. dr Dragana Šobić Šaranović
Prof. dr Vera Pravica
Prof. dr Jasna Jančić
Prof. dr Aleksandra Jotić
Prof. dr Marija Plješa Ercegovac
Prof. dr Srđan Lopičić
Prof. dr Katarina Paunović
Doc. dr Darko Antić

Sekretar
Dr sc. Viktorija Popović

Tehnički sekretar
Tijana Tošić

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MINI SIMPOZIJUM

POSLEDICE PANDEMIJE COVID-19 NA MENTALNO ZDRAVLJE

Medicinski fakultet, Univerzitet u Beogradu
Institut za mentalno zdravlje, Beograd

ŠTA JE NOVO DONELA COVID - 19 PANDEMIJA?

Olivera Vuković

Tokom ljudske istorije, malo je pojava poput pandemija koje su na specifičan način oblikovale kulturu i civilizaciju. Pandemije su neretko devastirale stanovništvo, uticale na ekonomiju, političke i društvenetokove, ishode ratova, ali su ujedno otvarale vrata inovacijama i naučnom napretku. Prvi deo rada posvetili smo *prošlosti kao prologu* imajući u vidu da nam analiza prethodnih iskustava pomaže da objektivnije sagledamo biološke, socijalne, političke i ekonomske posledice aktuelne COVID-19 pandemije.

I dok su pomno analizirane kroz istorijski objektiv, u domenu savremenih humanističkih nauka malo pažnje posvećenoje njihovom uticaju namentalno zdravlje. Ovaj podatak ne iznenađuje, imajući u vidu da su se gotovo sve panedemije, uz nekoliko izuzetaka („španske grozinice“ koja je obeležila kraj Velikog rata, „tinjajuće“ HIV pandemije, kao i SARS i MERS *epidemije*), izbijale pre pojavesavremene psihijatrije kao nauke i kliničke discipline.

Interesan je podatak da je *koncept stresa* u medicinu uveden sredinom 20. veka, tako da se ovaj fenomen nije ni mogao ispitivati do izbijanja aktuelne pandemije. Iz medicinske perspektive, bio je to vrlo zanmiljiv period koji je obeležio istorijski značajan preokret. Naime, bili smo ubeđeni da smo infektivne bolesti stavili „pod kontrolu“, a fokus smo preusmerili na hronične nezarazne bolesti kao vodeći uzrok mortaliteta i morbiditeta „savremenog“ čoveka.

COVID-19 pandemija nas je nanovo podsetila na univerzalnost fenomena „večnog vraćanja istog“, naterala nas je da bolje promislimo o tezi Stivena Pinkera o „boljim anđelima naše prirode“ i uticala da relativizujemo uverenje da naučna otkrića nude konačno rešenje problema. Ne ulazeći u biologističke hipoteze o tome da su tokom evolucije virusi uticali na to da budemo ljudi, nesumnjivo je da aktuelna situacija testira naše kapacitete da tolerišemo dvosmislenost u svakom smislu te reči. Inherentno duhu vremena čiji je zaštitni znak *postistina*, pokušali smo da sagledamo nekesavremene fenomene koje nam je COVID-19 pandemija hteli to ili ne nametnula u prvi plan.

Ključne reči: pandemija, COVID-19, posledice, psihijatrija.

Medicinski fakultet, Univerzitet u Beogradu
Institut za mentalno zdravlje, Beograd

STRES U DOBA PANDEMIJE

Bojana Pejušković

Stres je opšta reakcija, skup nespecifičnih reakcija organizma, na bilo koji zahtev za prilagođavanjem izmenjenim uslovima spoljašnje sredine. Pandemija izazvana korona virusom (COVID-19) svakako jeste značajno izmenila i promenila uslove življenja u spoljašnjoj sredini. Štaviše, pandemija predstavlja traumatski stresor jer je vrsta događaja koja predstavlja ozbiljnu pretnju sigurnosti, odnosno fizičkom, psihičkom i socijanom integritetu individue. Stres je psihoneuroendokrinoimunološki proces, koji je kao takav, uticao i na somatsko, i na mentalno zdravlje populacije. Brojna istraživanja pokazala su povećanu prevalencu emocionalnog distresa, kao i poremećaja u vezi sa stresom kao što su akutni stresni poremećaj i posttraumatski stresni poremećaj (PTSP). Takođe, uočena je povećna prevalenca anksioznosti, depresivnog poremećaja, zloupotrebe supstanci, kao i povećan suicidan rizik. Posledice su takođe i poremećaji spavanja, uz narušenu radnu funkcionalnost. Stres u doba pandemije ostavio je značajne posledice ne samo na individualnom, već i na kolektivnom nivou. Istaživanje i analiza posledica stresa, od zanačaja su kako za pojedinca, tako i za javno zdravlje i zdravstveni sistem u celini.

Ključne reči: stres, trauma, pandemija, mentalno zdravlje.

Medicinski fakultet, Univerzitet u Beogradu
Institut za mentalno zdravlje, Beograd

POSLEDICE PANDEMIJE PO MENTALNO ZDRAVLJE PSIHIJATRIJSKIH PACIJENATA I STARIH

Čedo Miljević

COVID-19 pandemija je pored somatskih i neuroloških posledica imala velikog uticaja ina mentalno zdravlje ljudi širom sveta. Pandemija i strah povezan sa njom dovela su do promene u svakodnevnom životu svakog pojedinca. “Nova realnost” je uključivala rad od kuće, izolaciju, nezaposlenost, školovanje od kuće, odsustvo fizičkog kontakta sa porodicom, prijateljima i sl. Psihički zdravi ljudi su reagovali na različite načine pri čemu se najveći broj uspešno adaptirao. Sa druge strane pacijenti sa postojećim, različitim psihijatrijskim poremećajima su se suočili sa brojnim izazovima počevši od pojačanog stresa, izazova zloupotrbe alkohola i supstanci ali i težom dostupnosti psiijatrijskim ustanovama.

Svetska zdravstvena organizacija procenjuje da je COVID-19 pandemija dovela do povećanja depresivnih poremećaja za oko 27.6% odnosno 25.6% u slučaju anksioznih poremećaja. Globalno se smatra da je samo u 2020. godini pandemija odgovorna za povećanje nesposobnosti od 137.1 (računato kao DALY parametar na 100000 stanovnika za depresivne poremećaje) odnosno 116.1 (računato kao DALY parametar na 100000 stanovnika za anksiozne poremećaje).

Kada je reč o pacijentima s apsihijatrijskim poremećajima postoje i dodatni izazovi u odnosu na mentalno zdrave ljude (u prvom redu pitanje otpornosi pacijenata na stress pandemije ali i neka praktična pitanja poput interakcije psihofarmaka sa lekovima koji s eprimenjuju u tretmanu COVID-a). Posebano osetljiv deo populacije pored pacijenata sa psihijatrijskim oboljenjima čini i starija populacija. Po svim pokazateljima ovaj deo populacije je posebno osetljiv na infekciju korona virusom koji kod njih ima i teže efekte i dovodi do veće smrtnosti. Psihološke posledice izolacije i straha kao i pridružena somatska oboljenja kod ovog dela populacije su takođe značajno povišena.

U radu će biti prikazni najnovniji podaci koji se tiču efekata pandemije na mentalno zdravlje starije populacije ali i psihičko zdravlje pacijenata sa različitim psihijatrijskim poremećajima.

Ključne reči: COVID-19, posledice, psihijatrijski poremećaji, psihijatrijska populacija, stari.

Medicinski fakultet, Univerzitet u Beogradu
Institut za mentalno zdravlje, Beograd

POSLEDICE PANDEMIJE PO MENTALNO ZDRAVLJE DECE I ADOLESCENATA

Danilo Pešić

Nasuprot činjenici da su adolescenti pod malim rizikom da razviju tešku kliničku sliku i komplikacije COVID-19 infekcije, oni su pod povećanom vulnerabilnošću za psihosocijalne stresore tokom pandemije, zbog same vulnerabilnosti ovog razvojnog perioda.

Sistematski pregledi uticaja pandemije na populaciju mladih tematski grupišu uticaj karantina i socijalne izolacije na sledeće grupe: na školsku decu (i na istraživanja nedostatka strukturišićeg uticaja školskog okruženja), na studentsku populaciju, na mlade sa već postojećim mentalnim problemima, na mlade sa razvojnim problemima, na mlade bez roditeljskog staranja i na posebno vulnerabilnu populaciju mladih koje nisu obuhvaćene gore navedenim grupama.

Globalno je pokazano da su tokom pandemije adolescenti ispoljavali visoke stope poremećaja povezanih sa stresom, anskioznost, depresiju, kao i povećanu uporebu kanabisa, alkohola ali razvijanje nehemijskih zavisnosti (posebno od online video igara i pornografije).

Oko 25 % mladih sa mentalnim problemima je imalo teškoće u pristupu sistemu zdravstvene zaštite, a kao posebno vulnerabilne grupe izdvojili su se LGBTQ adolescenti, oni koji boluju od anoreksije nervoze, ospesivno kompulsivnog poremećaja i oni sa istorijom zlostavljanja i zanemarivanja. Strateške intervencije koje su se pokazale efikasnim u radu sa ovom populacijom su zajednička saradnja sa stručnjacima za javnozdravlje, brza procena situacije krozonline ankete, razvoj kratakih fokusiranih bihejvioralnih intervencija, uvažavanje konteksta, fleksibilnost, pomoć grupama vršnjačke podrške i volonterima u zajednici. Istraživanja su pokazala da je zbogosećaja „nepobedivosti“ i prkosa prema preporukama, populaciju adolescenata potrebno motivisati na drugačiji način za održvanje mera socijalnog distanciranja od populacije odraslih.

S obzirom na to da je ovo ključan period razvoja regiona “socijalnog mozga“ i mehanizama regulacije anksionosti kroz “fine radove” na konektivitetu izmedju amigdala i prefrontalne kore, zbirni uticaj nekoliko faktora (hronični stres, konsekutivni povećan unos zasićenih masti, nedostatak fizičke aktivnosti, smanjenje “socijalnog dodira” i virtuelna komunikacija) u periodu najdubljeg i najbržeg učenja o socijalnom okruženju tek treba da bude istražen.

Ključne reči: deca, adolescenti, mentalno zdravlje, COVID-19.

MINI SIMPOZIJUM
VODA I ZDRAVLJE – STARI PROBLEMI I NOVI IZAZOVI

Institut za higijenu i medicinsku ekologiju, Medicinski fakultet, Univerzitet u Beogradu

NOVI VODIČ SVETSKE ZDRAVSTVENE ORGANIZACIJE ZA PROCENU VODOSNABDEVANJA, SANITACIJE I HIGIJENE U ZDRAVSTVENIM USTANOVAMA

Katarina Paunović

Snabdevanje zdravstveno ispravnom i bezbednom vodom za piće je ljudsko pravo zagarantovano Ustavom. Vodosnabdevanje, sanitacija i higijena ruku obuhvaćeni su pojmom „water, sanitation and hygiene – WASH" i danas se smatraju krucijalnim činiocima boravišne i radne sredine koji doprinose očuvanju zdravlja i poboljšanju kvaliteta života ljudi.

Novi vodič Svetske zdravstvene organizacije „Survey tool / Checklist on water, sanitation and hygiene in healthcare facilities, 2022", daje detaljna uputstva za procenu sanitarno-higijenskih uslova u zdravstvenim ustanovama prema kriterijumima WASH-a, za prikupljanje i obradu podataka i izračunavanje međunarodno prihvaćenih indikatora odnosno standarda. Koncept WASH-a u zdravstvenim ustanovama odnosi se na snabdevanje vodom za piće, sanitaciju ili uklanjanje fekalnih otpadnih materija, higijenu ruku zdravstvenih radnika i pacijenata, kao i upravljanje medicinskim otpadom i čišćenje prostorija u kojima se obavlja zdravstvena delatnost. Vodič je nastao iz iskustva autora tokom sprovođenja projekata o proceni kvaliteta vodosnabdevanja, sanitacije i higijene u zdravstvenim ustanovama u Srbiji, regionu i drugim evropskim zemljama. Vodič daje praktične smernice za sprovođenje sanitarno-higijenskog nadzora nad zdravstvenim ustanovama, sa posebnim naglaskom na procenu kriterijuma za snabdevanje higijenski ispravnom vodom za piće prema principima WASH-a.

Vodič Svetske zdravstvene organizacije pruža mogućnost lekarima specijalistima u oblasti preventivnih grana medicine i javnog zdravlja da se po prvi put upoznaju sa konceptom WASH-a, da steknu uvid u mogućnosti procene bezbednog snabdevanja ispravnom i kvalitetnom vodom za piće, kao i da dobiju praktična znanja za samostalnu procenu rizika po zdravlje koji voda za piće može imati za pojedinca i populaciju.

Usvajanje elemenata WASH-a u zdravstvenim ustanovama može doprineti poboljšanju pružanja zdravstvenih usluga, smanjenju obolevanja i umiranja od zaraznih bolesti, širenja bolničkih infekcija, kao i pojave antimikrobne rezistencije. Šire posmatrano, očekuje se da primena principa WASH-a u domaćinstvima, školama, zdravstvenim i drugim javnim ustanovama doprinese očuvanju i unapređenju zdravlja cele populacije, a posebno vulnerabilnih grupa stanovništva.

Ključne reči: voda za piće; sanitacija; higijena; WASH; Svetska zdravstvena organizacija

Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut", Beograd
Institut za higijenu i medicinsku ekologiju, Medicinski fakultet, Univerzitet u Beogradu

IZAZOVI SNABDEVANJA VODOM ZA PIĆE U DOMAĆINSTVIMA, ŠKOLAMA I ZDRAVSTVENIM USTANOVAMA U SRBIJI

Dragana D. Jovanović, Katarina Paunović

Pristup adekvatnom vodosnabdevanju u domaćinstvima i institucijama, kao što su škole i zdravstvene ustanove je od esencijalnog značaja za zdravlje stanovništva, zdravo odrastanje i razvoj dece, zdravlje pacijenata i zaposlenih u školama i zdravstvenim ustanovama. Adekvatno vodosnabdevanje podrazumeva pristup zdravstveno ispravne i bezbedne vode za piće u domaćinstvima i prostorijama institucija, vodu dostupnu svima u dovoljnim količinama i uvek kada je potrebna.

U Srbiji su sprovedene dve nacionalne i jedna regionalna studija od 2016. do 2019. godine koje su imale za cilj da između ostalog ispitaju, procene i sagledaju situaciju vodosnabdevanja pomenutih kategorija, uključujući i zdravstvenu ispravnost vode za piće. Akcenat je bio na seoskim domaćinstvima i školama, dok su istraživanjem uslova vodosnabdevanja u zdravstvenim ustanovama bile obuhvaćene obe sredine, gradska i seoska.

Rezultati su pokazali da je oko trećina uzoraka vode za piće iz seoskih domaćinstava i škola bila sa nalazom Escherichiae coli, dok je procenat mikrobiološki neispravnih uzoraka u zdravstvenim ustanovama bio 8%. Fizičko-hemijska neusaglašenost sa važećim Pravilnikom se kreće oko 70% u seoskim domaćinstvima i školama, dok je u zdravstvenim ustanovama manji, kao posledica veće usaglašenosti hemijskih parametara u gradskim sredinama i snabdevanja vodom iz javnih komunalnih preduzeća. Dodatno laboratorijskim analizama procenjeni su i sanitarno higijenski uslovi izvorišta za vodosnabdevanje, ali i same distributivne mreže.

Među najčešćim nedostacima su uočeni: oštećena ograda ili njeno odsustvo oko izvorišta, tehnički nedostaci i blizina izvora zagađenja. Ova istraživanja su ukazala na postojanje zdravstvenog rizika po stanovništvo, školsku decu, pacijente i osoblje zaposleno u školama i zdravstvenim ustanovama u ruralnoj sredini, kao posledice mikrobiološki i fizičko-hemijski neispravne vode za piće. Takođe, ona su ukazala na prioritetna mesta i polja delovanja za poboljšanje situacije.

Ključne reči: snabdevanje vodom za piće; higijenska ispravnost vode; zdravstvene ustanove; škole

Medicinski fakultet, Univerzitet u Novom Sadu
Institut za javno zdravlje Vojvodine, Novi Sad

PROCENA KARCINOGENOG RIZIKA USLED IZLOŽENOSTI TRIHALOMETANIMA U VODI ZA PIĆE I VODI BAZENA

Sanja Bijelović

Uvod: Iz hlornih preparata koji se koriste za dezinfekciju vode za piće i vode bazena u cilju obezbeđivanja mikrobiološke ispravnosti nastaju razgradni produkti dezinfekcije, ukoliko se za to stvore uslovi (organske materije, temperatura, pH). Najčešće se stvaraju trihalometani, ukupni i pojedinačni (hloroform, bromdihlormetan, dibromhlormetan i bromoform), od kojih su hloroform i bromdihlormetan mogući karcinogeni za ljude.

Cilj rada je da se proceni karcinogeni rizik za stanovništvo Grada Novog Sada na osnovu izloženosti ukupnim i pojedinačnim trihalometanima u vodi za piće i vodi bazena u periodu 2017-2021. godine.

Metod: Analiza 4660 uzoraka vode za piće i 344 uzoraka vode bazena je obavljena u Institutu za javno zdravlje Vojvodine u skladu sa akreditovanim, standardizovanim i propisanim metodama. Ukupni i pojedinačni trihalometani određeni su metodom statičkog „headspace" uzorkovanja i gasne hromatografije kuplovane sa masenom spektrometrijom prema referentnoj metodi definisanoj u ISO 10301. Za procenu rizika izloženosti ljudi korišćena je semi-kvantitativna metoda Svetske zdravstvene organizacije, dok je hroničan indeks opasnosti i karcinogeni rizik nakon ingestije i dermalne absorpcije, bez inhalatornog unosa, procenjen kvantitativnom metodom američke Agencije za zaštitu životne sredine.

Rezultati: Prosečna koncentracija ukupnih trihalometana u vodi za piće iznosila je 18,49±10,55 mg/l, nije prekoračivala propisanu vrednost (100 mg/l), među pojedinačnim trihalometanima dominirao je hloroform (38%) i rizik utvrđen semi-kvantitativnom metodom je bio mali. Prosečna koncentracija ukupnih trihalometana u vodi bazena iznosila je 101,42±96,76 mg/l, prekoračivala je propisanu vrednost (100 mg/l) u 79% kontrolisanih uzoraka, među pojedinačnim trihalometanima dominirao je hloroform (97%) i rizik utvrđen semi-kvantitativnom metodom je bio veoma velik. Ukupan karcinogeni rizik i iz vode za piće i vode bazena, nakon ingestije i dermalne absorpcije, je bio prihvatljiv (1,15E-06 za prosečne i 1,03E-05 za maksimalne vrednosti koncentracija). Hroničan indeks opasnosti pojedinačnih trihalometana je bio manji od 1, te nije utvrđen rizik oboljevanja ni za osetljivu populaciju.

Zaključak: Rizik za nastanak karcinoma među stanovništvom Grada Novog Sada nakon ingestije i dermalne absorpcije trihalometana iz vode za piće i vode bazena je prihvatljiv i nema rizika oboljevanja ni osetljive populacije nakon izloženosti pojedinačnim trihalometanima. Međutim, prekoračenje propisanih koncentracija trihalometana u vodi bazena i dominacija hloroforma kao pojedinačnog trihalometana ukazuje na neophdonost i daljeg kontinuiranog praćenja i procene rizika za stanovništvo Grada Novog Sada.

Ključne reči: voda, procena rizika, trihalometani

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet, Univerziteta u Beogradu

UNOS ALUMINIJUMA VODOM ZA PIĆE I NEURODEGENERATIVNE BOLESTI

Sonja Misirlić Denčić

Aluminijum je treći najrasprostranjeniji element u prirodi, najčešći metal u Zemljinoj kori, i konstituent prirodnih voda. Uprkos tome, aluminijum nema poznatu ulogu u biologiji i nije prisutan u znatnim koncentracijama u biološkim sistemima. I pored izuzetno male akutne toksičnosti, efekti aluminijuma na zdravlje ljudi su u stalnom fokusu naučnog mnjenja zbog njegove masovne upotrebe, te permanentnog unosa u organizam živih bića i sledstvene akumulacije u njemu.

Aluminijum se, naime, koristi u postupcima obrade hrane, prerade prirodnih voda i njihove distribucije, kao ambalaža, u sastavu posuđa, antiperspiranata, lekova i vakcina. SZO je poslednji put 2010. dala preporuku da koncentracija aluminijuma u vodi za piće ne treba da prelazi 0.1–0.2 mg/l. Međutim, Vlada Kanade 2019. godine objavljuje dokument po kome je preporučena koncentacija aluminijuma u vodi za piće višestruko niža - 0.05 mg/l, dok je koncentracija aluminijuma u pijaćoj vodi od 2.9 mg/l označena kao maksimalno prihvatljiva.

Apsorpcija aluminijuma sa kojim organizam čoveka može doći u kontakt je mala (svega 0.1% preko gastrointestinalnog trakta) jer se najveći broj njegovih jedinjenja ne rastvara pri pH znoja tj. u gastrointestinalnom traktu i u plućnom sekretu. Aluminijum dospeo u krvotok prolazi krvno-moždanu barijeru i narušava homeostazu u moždanom parenhimu, utiče na aksonalni transport i remeti sintezu neutoransmitera. Aluminijum se u jedinjenjima nalazi u oksidacionom stanju +3 tako da reaguje sa negativno nalektrisanim nukleinskim kiselinama, ali i sa ATP koji je osnovna energetska valuta ćelije. Aluminijum remeti homeostazu kalcijuma u ćeliji, stimuliše oksidativni stres, promoviše oligomerizaciju proteina i remeti njihovu razgradnju, deluje proinflamatorno.

Svi ovi događaji mogu se dovesti u vezu sa neurodegenerativnim oboljenjema čiji je zajednički patohistološki supstrat upravo akumulacija abnormalnih proteina u mozgu praćena umiranjem neurona i u nekim slučajevima inflamacijom. Međutim, do danas ipak nije potvrđena jasna i nedvosmislena udruženost aluminijuma iz vode za piće i Alchajmerove bolesti, najzastupljenije iz spektra neurodegenerativnih bolesti.

Ključne reči: voda za piće, aluminijum, neurodegenerative bolesti

Institut za patološku fiziologiju, Medicinski fakultet, Univerzitet u Beogradu

TOKSIČNO DEJSTVO FTALATA I BISFENOLA A IZ AMBALAŽE VODE

Jelena Nešović Ostojić

Ftalati su estri ftalatne kiseline i alifatičnih alkohola. Koriste se prvenstveno kao dodatak plastici, da bi se povećala fleksibilnost inače tvrdog polivinilhlorida. Ftalati se nalaze svuda oko nas: u hrani, vodi, majčinom mleku, vazduhu koji udišemo, prašini, zemljištu, odevnim predmetima, stambenim kućama, bolnicama i mnogim drugim mestima. Ftalati se otpuštaju iz plastičnih materijala (medicinska oprema kao što su plastične kese za krv i plazmu, oprema za dijalizu, kateteri i rukavice). Svi delovi ljudskog tela imaju potencijal za apsorpciju ftalata. Ftalati mogu preći preko placente, što može nepovoljno uticati na fetus i novorođenče.

Bisfenol A, BPA, 2,2 bis(4-hidroksifenil) propan, pripada grupi difenilmetan derivata i bisfenola. Koristi se u proizvodnji polikarbonatne plastike (velike plastične boce za višekratnu upotrebu, sportske boce, bočice za bebe, kutije za odlaganje hrane i pribor za jelo), i poliepoksida. U proizvodnji termalnog papira, služi kao razvijač boje.

Ftalate i bisfenol A zovu i endokrinim disruptorima (engl. *Endocrine Disrupting Chemicals, EDC).* Ftalati uglavnom deluju tako što interaguju sa hormonskim signalnim putevima, narušavajući ili oštećujući normalne fiziološke mehanizme, a to se može direktno odraziti na disfunkciju tkiva ili organa. Genotoksičnost ftalata posredovana je uglavnom epigenetskim promenama. U humanoj populaciji, prenatalna izloženost ftalatima (dietilheksil ftalat) dovodi do izrazite demetilacije *Igf2* i *H19* gena koji imaju ključnu ulogu za rast embriona i placente. Kod žena se ftalati mogu naći pored krvi, urina, cerebrospinalne tečnosti, i u folikularnoj i amnionskoj tečnosti i majčinom mleku.

Ftalati i bisfenol A dovode se u vezu sa smanjenjem gestacione zrelosti fetusa, preranim početkom puberteta kod devojčica, povećanim rizikom za nastanak endometrioze, usporenim sazrevanjem oocita, povećanim rizikom za nastanak neplodnosti, kao i većom verovatnoćom smrtnosti ploda. Potencijalni antiandrogeni efekat na fetus, pokazan je i usled dejstva ftalata i bisfenola A. Za bisfenol A takođe postoje podaci o estrogenskom (selektivni modulator estrogenskih receptora), antitireoidnom i inflamatornom dejstvu, kao i njegovoj sposobnosti izazivanja oksidativnog stresa.

Ključne reči: ftalati, bisfenol A, endokrini disruptori, plastični materijali, genotoksičnost

Institut za mikrobiologiju i imunologiju, Medicinski fakultet, Univerzitet u Beogradu

VODA KAO IZVOR GENA KOJI KODIRAJU REZISTENCIJU BAKTERIJA NA ANTIBIOTIKE

Ina Gajić

Rezistencija bakterija na antibiotike je jedan od deset najznačajnijih javno-zdravstvenih problema sa kojim se suočava čovečanstvo.

Bakterije rezistentne na antibakterijske agense, antibiotici i njihovi derivati su prisutni u različitim ekološkim nišama, pa i u vodenoj sredini. Iako je rezistencija bakterija na antibiotike prirodan fenomen, neadekvatna i nekritična upotreba antibiotika ubrzava razvoj rezistencije i širenje rezistentnih klonova. Putem urina i fecesa, rezistentne bakterije dospevaju u otpadne vode, zatim u sisteme za prečišćavanje voda, površinske vode, distribuiraju se u različite ekosisteme, a mogu se detektovati i u pijaćoj vodi.

Zahvaljujući horizontalnom genskom transferu, bakterije su sposobne da preuzimaju genetički material od bakterija iz svoje okoline. Tako se geni koji kodiraju rezistenciju na antibiotike mogu naći na mobilnim genetičkim elementima kao što su plazmidi, transpozoni i integroni, što olakšava širenje rezistencije. U tom smislu, otpadne vode poreklom iz zdravstvenih ustanova i životinjskih farmi, predstavljaju kritičnu sredinu, visokog mikrobnog biodiverziteta, u kojoj su prisutne brojne multirezistentne bakterije. Takođe, prisustvo antibiotika, deterdženata, dezinficijenasa selektivnim pritiskom dodatno pospešuje razvoj rezistencije bakterija na antimikrobne agense.

Iako se u mikrobiološki ispravnoj vodi za piće ne nalaze patogene bakterije, mikroorganizmi koji su prisutni u vodi mogu biti nosioci gena koji kodiraju rezistenciju na antibiotike. Tako se genetičke determinante rezistencije putem vode distribuiraju do ljudi i životinja, mogu postati deo njihovog mikrobioma, ali se dopremaju i do različitih ekoloških niša, gde mogu biti preuzete od strane različitih mikrobnih populacija.

Zbog svega navedenog, rezistencija bakterija na antibiotike predstavlja izazov kome se može pristupiti jedino integrisano, primenom koncepta "Jedno zdravlje". Objedinjen interdisciplinarni pristup u oblasti medicine, veterine, biologije, biotehnologije i poljoprivrede sveobuhvatno sagledava cirkulišuće rezistentne klonove, njihove glavne izvore i puteve diseminacije.

Ključne reči: vodena sredina, rezistentne bakterije, genetička osnova rezistencije

MINI SIMPOZIJUM

100 GODINA KATEDRE I INSTITUTA ZA PATOLOGIJU "PROF. DR ĐORĐE JOANNOVIĆ": OD MORFOLOGIJE DO MOLEKULARNE PATOLOGIJE

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

AUTOPSIJE – DA LI SU NAM I DALJE POTREBNE?

Radmila Janković

Autopsije su rađene od davnina i imale su ogroman značaj u razvoju patologije, ali i svih ostalih medicinskih disciplina. U jednom periodu smatrale su se osnovnom metodom naučnoistraživačkog rada, osnovnim sredstvom za usavršavanje lekara i edukaciju studenata medicine. Veoma dugo su se autopsije smatrale neizostavnim dijagnostičkim testom koji kao zlatni standard ima veoma visoku senzitivnost za utvrđivanje uzroka smrt. Međutim, poslednjih decenija je došlo do značajnog pada u broju kliničkih autopsija. Uzroci pada broja kliničkih autopsija su materijalni troškovi, strah lekara od otkrivanja propusta u lečenju i potencijalnih tužbi, kao i uverenje pojedinih lekara da su savremeni dijagnostički aparati superiornije dijagnostičko sredstvo od autopsija.

Kliničke autopsije su veoma važan faktor u proceni kvaliteta zdravstvene službe, posebno službe hitne medicinske pomoći i tercijarnih medicinskih ustanova i zasniva se na kliničko-autopsijskoj korelaciji. *Goldman* i saradnici su definisali tri kategorije kliničko-autopsijske diskrepance, odnosno grešaka, a definisani kriterijumi nazivaju se Goldmanovim kriterijumima. Prema ovim kriterijumima velike greške u završnim dijagnozama povezanim sa uzrokom smrti označene su kao *major* diskrepance sa potkategorijama I i II. Postojanje neslaganja u kliničkim i autopsijskim dijagnozama koje nisu direktno povezane za uzrokom smrti je označeno kao *minor* diskrepanca, a one su podeljene u dve kategorije: III i IV. Potpuno slaganje kliničkih dijagnoza i autopsijskog nalaza predstavlja kategoriju V. Procenjeno je da bi u slučaju 100% urađenih kliničkih autopsija u bolnicama procenat greške klase I bio sveden na najmanju moguću meru (*MochH*, 2018.).

Značaj kliničke autopsije je ponovo dospeo u žižu interesovanja lekara pojavom COVID-19 pandemije. Autopsijska istraživanja su velikoj meri doprinela otkrivanju brojnih činjenica o COVID-19, ali i o efikasnosti različitih terapijskih protokola.

Ključne reči: klinička autopsija, kliničko-autopsijska korelacija

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

HISTOPATOLOŠKI PROGNOSTIČKI PARAMETRI MELANOMA KOŽE U SRBIJI

Dimitrije Brašanac, Ivana Savić, Martina Bosić

Histopatološki prognostički parametri melanoma kože ukazuju na stepen rizika agresivnijeg biološkog ponašanja i određuju dalje dijagnostičke i terapijske procedure. Najvažniji parametri u primarnom melanomu kože su debljina tumora (Breslow) i prisustvo ulceracije. Budući da su melanomi kože dostupni kliničkom pregledu bez komplikovanih dijagnostičkih aparata, histopatološke karakteristike melanoma u populaciji govore o efikasnosti ranog otkrivanja koja direktno utiče na ishod i troškove lečenja.

U posmatranom periodu 2001-2015 analizirano je 1048 primarnih melanoma (uključujući 178 in situ lezija) iz biopsijskih uzoraka Instituta za patologiju Medicinskog fakulteta u Beogradu. Prosečna starost pacijenata bila je 56,8 godina uz nešto veću zastupljenost ženskog pola (53%). Srednja vrednost debljine tumora bila je 3,51 mm, uz prisustvo ulceracije u 36,3%. In situ melanomi su predstavljali 16,4% svih melanoma, uz značajan porast učešća tokom perioda posmatranja. Melanomi debljine do 1mm (pT1) predstavljali su 33,4% svih invazivnih tumora (uz lak porast učešća), a debljih od 4 mm (pT4) 28,9% (uz vrlo lako smanjenje udela). Melanomi pT4 kategorije imali su prosečnu vrednost Breslow debljine 8,66 mm, i ulceraciju u 70% slučajeva. Pacijenti starosti do 40 godina imali su znatno češće pT1 u odnosu na pT4 tumore (56% prema 9,8%), dok se ta razlika smanjivala kod starijih od 40 godina (42,7% prema 27,2%). Osobe muškog pola imale su skoro podjednak udeo pT1 i pT4 melanoma (36,5% prema 30%), dok je kod pacijenata ženskog pola udeo pT1 tumora značajno veći (50,6% prema 18,9%). Najlošiju kombinaciju prognostičkih parametara pokazivali su muškarci stariji od 40 godina, a najbolju žene mlađe od 40 godina.

U odnosu na studije zemalja Zapadne Evrope i Severne Amerike, melanomi u Srbiji pokazuju veći Breslow, češće ulceracije, veći udeo pT4 a manji pT1 tumora. Tokom posmatranog perioda došlo je do porasta udela in situ i pT1 melanoma, ali uz neznatno smanjenje pT4 i održavanje visoke zastupljenosti ulcerisanih tumora.

Ključne reči: melanom kože, histopatološki parametri, prognoza

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

BOLEST MASNE JETRE

Nada Tomanović

Bolest masne jetre obuhvata niz stanja koja nastaju usled nagomilavanja lipida u jetri. Ono može biti prouzrokovano ekscesivnom konzumacijom alkohola ili se javiti u sklopu opšteg poremećaja metabolizma, npr. u dijabetes melitusu. Kao posledica pandemije gojaznosti i dijabetesa, nealkoholna masna bolest jetre poslednjih godina postaje najznačajniji uzrok hronične bolesti jetre, naročito u razvijenim zemljama. Novija saznanja ukazuju da su ranije „kriptogene" ciroze najverovatnije posledica neprepoznate masne bolesti jetre.

Masna bolest prolazi kroz tri faze. U prvoj, postoji uglavnom krupnokapljična masna promena hepatocita, bez tkivnog oštećenja. Vremenom dolazi do progresije u drugu, nekroinflamatornu fazu koja se očituje steatohepatitisom. Metabolički preopterećeni hepatociti podležu različitim tipovima ćelijske smrti, od kojih neke poput piroptoze i nekroptoze izazivaju zapaljensku reakciju. U ovim fazama oštećenje je i dalje reverzibilno, i sa prestankom dejstva štetnog agensa dolazi i do regeneracije tkiva jetre. Steatohepatitis se češće i brže razvija ukoliko je masna bolest posledica hronične zloupotrebe alkohola.

Ako se štetno dejstvo nastavi, bolest prelazi u treću fazu koja se karakteriše fibrozom, koja započinje perisinusoidalno i pericelularno oko centralnih vena, a nastavlja se pojavom vezivnih septuma. Fibroza progredira i u završnoj fazi bolesti dolazi do pojave ciroze.

Aktivnost masne bolesti jetre procenjuje se na biopsijskom materijalu i izražava se kroz vrednost NAS skora. U sklopu ovog skora određuje se procenat hepatocita sa masnom promenom, lobularna inflamatorna aktivnost i broj baloniranih hepatocita. Pored NAS skora, za svakog pacijenta sa masnom bolesti jetre neophodno je odrediti i stadijum fibroze.

S obzirom na sve veći značaj koju ova bolest nosi, intenzivno se radi na ispitivanju genetičkih, molekularnih, celularnih i tkivnih faktora koji učestvuju u patogenezi masne bolesti jetre, a koji bi potencijalno bili od važnosti za njeno lečenje.

Ključne reči: masna bolest jetre, nealkoholna masna bolest, fibroza, ciroza

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

TIREOIDITISI, DIFERENCIJALNO DIJAGNOSTIČKE DILEME

Duško Dunđerović

Zapaljenja štitaste žlezde se nazivaju tiroiditisima. U tipičnim slučajevima Hashimotovog tireoiditisa postoji difuzno i simetrično uvećanje žlezde, ali u nekim slučajevim ase uočavaju jasno formirani nodusi. Najveći broj folikula štitaste žlezde je atrofičan, ali drugi mogu pokazivati osobine konzistentne sa regenerativnom hiperplazijom. Najveći broj folikula je obložen onkocitnim ćelijama različite veličine. Jedra ovih ćelija mogu biti uvećana i hiperhromatična, ili obrnuto, mogu biti hipohromna i preklapati se, što je slično jedrima kod papilarnog karcinoma. Fibrozna varijanta Hašimotovog tiroiditisa se može pomešati sa karcinomom kada je fibroza udružena sa epitelnim ostrvcima koja pokazuju skvamoznu metaplaziju. Nodularna varijanta Hašimotovog tiroiditisa je Hašimotov tiroiditis u kojem je prisutan jedan ili više hiperplastičnih nodusa koji su isključivo sačinjeni od onkocitnih ćelija u solidnom ili folikularnom aranžmanu. Pacijenti sa Hašimotovim tiroiditisom imaju povećan rizik da razviju maligne neoplazme uključujući limfome (najčešće B-ćelijske), papilarni karcinom, i neoplazme onkocitnih ćelija, te su ovo ujedno i najvažnije diferencijalne dijagnoze kod pacijenata sa Hašimotovim tireoiditisom. Diferencijalno dijagnostički u obzir dolaze i retka stanja poput plasma ćelijskog granuloma. Kod pacijenata sa Grejvsovom bolešću, mikroskopski, tiroidni folikuli su naglašeno hiperplastični, sa izraženim papilarnim protruzijama koji se mogu pomešati sa papilarnim karcinomom. Riedel-ov tiroiditis (invazivni tiroiditis) je ekstremno čvsta lezija, koja obuhvata mekotkivne strukture vrata. Riedel-ov tiroiditis je deo grupe idiopatskih poremećaja koji se označavaju terminom *inflamatorna fibroskleroza*. Sarkomatoidni karcinom je glavni entitet koji treba isključiti u tom pogledu, mada iako se izuzetno retko javljaju diferencijalno dijagnostički u obzir dolaze i primarni sarkomi. Multifokalni sklerozirajući tiroiditisje poremećaj koji se odlikuje multiplim fokusima fibroze u štitastoj žlezdi, često u zrakastoj konfiguraciji. Na malom uveličanju, izgled se ponekad ne može razlikovati od papilarnog mikrokarcinoma, ali na većem uveličanju se uočava izostanak neoplastične žlezdane komponente.

Ključne reči: tiroiditis, Hashimotovo oboljenje, Grejvsovo oboljenje, Riedel-ov tireoiditis, multifokalni fibrozirajući tireoiditis

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

SAVREMENI ASPEKTI U DIJAGNOSTICI MALIGNIH TUMORA UTERUSA I ADNEKSA

Dejan Oprić

U zadnjih dvadesetak godina napravljeni su krupni koraci u samoj dijagnostici patoloških promena u ženskom genitalnom traktu. Savremeni aspekti dijagnostike osim klasičnih metoda kao što su metaoda ex tempore, citološke analize i pregled rutinskih HE preparata danas se veoma uspešno kombinuje sa dodatnim imuno-histohemijskim bojenjima i analizama koje maksimalno doprinose preciznoj dijagnostici. Imuno-histohemijska bojenja postala su rutinska stvar koja podpomaže da se granične ili nejasne promene prelome i postavi tačna dijagnoza uzimajući

u obzir i komplikacije datih analiza u pravcu lažno pozitivnih ili lažno negativnih rezultata. U novije vreme sve više se uključuju i genetske dodatne analize koje nam pomažu u tome da otkrijemo da li je tumor „Wild type“ ili ne što je od velikog značaja za primenu onkološke terapije. U 15 % slučajeva tumorska promena nije „Wild type“ te se tu onda mogu primeniti citostatici treće zone odbrane koji imaju ciljano dejstvo na sam tumor. I da zaključimao, današnja savremena dijagnostika u ginekološkoj patologiji je kombinacija rutinskih metoda, imuno-histohemijskih metoda i samih genetskih ispitivanja.

Ključne reči: imunohistohemija, ginekološka patologija, digitalna patologija

Institut za patologiju “Prof. dr Đorđe Joannović”, Medicinski fakultet, Univerzitet u Beogradu

HISTOPATOLOŠKA DIJAGNOSTIKA TUMORA HIPOFIZE – JUČE, DANAS, SUTRA

Emilija Manojlović Gačić

Histopatološka dijagnostika tumora hipofize se razvijala u skladu sa razvojem patologije kao dijagnostičke i naučne discipline.

Dijagnostika tumora hipofize se primarno zasnivala na morfološkoj distinkciji tumora porekla adenohipofize i neurohipofize. Tumori adenohipfoize su do skoro nosili naziv adenomi hipofize. Njihova klasifikacija se zasnivala na tinktorijalnim svojstvima, na osnovu čega su grupisani u acidofilne, bazofilne i amfofilne adenome hipofize. Povezanost acidofilnih adenoma povezani sa akromegalijom i bazofilnih sa Kušingovom bolešću je bila dobro poznata. Uporedo sa razvojem imunohistohemije dolazi do primene antitela na hormone adenohipofize, čime je omogućena detekcija produkcije hormona u adenomima hipofize, na kojoj se dugo vremena zasnivala njihova klasifikacija. Otkrićem transkripcionih faktora za diferencijaciju ćelija adenohipofize se otišlo korak dalje u dijagnostici adenoma hipofize, budući da je potvrđeno da i adenomi hipofize prate linije diferencijacije vođene transkripcionim faktorima. Aktuelna klasifikacija tumora hipofize se zasniva na prepoznavanju linija diferencijatije, koja se vrši imunohistohemijski, primenom antitela na transkripcione faktore adenohipofize. Uvođenje metoda vizualizacije u rutinsku kliničku dijagnostiu tumora hipofize je omogućilo sagledavanje njihove invazivnosti i potencijalnog agresivnog biološkog ponašanja, zbog čega je naziv „adenom hipofize“ (koji ukazuje na benigni tumor) zamenjen nazivom „neuroendokrini tumor hipfoize“ u najnovijoj klasifikaciji Svetske zdravstvene organizacije (SZO). U retkim i neobičnim slučajevima neuroendokrinih tumora hipofize, kod kojih nije moguće odrediti liniju diferencijacije metodom imunohistohemije, se koristi sekvencioniranje nove generacije. Za razliku od klasifikacije tumora adenohipofize, koja ima tendenciju usložnjavanja, klasifikacija tumora neurohipfoize ima tendenciju simplifikacije. Tumori neurohipofize su morfološki heterogeni, zbog čega su u ranijim klasifikacijama nosili nazive u skladu sa morfološkim karakteristikama. U najnovijoj klasifikaciji SZO ovi tumori su predstavljeni kao podtipovi pituicitoma, budući da uniformna pozitivnost na biomarker TTF-1 ukazuje na njihovo zajedničko poreklo.

Broja naučna istraživanja se sprovode sa ciljem otkrića prognostičkih markera za agresivno biološko ponašanje tumora, za koje se nadamo da će predstavljati budućnost histopatološke dijagnostike tumora hipofize.

Ključne reči: neuroendokrini tumori hipofize, klasifikacija, imunohistohemija, transkripcioni faktori

Institut za patologiju “Prof. dr Đorđe Joannović”, Medicinski fakultet, Univerzitet u Beogradu

Institut za histologiju i embriologiju “Prof. dr Aleksandar Đ. Kostić”, Medicinski fakultet, Univerzitet u Beogradu

ZNAČAJ ELEKTRONSKE MIKROSKOPIJE I IMUNOFLUORESCENTNOG BOJENJA U DIJAGNOSTICI BUBREŽNIH OBOLJENJA

Ljiljana Bogdanović, Milica Labudović

Poznato je da histopatološki pregled biopsije bubrega olakšava dijagnozu i identifikaciju različitih patoloških stanja. Adekvatna dijagnoza glomerulonefritisa zahteva primenu direktne imunofluorescentne mikroskopije (DIF) zajedno sa svetlosnom mikroskopijom i komparacijom sa kliničkim podacima i serološkim testovima. DIF identifikujući mesta deponovanja imunskih kompleksa pomaže u rešavanju diferencijalne dijagnoze glomerulonefritisa. Međutim, još ranije sprovedena istraživanja ukazala su na činjenicu da se značajan deo biopsija bubrega ne može tačno dijagnostikovati bez primene transmisione elektronske mikroskopije (TEM) koja je, zajedno sa rutinskom svetlosnom mikroskopijom i DIF i/ili imunohistohemijom (IHC), veoma važna komponenta dijagnostičke obrade biopsija bubrega, posebno nativnih biopsija bubrega. U novije vreme Banff grupa preporučuje upotrebu TEM u ispitivanju biopsija transplantiranih bubrega, kako u slučajevima sumnje na rekurentne ili de novo glomerularne bolesti, tako i za identifikaciju ranih lezija transplantacione glomerulopatije. Smatra se da bi otkrivanjem lezija mnogo pre nego što one postanu vidljive svetlosnom mikroskopijom odgovarajućim lečenjem mogla da se spreči njihova progresija u očiglednu transplantacionu glomerulopatiju. Poslednjih decenija, širom sveta, usled značajnog napredka u IHH, kojom se mogu dijagnostikovati određene lezije bubrega, kao i drugih metoda u dijagnostici biopsija bubrega (molekularne metode), ali i zbog sve većeg pritiska da se smanje troškovi zdravstvene zaštite, mnogi zdravstveni centri umanjuju ulogu dijagnostičke TEM. Iskustvo, međutim, pokazuje da neizvođenje TEM, u određenim slučajevima, može da dovede do postavljanja netačne dijagnoze, sa mogućim kliničkim posledicama. S toga TEM ostaje važna komponenta dijagnostičke evaluacije biopsija bubrega.

Ključne reči: direktna imunofluorescencija, elektronska mikroskopija, biopsija bubrega

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

SAVREMENI PRINCIPI DIJAGNOSTIKE LIMFOMA

Tatjana Terzić

Limfomi su vrlo heterogena grupa malignih neoplazmi, koje se mogu javiti u limfnom čvoru (nodalno) ili u bilo kom tkivu ili organu (ekstranodalno). Nedavno publikovana 5. klasifikacija limfoidnih neoplazmi Svetske zdravstvene organizacije i Internacionalna konsenzus klasifikacija iz 2022. godine obuhvataju oko 120 entiteta, uključujući i po prvi put grupu tumoru sličnih lezija sa B- i T-ćelijskom predominacijom. Za svaki entitet jasno su definisani specifični dijagnostički kriterijumi, sa prognostičkim i terapijskim implikacijama, pre svega zahvaljujući primeni molekularno/citogenetskih studija. Poseban izazov predstavlja dijagnostika neneoplastičnih bolesti koje imitiraju limfome, kao što su hronične inflamacije, imunodeficijencije, autoimmune bolesti, virusne infekcije, a koje ujedno mogu biti i prelimfomske lezije.

Savremena dijagnostika limfoma se zasniva na koreliranju morfoloških, imunofenotipskih, molekularnih i kliničkih karakteristika. Zadatak patologa je da na osnovu morfološke i imunohistohemijske analize utvrdi tačan podtip limfoma, od čega zavise i terapijski pristup i prognoza. Pored dijagnostičkih, imunohistohemijska analiza ima značaj i u definisanju prognostičkih podtipova u okviru istog entiteta, kao i u ciljanom ("target") terapijskom pristupu.

Preduslov pouzdane dijagnostike i interpretacije morfološkog, imunohistohemijskog i molekularnog nalaza u limfoidnom tkivu je adekvatno uzet i tehnički dobro obrađen uzorak, zatim uvid u kliničke i laboratorijske podatke, kao i poznavanje dijagnostičkih i diferencijalno-dijagnostičkih principa u hematopatologiji.

Za većinu limfoma imunohistohemijska analiza je dovoljna za definitivnu dijagnozu. Međutim, mnogi limfomi imaju morfološka i fenotipska preklapanja, pa je u cilju diferencijalne dijagnoze potrebno dodatno ispitati klonalnost limfoidnih ćelija PCR metodom, ili identifikovati specifične hromozomske aberacije fluorescentnom *in situ* hibridizacijom, a značajne dopunske dijagnostičke metode su i protočna citometrija i metoda nove generacije sekvencioniranja.

Ključne reči: limfomi, klasifikacija, imunohistohemija, fluorescentna *in situ* hibridizacija

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

PATOLOGIJA ODBACIVANJA SRČANIH TRANSPLANTATA

Sofija Glumac

Transplantacija srca predstavlja najefikasniji način lečenja pacijenata u terminalnom stadijumu srčane insuficijencije. Stope preživljavanja su se značajno poboljšale, ne samo zahvaljujući napredovanju u imunosupresivnoj terapiji, već i u napretku prepoznavanja znakova odbacivanja transplantata.

Trenutno, endomiokardna biopsija (EMB) predstavlja zlatni standard u praćenju ovih pacijenata. EMB se pokazala kao bezbedna i prikladna tehnika, sa malom greškom pri uzorkovanju i do danas ostaje jedna od najpreciznijih metoda za dijagnostiku akutnog odbacivanja. Nakon transplantacije biopsije se izvode jednom nedeljno u prvom posttransplantacijskom mesecu, zatim se na svake dve nedelje radi kontrolna biopsija do desete nedelje , a do kraja šestog meseca jednom mesečno. Dalji program zavisi od samih rezultata patohistološkog pregleda biopsije.

Za definisanje i gradiranje odbacivanja preporučene su smernicama Međunarodnog društva za transplantaciju srca i pluća (ISHLT – Task Force) iz 2010. godine, koje definišu tri oblika odbacivanja: hiperakutno odbacivanje koje se javlja ubrzo nakon reperfuzije transplanta; akutno ćelijsko odbacivanje (engl. acute cellular rejection – ACR) i akutno antitelima posredovano odbacivanje (engl. acute macrophageal rejection – AMR).

ISHLT sistem gradiranja ACR definisan je sa četiri gradusa: gradus 0R (bez odbacivanja, infiltracije inflamatornim ćelijama i oštećenja kardiomiocita), gradus 1R (blago odbacivanje, intersticijalni ili perivaskularni inflamatorni infiltrat sa ili bez fokusa oštećenja kardiomiocita), gradus 2R (umereno odbacivanje, ≥ 2 fokusa infiltracije inflamatornim ćelijama sa oštećenjem kardiomiocita), gradus 3R (teško odbacivanje, difuzni inflamatorni infiltrat sa multifokalnim oštećenjem kardiomiocita, edemom, vaskulitisom i intersticijalnom hemoragijom).

Smernice ISHLT-a iz 2011. za dijagnozu AMR-a predlažu gradiranje na osnovu samo patoloških dijagnostičkih nalaza AMR-a (odbacivanje posredovano patološkim antitelima [pAMR]). Gradusi odbacivanja su definisani kao samo histopatološki AMR (pAMR1h), samo imunopatološki AMR (pAMR1i), kombinovani histološki i imunopatološki pozitivan nalaz AMR (pAMR2) i teški patološki AMR (pAMR3).

Praćenje pacijenata nakon transplantacije srca kao i pažljivo balansirana imunosupresivna terapija je od suštinskog značaja za poboljšanje preživljavanja ovih pacijenata.

Ključne reči: transplantacija, endomiokardna biopsija, AMR, ACR

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

MOLEKULARNE ANALIZE U MEZENHIMALNIM TUMORIMA: ŠTA RADIMO, A ČEMU STREMIMO?

Jelena Sopta, Simić Lj., Fekete M.

Još je 2001. godine procenjeno da će do 2005. godine više od 5% svih laboratorijskih ispitivanja biti zasnovano na DNK ili RNK analizi. Ipak , niko se nije nadao da će se 2021. godine (u jeku Covid-19 pandemije) taj procenat približiti 50%.

Testiranje zasnovano na nukleinskim kiselinama postalo je ključno dijagnostičko sredstvo u širokom spektru neoplastičnih i neneoplastičnih procesa. Pored dijagnostike, molekularno testiranje danas pomaže u definisanju terapiskog pristupa i pruža neophodnu osnovu za uspešnu primenu genske terapije ili terapije modifikatorima biološkog odgovora. Odličan je alat za procenu odgovora na terapiju, otkrivanje minimalne rezidualne bolesti, a time i predikciju prognoze. U kontekstu navedenih benefita, koje je molekularna dijagnostika donela savremenoj patologiji i onkologiji, njeno mesto je sve veće u procesu rutinske dijagnostike.

S toga, nesporno je da su savremene dijagostičke molekularne tehnike, koje su se kretale od IHH, FISH, CISH, PCR, pa sve do NGS učinile da patologija, kao naučna oblast, dobije potpuno drugu dimenziju i od morfološke pretenduje da postane molekularna disciplina. Upotreba molekulatnih tehnika u svakodnevnom radu na Institutau za patologiju MFUB je *condicio sine qua non, a* mezenhimalni tumori predstavjaju jednu od vodećih indikacija za njihovu primenu. Medjutim, kao što nema "zlatnog" histološkog kriterijuma, tako ne postoji ni "zlatna" molekularna aberacija koja je apsolutni dijagnostički/terapijski kriterijum. Moramo biti svesni da je molekularna tehnologija značajno limitirana činjenicama da jedan tumor može imati više molekularnih aberacija, ili pak različiti tumori mogu imati identičan genski rearanžman. Njihova molekularna potvrda, predstavlja potreban, ali ne i dovoljan uslov za postavljanje dijagnoze i izbor adekvatne terapije.

Kako bilo, nesumnjivo je da su molekularna testiranja sadašnjost (i budućnost) savremene medicine, pa i Instituta za patologiju MFUB, ali njihova adekvatno interpretacija moguća je jedino od strane visokospecijalizovanih patologa, a u kontekstu multidisciplinarnog kliničko-radiološko-laboratoriskog pristupa,

Ključne reči: mezenhimalni tumori, molekularne metode, diferencijalna dijagnoza

Faculty of Medicine, University of Belgrade, Institute of Pathology, Belgrade

Uppsala University

Department of Immunology, Genetics and Pathology

POSSIBILITIES AND CHALLENGES OF MULTIOMICS METHODS IN PATHOLOGY RESEARCH

Martina Bosic, Neda Hekmati, Fredrik Ponten

Application of advanced sequencing technologies in tissue and cell biology enabled deeper understanding of diseases pathogenesis, molecular classification, and remodeling at cellular resolution. As the tissue environment is lost in these methods, spatial context of cell-to-cell interactions can not be assessed thus only predicted by computational modeling. Access to fresh tissues and cost of these method represent a great challenge for their use in research. In addition, a comprehensive study of tissues requires in-depth study of DNA, RNA, and protein alterations in the same samples or in situ with new spatial omics methods. This can further raise the costs of research. A way to overcome this obstacle is to use open access data generated by other researchers and to exploit public data repositories (e.g. NCBI BioSample database or Gene Expression Omnibus) and webportals of research consortia (e.g. The Cancer Genome Atlas, Human Protein Atlas, Clinical Proteomic Tumor AnalysisConsortium). Novel bioinformatics techniques have enabled integration of large datasets from several resources and computational modeling of their cellular composition. In such way, differences in cellular composition and cell phenotypes related to histopathological, genetical, or clinical characteristics can be imputed. These differences should be further validated on protein level, using immunohistochemitry, a cost-effective approach which allows for analysis at single cell resolution. Although simultaneous evaluation of larger number of proteins by immunohistochemistry still represents a challenge, it can provide a spatial context of cellular alterations in tissues which can be further explored by computational image analysis and description of cellular neighbourhoods in the tissues. The final aim of such integrative evaluation of how tissue architecture- and cellular alterations are related to mutations, gene and protein expression, is to better understand dissease and to develop reliable biomarkers with clinical utility.

Keywords: genomics, transcriptomics, proteomics, open data, image analysis, biomarkers

MINI SIMPOZIJUM
SAVREMENA STREMLJENJA U KOŠTANO–ZGLOBNOJ TRAUMATOLOGIJI

Medicinski Fakultet, Univerzitet u Beogradu
Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

HIRURGIJA MUSKULOSKELETNE TRAUME - JUČE, DANAS, SUTRA

Goran Tulić

Uvod: Turbulentan pred-istorijski i istorijski razvoj medicine i hirurgije kroz više od 3.000 godine, neminovno je uticao i na razvoj muskuloskeletne hirurgije, počev od prvih zabeleženih hirurških lečenja preloma u starom Egiptu, preko prvih bolnica za povredjene u antičkom Rimu, do prvih mobilnih ortopedsko-hirurških ratnih ambulanti u vreme Napoleona. Otkriće anestezije, antiseptika i uvodjenje gipsane imobilizacije, spoljašnjih fiksatora i prvih koštanih implanta tokom XIX i početkom XX veka, te kulminacija u tehnološkoj revoluciji i evidence-based ortopaediji sredine XX i početka XXI veka, nepovratno su oblikovali izgled i perspektive muskuloskeletne hirurgije.

Materijal i metode: U radu se prikazuje konceptualni razvoj modernih principa lečenja povreda muskuloskeletnog sistema, sa posebnim osvrtom na hirurška i tehnička dostignuća, kao što su mini- invazivne metode lečenja, upotreba navigacionih, komjuterski-asistiranih i veštačkom- inteligencijom vodjenih procedura, te elaboriraju budući trendovi u lečenju, od ortobioloških do 3D printing tehnologija. Takodje se razmatraju osnovni postulati lečenja komplikacija u muksuloskeletnoj traumatologiji.

Diskusija: Često neprepoznata "pandemija" traume, nameće potrebu za visokospecijalizovanim kadrovskim, organizacionim, tehnološkim i finansijskim resursima. Stručni i ukupni zdravstveni sistem je, zato, neophodno inovirati u skladu sa zabeleženim trendovima u traumatologiji, kao što su: a) sve veći broj povredjenih, kako u životno najproduktivnijim populacionim grupama tako i u onim najstarijim; b) sve učestaliji mirnodopski i sve brojniji i nepredvidljiviji ratni konflikti; c) rastuće frekvence saobraćajnog i industrijsko-radnog traumatizma i politraume, d) neminovno sučeljavanje sa kompleksnim komplikacijama kako povreda tako i lečenja, te e) sve veći individualni zahtevi savremenog načina *života pojedinca.*

Zaključak: Formiranje modernih principa zbrinjavanja teško povredjenih i obolelih, uvodjenje algoritamskih protokola u svakodnevnu praksu, inovativnost i naučna zasnovanost u hirurškim i tehnološkim aspektima te multidisciplinarnost i personalizacija tretmana, omogućili su visoke standarde lečenja i uspešnu funkcionalnu i *životnu* rehabilitaciju pacijenata sa povredama muskuloskeletnog sistema.

Ključne reči: trauma, muskuloskeletni sistem, lečenje, moderni principi, protokoli

Medicinski Fakultet, Univerziteta u Beogradu
Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

LEČENJE POVREDA GORNJEG EKSTREMITETA

Marko Ilić

Povrede gornjeg ekstremiteta su veoma česte i čine više od 60 procenata od ukupnog broja ortopedskih povreda. Kao izolovane povrede javljaju javljaju se u više od 90 procenata. Više od polovine preloma je nedislocirano. Otvoreni prelomi se javljaju u manje od 4 procenata. Frakture gornjih ekstremiteta imaju bimodalnu dobnu distribuciju i bili su češći od onih na donjim ekstremitetima, koji pokazuju rastuću distribuciju prema godinama starosti. Ove povrede kod mlađih pacijenta najviše su vezane za različite sportske aktivnosti i češće su kod osoba muškog pola. Kod pacijenta starijih od 60 godina povrede su češće kod osoba ženskog pola, a najčešći mehanizam povrede je pad na istom nivou. Najćešće anatomsko mesto povrede predstavljaju distalni okrajak radijus i ulne. Povećan broj metafiznih i dijafiznih preloma kod strarijih pacijenata povezuje se sa smanjenom gustinom kosti, odnosno osteoporozom. Prelomi distalnog radijusa i ulne su najčešći prelomi gornjih ekstremiteta (16,2 preloma na 10 000 osoba), zatim prelomi šake (prelomi falangi i metakarpalnih kostiju; 12,5 odnosno 8,4 na 10 000), prelomi proksimalnog humerusa (6,0 na 10 000) i prelomi ključne kosti (5,8 na 10 000). Prelomi ramena, podlaktice i ručnog zgloba predstavljaju više od trećine osteoporotičnih preloma kod strarijih osoba. Veći deo preloma gornjeg ekstremiteta se i dalje leči neoperativno. Broj operativno lečenih pacijenta sa ovim povredama je u stalnom povećanju.

Ključne reči: trauma, gornji ektremitet, lečenje, protokoli

Medicinski Fakultet, Univerzitet u Beogradu

Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

ZBRINJAVANJE AKUTNE TRAUME ŠAKE

Slađana Matić

Uvod: Zbrinjavanje akutne povreda šake obuhvata poznavanje i ovladavanje čitavim dijapazonom hirurških tehnika, od koštane hirurgije do mikrohirurgije. Pri hirurškom radu je neophodno obratiti pažnju na detalje, preciznost i atraumatsku tehniku, čiji se značaj prvi put pominje u jednom radu Banela iz 1921. godine. Ovo su omogućili razvoj instrumentarija i mikroskopa.

Materijal i metodi: Prikazujemo kliničke karakteristike različitih povređenih struktura i tkiva. U kliničkoj slici možemo imati bol i otok, nekad i vidljiv deformitet, alineophodno je proceniti cirkulaciju povređene šake, kao i motoriku i senzibilitet. Osim preloma kostiju, ne manje značajne su i povrede mekih struktura šake. Otvorene povrede šake su zapravo veoma česte, a uglavnom se radi o istovremenoj povredi više različitih tkiva.

Rezultati:Hirurg mora da napravi logični plan lečenja da bi se dobio maksimalni funkcionalni oporavak. Svaki pacijent i svaka povreda šake su slučaj za sebe. Dijapazon hirurških tehnika ide od stabilizacije preloma, rekonstrukcije tetiva i nerava, revaskularizacije i rešavanja defekta kožnog pokrivača.

Zaključak: Ove povrede su često olako shvatane, a daju značajnafunkcionalna i estetska oštećenja. Zbrinjavanje povreda šake je vrlo složen proces i zateva dobro poznavanje anatomije i operativnih tehnika, čemu sledidobro vođen rehabilitacioni program.

Ključne reči: šaka, povrede, lečenje, protokoli

Medicinski Fakultet, Univerzitet u Beogradu

Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

SAVREMENI ASPEKTI LEČENJA POVREDA PREDNJE UKRŠTENE VEZE U ŽENSKOM FUDBALU

Darko Milovanović

Najbrže rastuća sportska aktivnost u svetu danas je ženski fudbal. Evropska fudbalska federacija je dokumentovala rast broja aktivnih sportistkinja od 7,1% na godišnjem nivou između 2016 i 2017 godine. Samim tim u poslednjoj deceniji širom sveta je primećen značajan rast ortopedskih povreda kod žena fudbalera. Epidemiološki je dokazano da incidence koštanozglobnih povreda iznosi 3.42 na 1000 sati igre. Studije pokazuju da su tri najčešće povrede - povrede kolena, skočnog zgloba i tetivne povrede i njihove incidence se značajno razlikuju od povreda kod muškaraca. Najčešća povreda od svih je povreda prednje ukrštene veze koja je najmanje dvostruko češća kod žena nego kod muškaraca bez obzira na izloženost povredama i nivou učešća u sportu. Obzirom na specifičnost sportske aktivnosti kojom se bave vremenom su se nametale i dileme vezane kako za operativno lečenje, ali i postoperativnu rehabilitaciju. Cilj ovog rada je da se prikažu savremeni aspekti operativnog lečenja od preoperativne pripreme, hirurškog lečenja koje u najvećoj meri podrazumeva adekvatan izbor grafta, preko operativne tehnike i primene bioregenerativne medicine, ali i specfičnosti postoperativnih rehabilitacionih protokola. U radu će biti prikazana iskustva iz dostupne literature, ali i lična iskustva u lečenju žena fudbalera u poslednje dve godine.

Ključne reči: ženski fudbal, povrede, prednja ukrštena veza, lečenje

Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

PRINCIPI LEČENJA PRELOMA KARLICE

Uroš Dabetić

Lečenje preloma karlice predstavlja jedan od najvećih izazova u ortopedskoj hirurgiji i traumatologiji. Radi se o povredama čiji mortalitet dostiže i 40% , te je od velike važnosti prepoznavanje i adekvatno lečenje. Najčešći uzrok smrtnog ishoda u prva 24h od povrede je krvarenje. Prelomi karlice variraju od jednostavnih preloma do kompleksnih fraktura sa posledičnom hemodinamskom nestabilnošću. Cilj ove studije je da proceni trenutne standarde zbrinjavanja preloma karlice, kao i da ukaže na moguću strategiju poboljšanja krajnjeg ishoda lečenja.

Kada protokol ne postoji, dežurni tim se vodi smernicama koje su im dostupne. U novije vreme damage control resuscitation (DCR) se smatra vodećim principom u zbrinjavanju politraumatizovanih pacijenata. Primarno je uspostaviti kontrolu krvarenja - primenom preperitonealnom tamponiranjem karlice (Preperitoneal Pelvic Packing – PPP), angiografskom embolizacijom ili Endovaskularna Balon Okluzija Aorte (Resuscitative Endovascular Balloon Occlusion of the Aorta- REBOA) metodom. Primena karličnih poveski se preporučuje u literaturi kao primarni vid zbrinjavanja povreda karlice od strane službe hitne pomoći ili obučenog lica u predbolničkim uslovima. Spoljašnja fiksacija nestabilnih preloma karlice je jedan od ključnih koraka u skopu DCR protokola. ORIF preloma karlice je definitivan tip fiksacije preloma, ali je indikovana kod hemodinamski stabilnog pacijenta.

Obzirom na anatomske karakteristike karlične duplje, povrede karličnog prstena predstavljaju samo deo spektra politraume, tako da se lečenje u početku bazira na hemodinamsku stabilizaciju pacijenta (DCR protokol). Lečenje ovakvih pacijenata zahteva multidisciplinarni pristup. Plasiranje spoljašnjeg fiksatora u sklopu DCO protokola ima ulogu u kontroli krvarenja, te je to metoda izbora kod hemodinamski nestabilnih pacijenata. Definitivna fiksacija preloma karlice (ORIF) se sprovodi kod stabilnih pacijenata koji nisu *životno* ugroženi

Ključne reči: karlica, prelomi, lečenje, principi

Medicinski Fakultet, Univerzitet u Beogradu

Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

SAVREMENO LEČENJE POVREDA KIČMENOG STUBA

Slavisa Zagorac

Povrede kičmenog stuba se ubrajaju u najčešće povrede koštano-zglobnog sistema koje nastaju kao posledica dejstva sile velike energije, a to se pre svega odnosi na saobraćajni traumatizam i padove sa visine.

U radu će biti prikazana epidemiologija povreda kičmenog stuba u tercijernoj zdravstvenoj ustanovi, sa posebnim osvrtom na udružene povrede, vreme hospitalizacije, vreme hirurške intervncije, primenjenu hiruršku tehniku, komplikacije i oporavak

Ono što razlikuje povrede kičmenog stuba od ostalih koštano-zglobnih povreda, je udruženost sa povredama kičmene moždine, koje sa sobom nose posledice po tipu paraplegije ili kvadripregije i koje , uprkos savremenom tehnikama fiksacije preloma, doprinose lošem ishodu hirurškog lečenja. Radi se uglavnom o osobama mlađe životne dobi, te je postojanje neurološkog deficita povezano sa različitim medicinskim i socio-ekonomskim teškoćama.

Zahvaljujući usavršavanju hirurške tehnike (minimalno invazivni pristup), postojećim implantima, savremenim dijagnostičkim sredstvima, povrede kičmenog stuba se danas veoma efikasno operišu i omogućavaju nesmetani daljnji oporavak povređenog.

Trend je da se povrede kičmenog stuba (pogotovu ukoliko postoji neurološki deficit), operišu u što kraćem vremenskom periodu, preopruka je u prvih 24h ili najkasnije u prvih 72h od povrede, jer su studije pokazale bolji oporavak u odnosu na pacijente koji su operisani 7 ili više dana posle povrede. Hirurgija kičmenog stuba je povezana sa komplikacijama, koje mogu biti opšte i lokalne, i njihova incidenca se u različitim studijama kreće od 2-5%.

Ključne reči: povrede kičmenog stuba, hirurško lečenje, komplikacije.

Medicinski fakultet, Univerzitet u Beogradu

Klinika za ortopedsku hirurgiju i traumatologiju, Univerzitetski klinički centar Srbije, Beograd

Centar za anesteziologiju i reanimatologiju, Univerzitetski klinički centar Srbije, Beograd

ANESTEZIJA I POVREDE KOŠTANO-ZGLOBNOG SISTEMA

Svetlana Srećković

Povrede koštano-zglobnog sistema smatraju se najvećom svetskom epidemijom, koja je praćena visokom stopom morbiditeta, mortaliteta i socioekonomskog opterećenja. Traumatske ortopedske povrede čine 10% smrtnih slučajeva širom sveta i vodeći su uzrok smrti pacijenata starosti do 65 godina. Aktivacija endogenih procesa, koja nastaje povredom tkiva odgovorna je za povećan mortalitet i lošiji ishod pacijenata sa politraumom. Imuno-inflamatorni odgovor na samu hiruršku intervenciju nije uvek proporcionalan stepenu oštećenja tkiva. Takođe njemu doprinose i drugi faktori u perioperativnom periodu uključujući tip anestezije, mehaničku ventilaciju ako i primenu krvi i krvnih produkata i antiemetičkih lekova. Neadekvatan, bilo prenaglašen ili nedovoljno izražen, imuno-inflamatorni odgovor odgovoran je za različite postoperativne komplikacije, pre svega nastanak infekcije, respiratorne komplikacije, delirijum i postoperativne kongnitivne poremećaje kao i oštećenje bubrežne funkcije.

Preoperativnom procenom i pripremom ortopedskih pacijenata, kao i adekvatnim izborom anestezije možemo uticati na stepen inflamatornog odgovora a samim tim i na smanjenje hirurškog i anesteziološkog perioperativnog morbiditeta i/ili mortaliteta uz mogućnost pravovremenog uspostavljanja funkcionalnosti pacijenta.

Ključne reči: anestezija, koštano-zglobni sistem, politrauma, imuno-inflamatorni odgovor

MINI SIMPOZIJUM

COVID-19 – FAKTORI RIZIKA ZA TEŽAK OBLIK BOLESTI

Medicinski fakultet, Univerzitet u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

FAKTORI RIZIKA ZA TEŽAK OBLIK BOLESTI COVID - 19 - REZULTATI PROJEKTA „V.I.R.U.S."

Branislava Milenković

Patofiziologija COVID-19 još uvek nije u potpunosti shvaćena, a pouzdani prognostički faktori ostaju nepoznati te je predloženo nekoliko specifičnih terapijskih strategija. Projekat "Survivors of COVID19: variety of immune responses to SARS-CoV-2 in correlation with clinical manifestation. Long term follow-up" se sprovodi u četiri naučno-istraživačke ustanove, nosilac je Medicinski fakultet u Beogradu, a finansira ga Fond za nauku Republike Srbije. Cilj projekta je bila analiza značaja antitela na SARS CoV 2, kao i povezanost sa težinom i ishodom COVID-19 sa kliničkim, radiološkim i biohemijskim karakteristikama obolelih. Takođe, cilj ovog istraživanja je da ispita dugoročne posledice COVID-19 koje su još uvek nedovoljno poznate, ali su verovatno značajne s obzirom na prisustvo poznatih faktora rizika za probleme nastale nakon pneumonije i lečenja u jedinicama intenzivne nege.

Klinički podaci su ukazali da biohemijski status pacijenata sa COVID19 odražava neke poremećene indekse povezane sa hemoglobinom (Hb), kao što su smanjeni Hb i povećan serumski feritin, brzina sedimentacije eritrocita, C-reaktivni protein, albumin i laktat dehidrogenaza. Dugo trajanje bolesti, primene oksigenoterapije, sprovođenje neinvazivne i mehaničke ventilacije kod pacijenata sa COVID-19 uticali su na lošije dugoročne ishode bolesti. Plućna fibroza je vrlo retko nastajala kao dugoročna plućna posledica COVID-19. Upoređivanje radiografije grudnog koša ili kompjuterske tomografije koji su korišćeni su kao dijagnostički alat prve linije, nije ukazalo na značajnu povezanost težine kliničke slike i obimnosti patoloških radioloških promena.

Takođe, analizirani su oksidativno oštećenje i zapaljenski proces koji mogu biti ključni faktori u patogenezi infekcije SARS-CoV-2 i mogu pokrenuti niz događaja koji dovode do oštećenja lipida, proteina i DNK, ćelijske disfunkcije i na kraju ćelijske smrti zbog prekomernog stvaranja reaktivnih vrsta kiseonika (ROS), modifikacija u metabolizmu kateholamina, povećanja taloženja gvožđa i porasta inflamatornih medijatora. Pored lipida, proteini su jedna od glavnih meta ROS, a proteinski proizvodi napredne oksidacije ukazuju na stepen oštećenja proteina oksidativnim stresom u nekoliko patoloških stanja.

Ključne reči: COVID-19, faktor rizika

Medicinski fakultet, Univerzitet u Beogradu
Centar za radiologiju, Univerzitetski klinički centar Srbije, Beograd

DA LI NAM RADIOLOŠKI NALAZ POMAŽE U PROCENI TEŽINE COVID - 19?

Ruža Stević

COVID-19 je virusno oboljenje sa širokim spektrom simptoma i znakova uključujući i respiratorne koji se mogu manifestovati različitim promenama u plućima. Radiološke metode imaju značajno mesto u njihovoj dijagnostici. Prva u algoritmu imidžing metoda je radiografija grudnog koša, zatim kompjuterizovana tomografija (CT) uključujući programe veštačke inteligencije. COVID-19 pneumonija se manifestuje širokim spektrom radiografskih nalaza od diskretnih senki inteziteta mlečnosg stakla, zadebljanog intersticijuma (retikularne promene) pa do opsežnih konsolidacija. Promene se u oko 90% slučajeva nalaze obostrano, dominantno periferno, opsežnije u donjim režnjevima. Sem samog izgleda, važna je i opsežnost promena na radiografiji. Istraživanja su pokazala da je opsežnost promena u korelaciji sa težinom bolesti. Opsežnost nalaza se preciznije određuje izračunavanjem radiografskog skora. Rezultat od 0-4 dodeljuje se svakom pluću u zavisnosti od stepena zahvaćenosti promenama. Rezultati za svako pluće se sabiraju da bi se dobila konačna ocena. Pacijenti sa umereno teškom bolešću, u većini slučajeva imaju bilateralne retikularne ili promene inteziteta mlečnog stakla(GGO) sa nižim radiografskim skorom. U teškim i kritičnim slučajevima, najčešće radiografske manifestacije bile su konsolidacije i GGO, najopsežnije u donjim režnjevima. Ovi nalazi su često progrediraju do ARDS-a što zahteva veštačku ventilaciju. Ovi pacijenti su imali značajno višu vrednost RTG scora od onih sa umereno teškim oblikom bolesti. Kompjuterizovana tomografija (CT) je senzitivnija metoda od radiografije grudnog koša za otkrivanje promena u plućima kod COVID-19. Polukvantitativna CT procena omogućava određivanje opsežnosti promena u različitim stadijumima ove bolesti. Ovaj sistem bodovanja na CT-u se koristi za procenu zahvaćenosti za svaki režanj pluća. Mogući skor promena po režnju je od 0-5, maksimalno 25 za oba pluća. Brojna istraživanja uključujući i naše pokazala su da težina pneumonije na CT-u korelira sa dužinom trajanja i krajnjim ishodom bolesti.

Zaključak: radiološke metode su značajne za dijagnostiku i procenu težine COVID-19 pneumonije.

Ključne reči: COVID-19, pluća, radiografija, kompjuterizovana tomografija

Fakultet medicinskih nauka, Univerzitet u Kragujevcu
Centar za medicinsku biohemiju, Univerzitetski klinički centar Srbije, Beograd

KORELACIJA BIOHEMIJSKIH PARAMETARA INFLAMACIJE I TEŽINE COVID-19

Sanja Stanković

U decembru 2019. godine zabeleženo je izbijanje pneumonije nepoznatog porekla u mestu Wuhan, u provinciji Hubei u Kini. Kao uzročnik je izolovan novi respiratorni virus čija je analiza genoma pokazala da se radi o novom koronavirusu povezanom sa SARS-CoV koji je nazvan SARS-CoV-2. Danas je broj zaraženih u svetu dostigao šesto miliona, a broj umrlih premašio šest miliona stanovnika. Patogenetski mehanizmi koje virus pokreće u organizmu su: inflamatorne kaskade, citokinska oluja i aktivacija koagulacionih kaskada. Jasno je da COVID-19 nije samo bolest pluća i disajnih puteva, već može da izazove i disfunkciju drugih organa kao što su srce, bubrezi, jetra itd., kao i da dovede do veoma ozbiljnih, čak i fatalnih komplikacija kao što su sepsa, diseminovana intravaskualrna koagualcija, akutni kardiovaskularni događaji. Rutinski heamtološki i biohemijski testovi su veoma korisni u praćenju toka bolesti, proceni rizika i prognozi pacijenata sa dijagnostikovanim COVID-19, koreliraju sa lošim ishodom kao što su potreba za mehaničkom ventilacijom ili intenzivnom negom, progresija do multiorganske disfunkcije i/ili smrtnog ishoda. Na osnovu publikovanih radova i meta-analiza, kao i preporuka IFCC (International Federation for Clinical Chemistry and Laboratory Medicine) identifikovane su promene kod pacijenata sa COVID-19: a) hematološki biomarkeri (povišen broj leukocita i neutrofila, povišen NLR (odnos neutrofila i limfocita) i MLR (odnos monocita i limfocita), snižen broj limfocita, trombocita, neutrofila, T/B/NK ćelija); b) biomarkeri koagulacije (produženo PT i aPTT, povišen D-dimer, povišen/snižen fibrinogen); v) biohemijski parametri (snižen albumin, povišeni CRP, feritin, brzina sedimentacije eritrocita, prokalcitonin, srčani troponin, ALT, LDH, bilirubin, urea, kreatinin, IL-6, MCP-3, INF-gama indukovani protein 10, presepsin); d) novi biohemijski markeri npr. homocistein, angiotenzin II. S obzirom da brojne studije i meta-analize pokazuju da inflamatorni odgovor ima krucijalnu ulogu u progresiji COVID-19, biće posebno analizirana povezanost najznačajnijih inflamatornih markera sa težinom oboljenja COVID-19.

Ključne reči: biomarkeri, infalamcija, COVID-19

Biološki fakultet, Univerzitet u Beogradu

PROJEKAT: "SURVIVORS OF COVID19: VARIETY OF IMMUNE RESPONSES TO SARS-COV-2 IN CORRELATION WITH CLINICAL MANIFESTATION. LONG TERM FOLLOW-UP"

Siniša Đurašević

Nova korona virusna bolest 2019 (COVID-19) postala je pandemija koja je ugrozila zdravstvene sisteme širom sveta. COVID-19 izazvan SARS-CoV-2 je složena bolest u kojoj su interakcija virusa sa ciljnim ćelijama, delovanje imunog sistema i sistemski odgovor organizma na ove događaje usko isprepleteni. Nadalje, klinički podaci ukazuju na mogućnost oštećenja različitih organa i tkiva infekcijom COVID-19 koja se manifestuje nekoliko meseci nakon oporavka. Patogeneza infekcije izazvane SARS-CoV-2 i dalje krije mnoge nepoznanice i sumnje, a glavna zagonetka je različit imuni odgovor pacijenta na infekciju. Jedan od mogućih faktora koji doprinosi određivanju ishoda je oksidativni stres, jer je to jedan od mehanizama oštećenja ćelija i tkiva izazvanih virusima kao što je grip.

Brojni glavni faktori rizika koji se odnose na težinu i smrtnost od COVID-19, kao što su starija životna dob, etnička pripadnost, pol, nizak socio-ekonomski status, hiperglikemija i gojaznost, svi su u korelaciji sa pojačanim oksidativnim stresom. Postoje naučni podaci o povezanosti oksidativnog stresa sa promenama pronađenim kod pacijenata sa COVID-19, kao što je njegovo učešće u amplifikaciji i održavanju citokinske oluje, koagulopatija i ćelijska hipoksija.

S obzirom da SARS-CoV-2 prodire u ćelije preko ACE2 receptora, visoko zastupljenog proteina u različitim ćelijama i tkivima u telu, infekcija COVID-19 može dovesti do oksidativnog oštećenja u nekoliko različitih organa i tkiva. Poznato je da je visok odnos neutrofila i limfocita uočen kod kritično bolesnih pacijenata sa COVID-19 povezan sa prekomernim nivoima reaktivnih vrsta kiseonika, koje promovišu kaskadu bioloških događaja koji pokreću patološke odgovore domaćina, kao što su tkivna oštećenja, tromboza i disfunkcija crvenih krvnih zrnaca, doprinoseći ozbiljnosti bolesti COVID-19.

Ključne reči: COVID-19, oksidativni stress

Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu

UTICAJ KRVNE GRUPE NA TOK I ISHOD COVID-19

Sandra Šipetić Grujičić

Nijedna krvna grupa ne daje apsolutnu zaštitu osobi od neke bolesti, ipak osobe sa određenim krvnim grupama mogu da imaju veću sklonost prema nekim bolestima zarazne ili nezarazne etiologije. Objedinjeni rezultati deset studija, kroz meta-analizu, pokazuju da osobe sa krvnom grupom A i B, ali ne i sa krvnom grupom AB, imaju značajno veći rizik od COVID-19 bolesti, u odnosu na osobe

sa drugim krvnim grupama. Nasuprot tome, krvna grupa O značajno štiti od nastanka infekcije, težeg toka bolesti i letalnog ishoda, u odnosu na osobe sa drugim krvnim grupama. Meta-analiza pet studija sugeriše da osobe sa krvnom grupom A, u odnosu na osobe drugih krvnih grupa, imaju značajno veći rizik od smrtnog ishoda usled COVID-19. Meta-analiza koja je obuhvatila 233.006 osoba sa COVID-19 je pokazala da nema značajne razlike u odnosu na tok i ishod bolesti(tj. intubaciju ili dispneju ili smrtni ishod) između pacijenata sa A ili AB krvnim grupama (bez anti-A antitela) i pacijenata sa B ili O krvnim grupama (sa anti-A antitelima). Međutim, u meta-analizama sprovedenim među španskim i italijanskim kohortama, nakon kontrole na konfaunding varijable (starost i pol), rizik za razvoj teže COVID-19 bolesti (definisane respiratornom insuficijencijom) je bio značajno većikod osoba sa A ili AB krvnim grupama nego kod osoba sa B ili O krvnom grupom. Studija sprovedena u Kanadi pokazala je da pacijenti sa težom formom COVID-19 bolesti su značajno češće bili na mehaničkoj ventilaciji, dijalizi i imali produženi boravak u jedinici intezivne nege ukoliko su imali krvnu grupu A ili AB, a ne krvnu grupu B ili O. Ranija istraživanja su potvrdila da osobe krvne grupe O imaju za oko 25% niže vrednosti faktora VIII i *von Willebrand*-ovog faktora (vWF) u plazmi u odnosu na osobe krvnih grupa A, B ili AB. Bez obzira na sve navedeno, ovi rezultati nisu konačni i neophodna su dalja istraživanja, posebno na molekularnom nivou ABO krvnih grupa.

Ključne reči: ABO krvne grupe, SARS-CoV-2 infekcija, tok bolesti, ishod bolesti

MINI SIMPOZIJUM
STO GODINA PULMOLOŠKE ŠKOLE U SRBIJI I 90 GODINA KLINIKE ZA PULMOLOGIJU UKCS

Medicinski fakultet, Univerzitet u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

INDIKACIJA ZA TRANSPLANTACIJU PLUĆA

Sanja Dimić Janjić

Uznapredovala hronična opstruktivna bolest pluća (HOBP), idiopatska plućna fibroza (IPF), cistična fibroza (CF), emfizem usled nedostatka alfa-1 antitripsina i plućna arterijska hipertenzija (PAH) su najčešće bolesti koje predstavljaju indikaciju za transplantaciju pluća.

Pri postavljanju indikacija i u pripremi za transplantaciju pluća ključna je multidisciplinarna evaluacija. Pacijente sa progresivnom bolešću pluća treba uputiti u centar za transplantaciju kada su još u mogućnosti da se podvrgnu relativno opsežnoj proceni kako bi se utvrdili potencijalni rizici i koristi od transplantacije pluća u njihovomslučaju. Najvažnije je identifikovati faktore rizika koji bi uticali na izbor pacijenata za transplantaciju ili ishod nakon transplantacije.

Ključne reči: transplantacija pluća, indikacije

Medicinski fakultet Univerziteta u Beogradu, Srbija
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

KAKO LEČIMO HOBP U 21. VEKU?

Branislava Milenković

HOBP predstavlja značajno opterećenje za zdravstveni sistem i pacijente. Može se kontrolisati prevencijom na individualnom i populacijskom nivou, zajedničkim delovanjem zdravstvenog i nezdravstvenog sektora, ranim otkrivanjem i preventivnim merama. Rano otkrivanje HOBP je veoma važno jer dijagnostikovanje u ranim stadijumima bolesti omogućava uvođenje rane terapije, poboljšanje kvaliteta života i bolje preživljavanje. Rano otkrivanje HOBP kod odraslih uključuje osobe koje imaju neke od sledećih faktora rizika, posebno ako su kombinovani: konzumiranje duvana i duvanskih proizvoda, (najveći rizik su sadašnji ili bivši pušači sa kumulativnim efektom pušenja većim od 20 paklica/ godine), HOBP u porodici, godine starosti (najveći rizik imaju oni stariji od 40 godina), anamneza astme (12 puta veća šansa), hronični kašalj i kratak dah pri naporu i izloženost zagađenom vazduhu na radnom mestu ili u okolini. Rano započinjanje terapije lekovima je veoma važno i zasniva se pre svega na redovnoj upotrebi inhalacionih bronhodilatatora dugog dejstva, dok su inhalacioni kortikosteroidi indikovani kod pacijenata sa čestim egzacerbacijama HOBP i povećanim eozinofilima u krvi i indukovanom sputumu. Inhalacioni put primene leka je idealan za pacijente sa HOBP.

Ključne reči: HOBP, lečenje, lekovi

Medicinski fakultet Univerziteta u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

HOBP U COVID-19 PANDEMIJI – ŠTA SMO NAUČILI?

Ljudmila Nagorni-Obradović, Dragana Marić, Sanja Dimic-Janjić, Snezana Cvetković

Prema objavljenim podacima iz literature, teški akutni respiratorni sindrom korona virus 2 (SARS-CoV-2) izazvao je pandemiju bolesti izazvane korona virusom 2019 (COVID-19), koja se veoma brzo proširila svetom. Bolest se manifestuje različitim stadijumima težine. Asimptomatski i blagi oblik bolesti obično prolazi nezapaženo. Pacijente sa teškim oblikom COVID-19 karakteriše groznica i respiratorni simptomi, od kojih su najčešći kašalj i dispneja. Ostali simptomi uključuju umor, mijalgiju, gastrointestinalne smetnje i druge. Kod teške bolesti, sistemska upala koja se naziva „oluja citokina“ brzo se razvija i uzrokuje oštećenje endotela, kao i trombotičku mikroangiopatiju. HOBP je jedan od faktora rizika za teži oblik infekcije COVID-19 kao i za lošiji ishod bolesti. Prevalencija HOBP varira od 4 do 38% među pacijentima sa COVID-19 koji se leče u jedinicama intenzivne nege.

Ove hronične plućne bolesti često mogu imati različite komorbiditete koji takođe mogu biti faktori za povećanje smrtnog ishoda pacijenata sa HOBP i COVID-19.

Ključne reči: HOBP, terapija, COVID 19

Medicinski fakultet, Univerzitet u Beogradu
Klinika za kardiologiju, Univerzitetski klinički centar Srbije, Beograd

DIJAGNOSTIKA I LEČENJE POST-TROMBOEMBOLIJSKE PLUĆNE HIPERTENZIJE

Arsen D. Ristić

Kod većine bolesnika koji prežive plućnu emboliju, za oko mesec dana dolazi do razgrađivanja trombnih masa i normalizacije pritisaka u plućnoj cirkulaciji. Kod oko 4% bolesnika dolazi do organizacije i endotelizacije tromba, vaskularnog remodelovanja i razvoja hronične tromboembolijske plućne hipertenzije. Post-tromboembolijska plućna hipertenzija je prekapilarna što znači da je pritisak u plućnim arterijama povišen (srednji pritisak u plućnoj arteriji ≥ 20 mmHg) ali da pritisak u plućnim kapilarima nije povišen (PCWP≤15 mmHg uz povišenu plućnu vaskularnu rezistenciju – PVR ≥3 WU).

Dijagnoza post-tromboembolijske plućne hipertenzije se postavlja na osnovu pojačanog zamaranja i gušenja koje se pogoršava i više od 3 meseca od prethodne plućne embolije uz uvećenje desnih srčanih šupljina na ehokardiografiji i povišen BNP ili pro BNP. Trombne mase u plućnoj cirkulaciji se verifikuju MSCT pregledom, perfuziono-ventilacionom scintigrafijom ili angiografijom. Definitvna dijagnoza se postavja kateterizacijom srca. Šestominutni test hodanja, određivanje natriuretskih peptida u krvi (BNP ili NT-pro BNP), kao i ergospirometrijski test su korisni ne samo u inicijalnoj procenu težine bolesti, već i za praćenja progresije bolesti i odgovora na terapiju.

Posttromboembolijska plućna hipertenzija se leči pulmonalnom endarterektomijom ukoliko su okludirani proksimalni segmenti velikih grana plućne arterije ili pulmonalnom balon angioplastikom kod subokluzija ili značajnih stenoza intermedijernih grana plućne arterije. Lek prvog izbora za medikamentoznu terapiju je riociguat uz doživotnu anti-koagulantnu terapiju i diuretsku terapiju u zavisnosti od nivoa desnostrane srčane slabosti.

Ključne reči: plućna hipertenzija, plućna embolija, pulmonalna balon angioplastika, pulmonalna endarterektomija

Medicinski fakultet, Univerzitet u Beogradu

Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

NOVITETI U LEČENJU SARKOIDOZE

Ivana Buha

Uvod: Lečenje sarkoidoze je složeno i nestandardizovano za kliničare i pacijente. S obzirom da sarkoidoza može da zahvati skoro sve organe i može imati drugačiji klinički tok, pokušano je da se pronađe fenotip sarkoidoze, koji bi sadržao stadijum i aktivnost bolesti. Ovo nije postignuto zbog nedostatka kliničkih ispitivanja i smernica za lečenje i odabir pacijenata za terapiju. Razlog za to je retkost bolesti i heterogeni klinički tok. Odluka o lečenju uglavnom zavisi od opterećenja simptomima, rizika od gubitka funkcije organa i kvaliteta života.

Metode: Ovo je pregled literature koji se fokusira na multidisciplinarni tretman, primenu imunosupresivnih lekova, rešavanjekomplikacija hronične granulomatozne inflamacije i procenu toksičnosti lečenja.

Rezultati: Istraživanja su pokazala da postoji značajan broj recidiva bolesti nakon prekida terapije u periodu od 1 do 2 godine. Ponavljanje bolesti nakon prestanka terapije kortikosteroidima varira između 20 i 80%. Recidiv bolesti nakon ukidanja metotreksata u hroničnoj terapiji javlja se u oko 80% slučajeva, a kod pacijenata lečenih infliksimabom u 50% u roku od 6 do 12 meseci.

Zaključak: Buduće težnje za efikasinijim lečenjem će verovatno biti usmerene na otkrivanje i prevenciju izlaganja uročniku, ciljano antigensko lečenje, ublažavanje granulomatozne inflamacije i uticaj na prekid fibroznih puteva. Odluke o lečenju treba da evoluiraju kako bi uključile personalizovanu terapiju zasnovanu na farmakogenomici, fenotipu sarkoidoze i novim terapijskim modalitetima kako bi se smanjio rizik od toksičnih efekata dugotrajne terapije.

Ključne reči: sarkoidoza, terapija

Medicinski fakultet, Univerzitet u Beogradu

Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

SAVREMENA TERAPIJA IDIOPATSKE PLUĆNE FIBROZE

Mihailo Stjepanović

Idiopatska plućna fibroza (IPF) predstavlja hroničnu progresivnu intersticijsku bolest pluća, nepoznate etiologije, koju odlikuje ireverzibilni gubitak arhitektonike plućnog tkiva, i samim tim, plućne funkcije. Nakon postavljanja dijagnoze medijana preživljavanja kod IPF-a iznosi 3–5 godina. Mehanizmi patogeneze plućne fibroze nisu do kraja istraženi, ali je tokom poslednjih godina napravljen značajan napredak. Ranija stanovišta o hroničnoj inflamaciji, kao glavnom pokretaču fibroze su odbačena, a antiinflamatorna kortikosteroidna terapija je izgubila svoju prethodnu primenu.

Tokom prethodnih decenija sprovedena su brojnerandomizovane, multicentrične, placebo-kontrolisane kliničke studije, a u fazama III/IV ovih ispitivanjaidentifikovane su prve uslovno preporučene terapijeza idiopatsku plućnu fibrozu, koje modifikuju bolest: nintedanib i pirfenidon

Evropska komisija je početkom 2011. odobrila primenu pirfenidona za lečenje IPF-a u Evropskoj uniji, dok je Agencija za lekove i medicinska sredstva (Foodand Drug Administration – FDA, USA) oktobra 2014. godine odobrila upotrebu ova dva leka za lečenje idiopatske plućne fibroze. Komitet, koji čine istaknuti stručnjaci američkog, evropskog, japanskog i južnoameričkog respiratornogudruženja (ATS/ERS/JRS/ALAT), dao je nove smernice 2015. godine, u sklopu Vodiča kliničke prakse zalečenje IPF-a, prema kojem ova dva leka imaju uslovnu preporuku za primenu. Dugoročne studije pokazuju da su pirfenidon Inintedanib efikasni IPF tretmani, s prihvatljivombezbednošću i podnošljivošću, a kliničkim ispitivanjima pokazana je bezbednost i njihove kombinovane primene. Uprkos boljim rezultatima u odnosu naprethodno predložene terapije, njihov kapacitet dauspore progresiju bolesti, ali ne i potpuno zaustave ilipoboljšaju funkciju pluća tokom vremena, predstavljapriliku za nove ili dodatne farmakološke agense.

Naime, obećavajući rezultati su nedavno objavljeni u nekoliko faza II kliničkih studija sa novim ciljevima, uključujući put autotaksin-lizofosfatidne kiseline (ATKS/LPA), vezivni faktor rasta tkiva (CTGF), pentraksin-2, agonisti/antagonisti receptora vezanihza G protein, avb6 integrin, i galektin-3.

Ključne reči: idiopatska plućna fibroza, terapija, pirfenidon, nintedanib

Medicinski fakultet, Univerzitet u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

RIGIDNA BRONHOSKOPIJA – PROCEDURA 21. VEKA?

Spasoje Popević

Rigidna bronhoskopija je tehnika kojom se vizualizuje traheja kao i proksimalni bronhi. Najčešće se koristi za lečenje pacijenata koji imaju opstrukciju traheje ili proksimalnog bronha, s obzirom da veliki lumen rigidnog bronhoskopa olakšava aspiraciju i uklanjanje debrija ili stranog tela. Takođe se koristi za intervencijske procedure kao što je plasiranje stentova u disajne puteve, što ga čini optimalnim i neprocenjivim sredstvom za dijagnostiku i posebno lečenje (u kombinaciji sa laserom, argon plazma koagulacijom ili kriotehnikama) stenoze centralnih disajnih puteva u 21. veku.

Ključne reči: rigidna bronhoskopija, interventna pulmologija, terapija

Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

NAŠA ISKUSTVA U LEČENJU EGFR I ALK POZITIVNIH BOLESNIKA - DESETOGODIŠNJA ISTORIJA LEČENJA NA KLINICI ZA PULMOLOGIJU UKCS

Natalija Samardžić

Uvod: U poslednjoj deceniji došlo je do širenja znanja u vezi sa molekularnom biologijom raka pluća i tumora medijastinuma. Identifikovan je veliki broj značajnih aktivirajućih mutacija i razmotrene su terapijske opcije povezane sa genetikom tumora. Genomsko testiranje dovodi do personalizovanog tretmana i postižu se značajno bolji rezultati lečenja. Poznat je veliki broj tumorskih biomarkera koji su važni za prognozu i lečenje karcinoma, a stalno se otkrivaju novi. Od 2011. godine, o trošku zdravstvenog osiguranja za građane Srbije, primenjuje se ciljana terapija za pacijente koji imaju mutacije u genu za receptor epidermalnog faktora rasta (EGFR) kod lokalno uznapredovalog ili metastatskog nesitnoćelijskog karcinoma pluća. U maju 2020. godine, inhibitori tirozin kinaze (TKI) su odobreni za pacijente sa prisutnom ekspresijom ALK i lekovi za stečenu rezistenciju na prvu ili drugu generaciju EGFR TKI.

Metod: Retrospektivna analiza pacijenata lečenih molekularnom terapijom odnesitnoćelijksog karcinoma pluća u poslednjoj deceniji u Klinici za pulmologiju / UKCS.

Rezultati: Naša klinika ima bogato iskustvo u ciljanoj terapiji, više od 360 ALK i EGFR mutiranih pacijenata, primenjujući sekvencijalnu terapiju u progresiji bolesti i na prethodnu liniju.

Zaključak: Primenom molekularne terapije očekuje se duže preživljavanje pacijenata, uz poboljšan kvalitet života, u odnosu na hemoterapiju koja je decenijama bila standard zbrinjavanja pacijenata sa uznapredovalim stadijumom NSCLC

Ključne reči: NSCLC, TKI, ukupno preživljavanje

Sağlık Bilimleri Üniversitesi, Dr. Suat Seren Göğüs Hast. ve Cerr. Eğitim ve Araştırma Hastanesi, Turkey

TISSUE ACQUISITION IN SUSPECTED LUNG CANCER - TECHNIQUES AND SAMPLING ADEQUACY FOR MOLECULAR TESTING

Semra Bilaceroglu

Diagnosis and staging of lung cancer (LCa) should be managed promptly and accurately by anefficient process minimizing procedures before treatment. Within the multidisciplinary team approach for the treatment of LCa, minimally invasive bronchoscopic and/or transthoracic procedures provide rapid and safe tissue acquisition for diagnosis, staging, and molecular testing. Ideal tissue acquisition for simultaneous diagnosis, tumor classification, molecular testing andstaging by the initial procedure depends on the individual patient and need for sufficient tissue for cytologic/histologic, immunohistochemical and molecular studies. Combining diagnosticor staging techniques strategically provides more successful yields and better outcomes in themanagement. For pathologic, immunohistochemical and molecular studies, cytologic/histologic specimens should be sufficient in quality and quantity. Smears should be combined with cellblock preparations to increase diagnostic yield and molecular adequacy. A panel of immunostainsshould be performed judiciously to preserve cellular material for downstream molecular testing ifhistology/cytology cannot distinguish squamous cell carcinoma from adenocarcinoma. Molecularanalysis of all lung adenocarcinomas may be performed by PCR-based techniques, FISH assay, or screening immunohistochemistry. However, increasing genomic targets for LCa and one-offtesting approach in molecular analysis will result in depletion of cellular specimen. Consequently, multiplexed panels for genomic analysis will be a must in the near future. Next generationequencing (NGS) becomes the optimal and cost-effective strategy for a panel beyond three biomarkers. Rapid on-site evaluation, sensitive genotying assays (e.g. NGS) and/or liquid biopsy canbe used to overcome challenges such as inadequate LCa tissue, LCa heterogeneity, heterogeneousesistance mechanisms, and poor performance status.

Keywords: EBUS. Biopsy, molecular testing

Medicinski fakultet, Univerziteta u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

NE(ŽELJENI) EFEKTI IMUNOTERAPIJE

Milica Kontić Jovanović

Neželjeni efekti imunoterapije mogu varirati u zavisnosti od vrste primenjenog lečenja. Kod oko 30 do 50 procenata pacijenata ispoljavaju se blagi neželjeni efekti. Neželjeni efekti najčešće uključuju: artritis, drhtavicu, konstipaciju, kašalj, smanjen apetit, dijareju, groznicu i simptome slične gripu, glavobolju, hipotireozu, bolove u mišićima, mučninu, osip, povraćanje. Iako su teški neželjeni efekti retki, kada se pojave, mogu biti opasni po život i zahtevati hitnu medicinsku intervenciju. Da li je težina imunski posredovanih neželjenih događaja mera učinkovitosti antitumorskog odgovora? Postoji razuman broj studija koje zagovaraju da pacijenti sa neželjenim događajima povezanim sa imunitetom imaju veće stope odgovora od pacijenata bez takvih događaja, međutim, ovi nalazi nisu univerzalno prepoznati.

Ključne reči: NSCLC, neželjeni efekti, imunoterapija

Medicinski fakultet, Univerzitet u Beogradu
Klinika za pulmologiju, Univerzitetski klinički centar Srbije, Beograd

IMUNOTERAPIJA U LEČENJU SITNOĆELIJSKOG KARCINOMA PLUĆA

Dragana Marić

Sitnoćelijski karcinom pluća (*engl.* small cell lung cancer SCLC) je agresivan malignitet sa lošom prognozom uprkos agresivnom lečenju. Za SCLC u ekstenzivnoj fazi standard terapije u poslednjih nekoliko decenija nije evoluirao sve do ere imunoterapije. Platina-etopozid hemoterapijski protokol je bio kamen temeljac u lečenju. Njegova sposobnost da izazove terapijski odgovoru SCLC je značajna, ali nije trajna. Potencijalna sinergija u dodavanju imunoterapije hemoterapiji zasniva se na činjenici da je SCLC kancer povezan sa pušenjem sa visokim mutacionim opterećenjem tumora (*engl.* tumor mutation burden TMB), što sve može olakšati prezentaciju tumor-specifičnih antigena. Nedavnu (r)evolucijupredstavlja integracija imunoterapije u ovo okruženje. Inhibitori imunske kontrolne tačke (*eng.* immune checkpoint inhibitors ICI) su primarni tip imunoterapije koji se koristio najpre u uznapredovalom stadijumu bolesti, dok se sada sprovode studije o uticaju ICI u ograničenom stadijumu bolesti. Višestruka ispitivanja kombinacije ICI-hemoterapije u prvoj liniji lečenja pokazala su korist za preživljavanje u poređenju sa samo hemoterapijom kod pacijenata sa uznapredovalim stadijumom SCLC, postavljajući kombinovanu terapiju kao terapijski standard. Očekujući primenu imunoterapije u lečenju SCLC u Srbiji, želeli bismo da predstavimo osnovne dokaze za opravdano dodavanje ICI hemoterapiji u ekstenzivnom stadijumu bolesti, kao i ispitivanje imunoterapije koja bi potencijalno mogla promeniti dosadašnju praksu lečenja ograničenog stadijuma SCLC.

Ključne reči: SCLC, imunoterapija

Medicinski fakultet, Univerzitet u Beogradu
Klinika za pulmologiju, Univerzitetski Klinički Centar Srbije, Beograd
Institut za mikrobiologiju i imunologiju

TUBERKULOZA AKTUELNE TEME: KONVENCIONALNE I MOLEKULARNE DIJAGNOSTIČKE METODE ZA OTKRIVANJE TUBERKULOZE

Vesna Škodrić Trifunović, Irena Aranđelović

Konvencionalna mikrobiološka dijagnostika podrazumeva mikroskopiju preparata iz uzoraka obojenih po Ziehl–Neelsenu; kultivaciju mikobakterija na čvrstoj Lowenstein podlozi; identifikaciju bacila TB-a na osnovu mikroskopskih, kulturalnih i biohemijskih osobina izolovane kulture; testa za ispitivanje osetljivosti na antituberkulotike (ATL) prve linije za Mycobacterium tuberculosis na Lowenstein podlozi. Konvencionalna dijagnostika je dugotrajan proces, traje dva do tri meseca. U poslednjim decenijama metode za brzu dijagnostiku tuberkuloze su od velikog značaja i našle su mesto u praktičnom radu u opremljenim laboratorijama, a rezultati se dobijaju za dan-dva. Osetljivost i specifičnost molekularnih testova za tuberkulozu je visoka. U Nacionalnoj referentnoj laboratoriji se u ovu svrhu koriste eseji GenoType MTBDRplus (Hain, Lifescience) i Xpert MTB/RIF (Cefeid), koji se od 2010. primenjuju u Klinici za pulmologiju UKCS. Kod sumnje na TB ako su na direktnom preparatu iz kliničkih uzoraka prisutni acidoalkoholorezistentni bacili (ARB) ne može se postaviti dijagnoza oboljenja jer ARB pored M. tuberculosisa mogu biti i netuberkulozne mikobakterije (NTM) i druge bakterije. Iz kliničkih uzoraka (sputum, bronhoaspirat, urin, likvor, ekskreti itd.) za brzu dijagnostiku TB-a mogu se primeniti molekularne tehnike (Xpert MTB/RIF i HAIN GenoType MTBDRplus); kultivisanje mikobakterija u tečnim podlogama sa sistemima za ranu detekciju porasta mikobakterija – BACTEC MGIT (Becton Dickinson) i MB/BacT (bioMérieux), kao i manuelni BBL MGIT sistem. M. tuberculosis daje porast na tečnim podlogama za oko 10 dana; za brzu identifikaciji izolovanih kultura mikobakterija primenom imunohromatografskih eseja i molekularnih tehnika rade se molekularni testovi Hain GenoType Mycobacterium za vrste M. tuberculosis kompleksa i za NTM. Rezultat molekularnog testa za identifikaciju je dostupan za jedan do dva dana od pozitivne kulture; ispitivanje osetljivosti izolovanih kultura bacila TB na ATL primenom brzih tehnika – u te svrhe se u Srbiji radi fenotipski test za ATL prve linije primenom MGIT sistema i molekularni testovi Hain GenoType MTBDRplus za detekciju rezistencije M. tuberculosisa na rifampicin i izoniazid i HAIN GenoType MTBDRsl za detekciju rezistencije M. tuberculosisa na ATL druge linije.

Ključne reči: tuberkuloza, dijagnostika tuberkuloze Xpert MTB/RIF, HAIN GenoType MTBDRplus.

MINI SIMPOZIJUM
HRONIČNA LIMFOCITNA LEUKEMIJA: OD SAVREMENE DIJAGNOSTIKE DO CILJANE TERAPIJE

Medicinski fakultet, Univerzitet u Beogradu
Klinika za hematologiju, Univerzitetski klinički centar Srbije, Beograd

MEHANIZMI REZISTENCIJE NA NOVE CILJANE LEKOVE

Biljana Mihaljević

Novi ciljani lekovi su značajno produžili preživljavanje bolesnika sa hroničnom limfocitnom leukemijom (HLL), naročito onih sa nepovoljnim molekularno-citogenetičkim profilom. Među ovim agensima načvršće pozicije u ovoj indikaciji zauzeli su inhibitori Brutonove tirozin kinaze (BTKi) i BCL-2 inhibitori. Kovalentni BTKi (ibrutinib, akalabrutinib i zanubrutinib) svoje dejstvo ostvaruju ireverzibilnim vezivanjem leka za cisteinsku reziduu na poziciji 481 molekula BTK što onemogućava njegovu konstitutivnu aktivnost i nishodnu aktivaciju puta B-ćelijskog receptora, rezultirajući smanjenom proliferacijom B-ćelija. Do 16% HLL bolesnika su primarno rezistentni na ibrutinib, a do 18% stiče sekundarnu rezistenciju na ovaj lek, i to 70% njih zahvaljujući mutaciji koja dovodi do zamene cisteina serinom (C481S) koja onemogućava kovalentnu vezu ibrutiniba i BTK. Druga najčešća mutacija koja u 11% slučajeva dovodi do rezistencije na ibrutinib je u *PLCG2* genu za enzim fosfolipazu C gama 2, direktni supstrat BTK. Obe su takođe odgovorne za rezistenciju na kovalentne BTKi druge generacije (akalabrutinib i zanubrutinib). Rezistenciju posredovanu mutacijama *BTK* C481S i *PLCG2* prevazilaze novi nekovalentni BTKi, kao pirtobrutinib, međutim i sami podložni razvoju sekundarne rezistencije koja je posredovana nedavno identifikovanim mutacijama u kinaznom domenu BTK (V416L, A428D, M437R, T474I i L528W).

Konstitutivno povećana ekspresija BCL-2 antiapoptotskog proteina je jedan od glavnih mehanizama akumulacije B-ćelija u HLL što je osnov za primenu BCL2 inhibitora venetoklaksa u lečenju HLL bolesnika. Venetoklaks dovodi do odličnog odgovora kod refraktarnih i pretretiranih bolesnika, međutim, njegova dugotrajna primena je skopčana sa razvojem rezistencije kod oko 50% lečenih. Jedan od glavnih mehanizama rezistencije je mutacija u genu *BCL2* koja dovodi do zamene glicina valinom na poziciji 101 u BCL2 proteinu (G101V). Osim ove mutacije nedavno je identifikovana i mutacija *BCL2* D103Y, ali i brojne *de novo* mutacije koje koegzistiraju sa mutacijom *BCL2* G101V i nađene su kod čak 90% bolesnika koji su rezistentni na venetoklaks. Rezistencija na nove "target" molekule obavezuje na kontinuirane napore u njenom prevazilaženju u cilju daljeg produžvanja životnog veka ovih bolesnika.

Ključne reči: hronična limfocitna leukemija; ibrutinib; venetoklaks; rezistencija

Medicinski fakultet, Univerzitet u Beogradu
Klinika za hematologiju, Univerzitetski klinički centar Srbije, Beograd

DIJAGNOSTIKA U HRONIČNOJ LIMFOCITNOJ LEUKEMIJI: AKTUELNE PREPORUKE

Darko Antić

Pravilno i pravovremeno sprovođenje algoritma dijagnostike kod pacijenata sa hroničnom limfocitnom leukemijom (HLL) je od velikog značaja za izbor adekvatne terapije.

Tri najvažnije analize koje predstavljaju osnov su fluorescentna in situ hibridizacija (FISH), utvrđivanje postojanja mutacije u genu za TP53 I određivanje mutacionog statusa gena za varijabilni deo teškog lanca imunoglobulina (IGHV).

U aberacije TP53 gena spadaju delecija TP53 gena i mutacije TP53 gena. Del17p, najnepovoljnija citogenetička aberacija u HLL, rezultira gubitkom TP53 gena I detekcija del17p vrši se FISH metodom. Del17p je uglavnom obeležje agresivne i refraktarne bolesti sa kratkim preživljavanjem te se ovi bolesnici nazivaju "visokorizičnim". Čak 80% bolesnika sa del17p ima mutaciju TP53 gena u preostalom alelu, što se naziva fenomenom gubitka heterozigotnosti, a rezultira potpunim gubitkom funkcije p53 proteina . Mutacije TP53 gena mogu postojati i bez del17p i takođe su jedno od obeležja "visoko rizičnih" bolesnika. Registruju se kod 4-5% HLL bolesnika koji nisu lečeni, pa do 18% kod refraktarnih pacijenata Prognoza bolesti je loša bez obzira da li je reč o monoalelskom ili bialelskom defektu TP53 gena. Sprovođenjem samo ove analize propušta se oko 30-40% pacijenata sa mutacijom TP53 gena. Iz tog razloga je preporučeno da se pored FISH analize, vrši provera postojanja TP53 mutacije metodom sekvenciranja pre započinjanja lečenja HLL pacijenata i to kako pre prve, tako i pre svake sledeće terapijske linije jer se navedene aberacije mogu javiti i kasnije tokom bolesti

Pacijenti sa mutiranim IGHV statusom imaju dobar terapijski odgovor na imunohemioterapiju, za razliku od pacijenata sa nemutiranim IGHV statusom kod kojih je ciljana (target) terapija agensima poput inhibitora bruton-tirozin kinaze ili bcl-2 inhibitorima terapija izbora

U bliskoj perspektivi očekuje se da I određivanje kariotipa bude deo dijagnostičkog algoritma imajući u vidu da pacijenti sa kompleksnim kariotipom (≥ 3 abnormalnosti) imaju lošiju prognozu.

Ključne reči: CLL, p53 mutacija, mutacioni status IGHV

Univerzitet u Beogradu
Institut za molekularnu genetiku i genetičko inženjerstvo, Beograd

ZNAČAJ STEREOTIPIJE B-ĆELIJSKOG RECEPTORA U HRONIČNOJ LIMFOCITNOJ LEUKEMIJI

Teodora Karan Đurašević, Sonja Pavlović

Brojna istraživanja na polju imunogenetike hronične limfocitne leukemije (HLL), sprovedena u proteklih 25 godina, dovela su do revolucionarnih promena u razumevanju biologije ove bolesti i ukazala na centralnu ulogu klon-specifičnog B-ćelijskog receptora (BĆR) u patogenezi i evoluciji HLL. Status somatskih hipermutacija (SHM) IGHV gena u rearanžmanima teških lanaca imunoglobulina (IGH) koji ulaze u sastav BĆR leukemijskog klona izdvojio se kao najinformativniji i najstabilniji prognostički i prediktivni marker, nezavistan od stadijuma bolesti i ostalih biomarkera, i uveden je u svakodnevnu kliničku praksu u mnogim zemljama. Međutim, prognostički značaj molekularne strukture BĆR se ne završava na SHM statusu. Naime, pokazano je da je genski repertoar IGH asimetričan, u smislu češćeg prisustva određenih IGHV gena nego što bi se očekivalo na osnovu nasumičnog rekombinovanja, kao i da je ovaj repertoar različit od normalnog B-ćelijskog repertoara i specifičan za HLL. Pored toga, otkriveno je i preferencijalno kombinovanje određenih IGHV, IGHD i IGHJ gena, od kojeg zavisi struktura VHCDR3 regiona IGH lanaca, ključnog za antigensku specifičnost BĆR. Sekvenciranjem IGH rearanžmana velikog broja HLL pacijenata pokazano je da 30-35% njih eksprimira BĆR sa visoko-homologim, skoro identičnim VHCDR3, što je dovelo do koncepta „BĆR stereotipije". Na osnovu sekvence VHCDR3 leukemijskog klona identifikovano je više stotina klasa stereotipnih BĆR, od kojih je 19 najčešćih prisutno kod 12% pacijenata. Pokazano je da pacijenti koji pripadaju istoj stereotipnoj klasi imaju slične biološke i kliničke karakteristike, uključujući tok i ishod bolesti, tako da bi određivanje BĆR stereotipije moglo doprineti rafinisanju prognostičkih modela i, eventualno, razvoju terapeutika primenljivih na svaku od glavnih stereotipnih klasa. Postojanje BĆR stereotipije jasno ukazuje na ulogu (auto) antigenske stimulacije u ontogeniji i evoluciji HLL, kroz aktivaciju proliferacije i ekspanzije B ćelija koje eksprimiraju određeni BĆR. Dalja istraživanja stereotipije i otkrivanje prirode ovih antigena doprineće rasvetljavanju mehanizama odgovornih za nastanak i kliničku heterogenost HLL, kako kod pacijenata koji pripadaju nekoj od stereotipnih klasa, tako i kod onih koji pripadaju nestereotipnoj frakciji HLL.

Ključne reči: hronična limfocitna leukemija; IGH rearanžmani; B-ćelijski receptor; stereotipija

Institut za patologiju "Prof. dr Đorđe Joannović", Medicinski fakultet, Univerzitet u Beogradu

ULOGA IFISH I KONVENCIONALNE CITOGENETIKE U HRONIČNOJ LIMFOCITNOJ LEUKEMIJI

Marija Denčić Fekete

Genetičke aberacije se smatraju jednim od najznačajnijih pokazatelja odgovora na terapiju i preživljavanja kod bolesnika sa hroničnom limfocitnom leukemijom (HLL). Prve aberacije otkrivene su upotrebom konvencionalne citogenetičke analize 80-tih godina prošlog veka. U to vreme, kao razlog slabog in vitro proliferativnog kapaciteta HLL ćelija, patološki kariotip je bio prisutan kod manje od 30% bolesnika.

Od 2000. godine, interfazna fluorescentna in situ hibridizacija (iFISH) postaje metoda izbora za detekciju aberacija u HLL-u, otkrivajući ih u gotovo 80% slučajeva.

Takođe početkom 2000., kultivacija uzoraka periferne krvi HLL bolesnika u prisustvu odgovarajućih mitogena (CD40 ligand (CD40L) ili CpG-oligonukleotida DSP30 zajedno sa interleukinom-2 (IL-2), podigla je nivo detekcije aberantnih kariotipova na onaj koji se otkriva iFISH metodom. Ovom metodologijom, prepoznate su dodatne hromozomske abnormalnosti sa potencijalnim prognostičkim značajem. Stimulisani metafazni kariotipovi sa ≥3 hromozomskih abnormalnosti su kasnije prepoznati kao nezavisni i izrazito loši pokazatelji prognoze bolesti.

Studije u kojima su uporedo primenjene standardna citogenetička i iFISH analiza, pokazale su da ove metode nadopunjuju jedna drugu. Kod bolesnika sa normalnim FISH nalazom, u kariotipu su otkrivene aberacije koje nisu obuhvaćene standardnim HLL FISH panelom proba.

Nasuprot tome, FISH-em su detektovane aberacije koje nisu viđene u metafaznom kariotipu, usled nedovoljne rezolucije ove tehnike. Stoga, uporeda primena obe metode može omogućiti sveobuhvatniju karakterizaciju genomskih promena u HLL-u.

Preporuke internacionalne grupe za HLL nalažu da se testiranje kariotipa HLL bolesnika konvencionalnom citogenetičkom i FISH metodom, obavezno izvrši pre primene prve terapije. Imajući u vidu da se dodatne genetičke aberacije mogu pojaviti u daljem toku bolesti, kao i zbog eventualne ekspanzije minornih klonova koji nisu detektovani pri inicijalnom testiranju, preporučuju se dodatne genetičke analize pre svake naredne terapijske linije.

Prisustvo genetičkih aberacija, na prvom mestu delecije 17p ili 11q, može pružiti ključne informacije za optimalni izbor imunohemoterapije, kinaznih inhibitora, BCL2 inhibitora ili transplantacije matičnim ćelijama.

Ključne reči: interfazna fluorescentna in situ hibridizacija; konvencionalna citogenetika; hronična limfocitna leukemija; preporuke

Medicinski fakultet, Univerzitet u Beogradu
Klinika za hematologiju, Univerzitetski klinički centar Srbije, Beograd

TP53 I HRONIČNA LIMFOCITNA LEUKEMIJA

Vojin Vuković

Hronična limfocitna leukemija (HLL) je oboljenje koje se odlikuje proliferacijom i akumulacijom monoklonskih zrelih B limfocita. Jedna od glavnih karakteristika HLL je izrazita heterogenost kliničkog toka, što je u prvom redu posledica različitih bioloških karakteristika neoplastično izmenjene B-ćelije. TP53 je poznat tumor-supresorki gen čija disfunkcija ima reperkusije na klinički tok različitih malignih oboljenja uključujući i hematološka, imajući u vidu posledičnu kompromitaciju mehanizma apoptoze malignih ćelija i reparacije oštećenja ćelijske DNK. Ranije studije na HLL bolesnicima su pokazale da delecija kratkog kraka hromozoma 17 (del17p13) dovodi do delecije TP53 gena, te da se kod ovakvih bolesnika razvija rezistencija na imunohemioterapiju, da bi kasnija istraživanja pokazala da do istog efekta dovodi i mutacija ovog gena. Del17p13 se javlja kod oko 4-8% nelečenih bolesnika, s tim da oko 90% ovih bolesnika istovremeno ima mutaciju drugog alela TP53 gena. Sa druge strane, oko 5% nelečenih ima izolovanu mutaciju TP53 što čini oko 30-50% svih nelečenih bolesnika sa disfunkcionalnim TP53 genom. Bolesnici sa aberantnim TP53 su u eri imunohemioterapije imali preživljavanje bez progresije do 2 godine i nešto duže ukupno preživljavanje što je delimično prevaziđeno primenom nove „target" terapije, u prvom redu inhibitora Brutonove tirozin kinaze. U relapsu bolesti procenat bolesnika sa disfunkcionalnim TP53 genom značajno raste. Sve vodeće međunarodne preporuke za dijagnostiku i lečenje HLL savetuju obavezno određivanje statusa TP53 gena fluorescentnom in situ hibridizacijom i nekom od metoda genskog sekvenciranja pre lečenja u svakoj liniji terapije, imajući u vidu rezistenciju na imunohemioterapiju i korist od primene „target" lekova kod bolesnika sa potvrđenom delecijom/mutacijom TP53. Uvođenjem metode sekvenciranja sledeće generacije (next-generation sequencing, NGS) identifikuju se bolesnici sa frekvencijom mutiranih alela TP53 gena < 10% kod kojih primena imunohemioterapije dovodi do selekcije klonova sa nepovoljnim genetičkim karakteristikama. Nedavna istraživanja pokazuju uticaj broja detektovanih promena TP53 gena na preživljavanje HLL bolesnika na ibrutinibu.

Ključne reči: hronična limfocitna leukemija; TP53 gen; imunohemioterapija; sekvenciranje; preživljavanje

MINI SIMPOZIJUM
KAROTIDNA STENOZA POD LUPOM NEUROLOGA I VASKULARNOG HIRURGA

Medicinski fakultet, Univerzitet u Beogradu
Klinika za neurologiju, Univerzitetski klinički centar Srbije, Beograd

KARAKTERISTIKE MOŽDANOG UDARA U KAROTIDNOM SLIVU

Dejana Jovanović

Aterosklerotična karotidna stenoza je važan uzrok ishemijskog moždanog udara koja je udružena sa prisustvom velikih vaskularnih faktora rizika. Stenoza karotidne arterije, čak i kada je veoma izražena, često je asimptomatska zbog postojanja kolaterala koje omogućavaju nadokanadu smanjenjenog protoka. Najčešći mehanizam moždanog udara usled karotidne stenoze nije hemodinamskog porekla, već ruptura plaka ili tromboza na mestu rupturiranog plaka i distalna tromboembolija sadržajem plaka ili partikulama tromba koja dovodi do okluzije velikih završnih grana karotidne arterije. Ova distalna embolizacija može istovremeno zahvatiti više distalnih cerebralnih arterija, a kada se radi o malim holesterolskim embolusima može doći do okluzije retinalnih arterija.

Karotidna stenoza se može manifestovati kompletnim moždanim udarom, tranzitornim ishemijskim atakom (TIA) ili kao *amaurosis fugax*. Tipična manifestacija moždanog udara usled karotidne okluzije je iznenadna devijacija pogleda u stranu, afazija ili dizartrija i faciobrahijalna hemipareza sa hemihipestezijom. Simptomi mogu biti blaži i prolazni kada se radi o TIA ili manjem moždanom udaru, ali i izuzetno teški kada dođe do okluzije terminalne karotidne račve. Prolazan, kratkotrajan monokularni gubitak vida usled prolazne retinalne embolije označava amaurosis fugax. Ovo je čest simptom subokluzivne karotidne stenoze koji se može ponavljati i prethoditi teškom obliku moždanog udara.

Prisustvo simptoma koji se ponavljano pojavljuju i povlače u istom vaskularnom slivu govore u prilog visokostepene karotidne stenoze i uglavnom se retko sreću kod moždanih udara kardioembolijskog ili lakunarnog tipa.

Hemodinamske TIA i moždani udari nisu uobičajeni, ali se dešavaju. U ovom slučaju pacijenti imaju ponavljane simptome i više puta tokom dana koji se mogu potencirati sa ustajanjem iz sedećeg položaja. Tipičan simptom je podrhtavanje kontralateralne ruke i noge u uspravnom položaju. Pored teške ipsilateralne karotidne stenoze, ovi pacijenti imaju i druge razloge koji doprinose cerebralnoj cirkulatornoj insuficijenciji kao što što je odsustvo kolateralnog protoka ili/i prisustvo teške kontralateralne karotidne stenoze ili nagli razvoj hipotenzije.

Ključne reči: karotidna stenoza, moždani udar, TIA, klinička prezentacija

Medicinski fakultet, Univerzitet u Beogradu
Klinika za vaskularnu i endovaskularnu hirurgiju, Univerzitetski klinički centar Srbije, Beograd

HIRURŠKI TRETMAN ASIMPTOMATSKIH KAROTIDNIH STENOZA

Lazar B. Davidović

Uvod: Mišljenja o tretmanu asimptomatske stenoze karotidnih arterija (ASKA) su kontroverzna. Razlozi za karotidnu endarterektomiju (KEA) su „nemi“ infarkt mozga (prevalenca 14-18% kod ASKA veće od 70%) i rizik od CVI (3.6% kod ASKA veće od 60%). U obzir se moraju uzeti: životna dob bolesnika, komrbiditet, stanje kotralateralne karotidne arterije, morfologija plaka i predstojeće operacije.

Metodologija: Stavovi koji će ovde biti izneti zasnovani su na analizi literaturnih podataka i rezultatima observacione studijeKlinika za vaskularnu i endovaskularnu hirurgiju UKCS iz 2015 godine sa 1567 pacijenata operisanih zbog ASKA.

Rezultati: Prema nekim najnovijim studijama ni optimalna medikamentozna terapija ne snižava rizik od CVI-a kod visiko stepene ASKA. Prema ACST-1 KEA ASKA značajno snižava perioperativnu smrtnost i stopu CVI, kao i stopu CVI pet i deset godina nakon operacije u odnosu na pacijente operisane u simptomatskoj fazi. U našoj studiji perioperatvna smrtnost je iznosila 0.38%, a ukupna stopa perioperativnog CVI i TIA 2.81%. Rizik perioperitvnog CVI-a značajno su povećavali ženski pol (p=0.015) i gojaznost (p=0.056), a nisu starost preko 75 godina, pridružena hemodinamski značajna stenoza ili okluzija kontralateralne karotidne arterije. Smrtnost je bila značajno viša kod pacijenata kojima je predstojala hirurška revaskularizacija miokarda (p=0.018). Neke prethodne studije su pokazale da je KEA ASKA preporučljiva ako je plak komplikovan, a kontraindikovana kod osoba sa veoma značajnim komorbiditetom. Mišljenja o profilaktičkoj KEA zbog ASKA pre velikih kardiovaskularnih operacija su kontroverzna.

Zaključak. KEA ASKA indikovana je kod bolesnika bez suviše značajnog komorbiditeta, a sa očekivnim životom preko pet godina. Razlog više predstavljaju komplikovaniplak; bolest kontralateralne karotidne arterije ipredstojeće operacije skopčane sa velikim krvarenjima i hemodinamskom nestabilnošću ako je kontralateralna karotidna arterija okludirana ili značajno stenozirana.

KEA zbog ASKAje dozvoljena ako se bolesnicima može garantovati ukupan rizik od perioperativnog smrtnog ishoda i CVI-ado 3%.

Ključne reči: asimptomatska stenoza karotidnih arterija, hirurški tretman.

Medicinski fakultet, Univerzitet u Beogradu

Klinika za neurologiju, Univerzitetski klinički centar Srbije, Beograd

KAROTIDNA STENOZA I KOGNITIVNO OŠTEĆENJE

Elka Stefanova

U poslednjih godina faktori rizika za kardiovaskularne bolesti se vezuju za kognitivno oštećenje ne samo u vaskularnoj demenciji, već i za Alzheimerovu bolest. Odredjeni broj studija su pokazale da cerebrovaskularna bolest igra važnu ulogu u razvoju kognitivnih poremećaju ili demenciji u pacijenata bez očigledne istorije o bilo kakvom cerebrovaskulnom dogadjaju. Kao jedan važan faktor u vaskularnom doprinosu kognitivnim poremećajima i demencijama, sve češće se pominje karotidna ateroskleroza. Pacijenti sa karotidnom arterijskom okluzijom (KAO) imaju povećan rizik od kognitivnih oštećenja . Moguća objašnjenja su da postoje posledične lezija bele mase, ili se radi o strateški lociranoj ishemiji, ali može biti uzrokovana i cerebralnim hemodinamskim oštećenjima bez strukturnih promena u mozgu . Cerebralna hipoperfuzija može biti rezultat teške stenotične ili okluzivne bolest cerebropetalnih arterija, ali može biti uzrokovana i sistemskim hemodinamskim oštećenjem poput zatajenja srca ili hipotenzijom. Nedavna istraživanja pokazuju da je karotidna ateroskleroza nezavisan faktor rizika za kognitivno oštećenje i demencije takođe kod pojedinaca bez kliničkog moždanog udara.

Uloga subkliničke ateroskleroze u odnosu na kognitivne funkcije mogu biti proučavana pomoću ultrazvučnog merenja karotidne arterije. Većina perspektivnih opservacijskih studija pronalaze povezanost između subkliničke karotidne zadebljanje intima medije, plakova i stenoza s jedne strane, i kognitivnog oštećenja sa druge strane. Dve studije su takođe otkrile da je početni IMT prediktivan za AB. Ultrazvuk je lako procenjiva i neinvazivna metoda koja može izmeriti različite faze aterosklerotskog procesa na karotidnim arterijama, karotidna bifurkacija i proksimalni deo unutrašnje karotidne arterije su mesta predilekcije za aterosklerotične plakovi. Zadebljanje intima medije sloju karotidne arterije je prvi znak ateroskleroze. Subklinička karotidna ateroskleroza merena kao zadebljanje intimnih medija, karotidni plakovi i astenoza su obrnuto povezani sa kognitivnim sposobnostima u nekoliko prospektivnih studija. Dve velikeprospektivne studije su otkrile povećan rizik od demencija i AB sa karotidnom intima medije zadebljanja.

Na osnovu više opservacionih studija, moglo bi se pretpostvi da prevencija karotidne ateroskleroze može da nas zaštiti od kognitivnog oštećenja, ali potrebne su pravilno osmišljene intervencione studije da bi se dokazala prevencija ili lečenje karotidne ateroskleroze da može smanjiti rizik od kognitivnog oštećenja u pojedinaca bez prethodnih klinički ispoljenih cerebrovaskularnih bolesti.

Ključne reči: vaskularni kognitivni poremećaj, karotidna stenoza, endarektomija

Medicinski fakultet, Univerzitet u Beogradu

Klinika za vaskularnu i endovaskularnu hirurgiju, Univerzitetski klinički centar Srbije, Beograd

HIRURŠKO LEČENJE SIMPTOMATSKE KAROTIDNE BOLESTI

Marko Dragaš

Optimalno vreme za izvođenje karotidne endarterektomije kod pacijenata sa simptomatskim suženjem karotidne arterije je i dalje predmet debata. Nakon pionirskih radova argentinskih, evropskih i američkih hirurga na uvođenju hirurgije u lečenje cerebrovaskularne bolesti, početni entuzijazam da se posledice akutne ishemije mozga mogu izbeći ili umanjiti hitnom revaskularizacijom, analogno drugim organima, nestao je početkom 70-tih godina, publikovanjem prvih serija operisanih bolesnika. Mortalitet pacijenata operisanih u akutnom insultu kretao se od 20% do 60%, a kod manje od trećine je zabeležen neki stepen poboljšanja neurološke funkcije, uglavnom kao posledica loše selekcije bolesnika. Prva velika studija vezana za karotidnu hirurgiju *Joint Study of Extracranial Arterial Occlusion*, ukazala je na izuzetno loše rezultate operacija izvedenih u akutnoj fazi šloga. Velike prospektivne kliničke studije koje su usledile (NASCET, ECST), dovele su do razumevanja prevashodno preventivne uloge karotidne endarterektomije i pažljive selekcijebolesnika, što je dramatično poboljšalo rezultate hirurškog lečenja.

Simptomatsko suženje karotidne arterije predstavlja jedan od najznačajnijih faktora rizika za razvoj moždanog udara. Simptomatski, medikamentozno tretirani pacijenti u *NASCET*i *ECST*studiji sa suženjem karotidne arterije od 70-99% dijametra, imali su rizik od ipsilateralnog šloga od 26% i 21% nakon pet, odnosno tri godine praćenja. Rezultati ovih, kao i drugih studija pokazali su da je ovaj rizik najveći neposredno nakon inicijalnog neurološkog događaja i da iznosi oko 7% u prvih 48h, odnosno 10% u prvih 7 dana nakon tranzitornog ishemijskog ataka ili moždanog udara. Ovi rezultati ukazali su na potrebu za ekspeditivnim tretmanom pacijenata sa simptomatskom karotidnom stenozom. U prilog ekspeditivnom hirurškom tretmanu simptomatskih pacijenata govore i izvanredni rezultati hirurškog lečenja u akutnom periodu publikovani iz više centara.

Shodno navedenim dokazima, preporuka da se karotidna endarterektomija izvodi što ranije, a najkasnije unutar dve nedelje od indeksnog neurološkog događaja, postala je i sastavni deo evropskog odnosno američkog vodiča dobre kliničke prakse.

Ključne reči: karotidna endrterektomija, simptomatska karotidna bolest.

Medicinski fakultet, Univerzitet u Beogradu
Klinika za neurologiju, Univerzitetski klinički centar Srbije, Beograd

PRIMENA NEUROSONOLOŠKIH METODA U IDENTIFIKACIJI VISOKO RIZIČNIH PACIJENATA SA KAROTIDNOM STENOZOM

Milija D. Mijajlović

Karotidna stenoza (KS) je čest uzrok ishemijskog moždanog udara sa visokim stopama recidiva. Karotidna endarterektomija (KEA) ili karotidni stenting (KAS) se visoko preporučuju za sekundarnu prevenciju simptomatske KS tokom prvih 14 dana nakon indeksnog ishemijskog događaja, a takođe mogu preporučiti u odabranim slučajevima sa teškom asimptomatskom stenozom. KEA i KAS uz optimalnu medikamentoznu terapiju prepolovili su dogotrajni rizik od moždanog udara kod KS. Identifikacija pacijenata sa KS (posebno onih sa asimptomatskom KS) koji su u povećanom riziku od moždanog udara može da maksimizira efekat karotidnih intervencija. Dupleks ultrasonografija ima dokazanu ulogu u proceni stepena karotidne aterosklerotske stenoze. Međutim, stepen karotidne stenoze nije najbolji prediktor rizika od moždanog udara kod karotidne stenoze. Kliničke i imidžing karakteristike kao što su kontralateralni simptomi, nemi moždani udari na neuroimidžingu, cerebralni mikroembolijski signali na transkranijalnom Doppleru, progresija karotidne stenoze i oštećena cerebralna vazomotorna reaktivnost, udruženi su sa povećanim rizikom od pojave moždanog udara kod KS. Karakteristike plakova kao što su eholuscencija, prisustvo velikih plakova (≥80 mm), hemoragija u plaku, plakovi bogati lipidima ili sa nekrotičnim centrom, neovaskularizacija plaka, kao i pojava istanjene ili rupturirane fibrozne kapice sa ulceracijom plaka takođe značajno povećavaju rizik od moždanog udara kod KS. Napredak neurosonoloških imidžing metoda omogućio je ispitivanje ovih karakteristika KS koje nose visoku senzitivnost i predikciju pojave simptoma cerebralne ishemije kako kod asimptomatske tako i kod simptomatske KS. Skorašnja istraživanja su rezultirala pojavom prve generacije trodimenzionalnih ultrazvučnih sondi koje dodatno smanjuju zavisnost pregleda od ispitivača, subjektivnost i varijabilnost. Konačno, ultrasonografija omogućava pregled u realnom vremenu, ako je potrebno i pored kreveta pacijenta, sajedinstvenom mogućnošću prevencije moždane ishemije i intraoperativno, tokom karotidne revaskularizacije (KEA ili KAS) ili tokom hibridnih intervencija.

Ključne reči: karotidna stenoza; dupleks ultrasonografija; transkranijalni Doppler; moždani udar; procena rizika

Department of Clinical Neurophysiology, Maastricht University Medical Center, Maastricht, The Netherlands

DETECTION OF MICROEMBOLIC SIGNALS WITH TRANSCRANIAL DOPPLER. CONCEPT, APPLICATION AND CHALLENGES

Werner H. Mess

Transcranial Doppler (TCD) sonography has been introduced almost 40 years ago. It allows for non-invasively measuring the blood flow velocity of the large intracranial vessels. The received signal stems from the so-called backscatter of the flowing red blood cells. If an embolus, i.e. a relatively large particle is passing through the vessel that is evaluated, a sudden intensity increase will occur. This increase can be heard when listening to the Doppler signal and also seen e.g. in the fast Fourier transform. It is called a microembolic signal (MES).

The emboli giving rise to an MES are rather small and hence are called microemboli. They will go unnoticed to the patient, in other words they are asymptomatic. However, they indicate the presence of a potentially harmful embolic source. Microemboli can be of either particulate or gaseous nature, depending on the source. For example, particles shedding off from a carotid artery plaque belong to the first group, while microemboli stemming from artificial heart valves are caused by cavitation and belong to the second group. MES detection is unique since it is the only ancillary method that can reveal an emboli shedding source.

The presence of MES is always anomalous, they have never been found in completely healthy human beings. In fact, they indicate an increased risk of cerebral malfunctioning to a varying degree depending on the nature, the source and the quantity of the MES as well as the condition of the patient. The rule of thumb is that particulate MES indicate a relatively high risk, the quantity is often less important. Patients with an asymptomatic carotid artery plaque are a typical example. The incidence can be quite low with only one or two MES within a several hour long measurement. Yet, these MES have been shown to be the best predictor for a future cerebrovascular event among all available ancillary examination modalities. On the other hand, gaseous MES due to an artificial heart valve might occur 100.000 times per year or more and yet have only a doubtful meaning.

Despite the fact that numerous studies on the positive correlation between the occurrence of MES and an elevated risk of cerebral malfunctioning have been performed, MES detection is practically absent from relevant guidelines. This is due to mainly two reasons, which are intervowen. There are hardly any let alone large scale studies showing that adapting the regimen of a given patient based on the results of an MES evaluation will actually improve the outcome. The lack of such studies partly is caused by the method itself. It is long-lasting and puts especially in the absence of well-performing automatic MES detection software a large burden on the examiner.

Unfortunately, almost no convincingly performing detection software is available at this moment.

So, taken together MES detection with TCD is unique in being able to reveal a cardiovascular emboligenic proces. Clearcut correlations between the occurrence of MES and an elevated risk for cerebral malfunctioning have been shown. Yet, MES detection is hardly implemented in routine patient care. Insufficient knowledge about the method, a scarcity of randomized control trials showing its clinical relevance as well as the lack of a reliable automated MES detection hamper its broad scale use and hence are challenges for the future.

Keywords: Transcranial Doppler sonography, microembolus detection, carotid artery plaque, stroke, TIA, individualised patient care, randomised clinical trials.

Centar za radiologiju i magnetnu rezonancu, Univerzitetski klinički centar Srbije, Beograd

ENDOVASKULARNE METODE REVASKULARIZACIJE KOMPLEKSNIH KAROTIDNIH STENOZA

Vladimir Cvetić

Endovaskularno lečenje sa implantacijom karotidnih stentova (CAS) je postala standardna alternativa hirurškom lečenju pacijenata sa hemodinamski značajnom karotidnom stenozom.

Shodno literaturnim preporukama poštujući jasne indikacije za CAS, počev od 2006. do 2022. godine u Univerzitetskom kliničkom centru Srbije izvedeno je više od 900 endovaskularnih procedura na karotidnim arterijama. Implantirani su karotidni stentovi otvorenog i zatvorenog dizajna, kao i najsavremeniji stentovi sa duplom mrežicom, uz obaveznu primenu cerebralne protekcije, proksimalne i distalne (filter).

Shodno literaturnim preporukama postoje jasne indikacije za CAS, a to su: restenoze nakon ranije učinjene hirurške endarterektomije, visoke hirurški nepristupačne lezije na unutrašnjoj karotidnoj arteriji, stenoze uzrokovane iridijacionim arteritisom, značajno oboljenje srca koje bi klasičnu operaciju činilo suviše rizičnom, značajni komorbiditet na plućima, pacijenti sa anomalijama kičme.

Komplikacije tokom ovih procedura mogu biti na mestu punkcije (hematom, AV fistula, pseudoaneurizme, perforacije krvnog suda), prilikom plasmana katetera, uvodnika (*Mb Leriche*, elongacije, tortuozitet arterija, kompleksni aortni luk, anatomske varijacije), tokom ugradnje stenta(migracija, deformacija, fraktura, akutna tromboza, pomeranje plaka van stenta), prilikom balon dilatacije(distalna embolizacija) i komplikacije vezane za korišćenje cerebralne protekcije. Kasne komplikacije podrazumevaju restenozu, odnosno trombozu stenta.

CAS je metoda izbora u lečenju karotidne bolesti, kod adekvatno selektovanih pacijenata uz izbor optimalnog materijala. Prepoznavanje komplikacija tokom endovaskularnog tretmana karotidnih stenoza, kao i mogućnost tretmana kompleksnih lezija, uslovljen je krivom učenja, iskustvom operatera i brojem procedura koje se izvode u specijalizovanim centrima.

Ključne reči: stenoza, karotidna arterija, stent, endovaskularno.

MINI SIMPOZIJUM
ZNAČAJ MULTIDISCIPLINARNOG PRISTUPA U LEČENJU PACIJENATA SA COVID 19: NAŠA ISKUSTVA

Medicinski fakutet, Univerzitet u Beogradu
Kliničko bolnički centar „Bežanijska kosa", Beograd

KARDIOMAGNETNA REZONANCA U DIJAGNOSTICI I PRAĆENJU SRČANE INSUFICIJENCIJE I ZAPALJENJSKIH BOLESTI MIOKARDA I PERIKARDA KOD PACIJENATA NAKON COVID-19 INFEKCIJE

Marija Zdravković

Magnetna rezonanca srca je sofisticirana, nejonizujuća dijagnostička metoda sa visokom reproducibilnošću i sa malim stepenom varijabilnosti u interpretaciji nalaza, koja može pružiti važne informacije vezane za funkciju i masu leve i desne komore, tkivnu karakterizaciju i kvantifikaciju fibroznih promena u miokardu. Od izuzetnog je značaja u dijagnostici, proceni etiologije, efekta terapije, kao i u stratifikaciji rizika kod pacijenata sa srčanom slabošću. Pacijenti sa srčanom slabošću imaju povećan mortalitet, te su pravovremena dijagnostika i započinjanje terapije od izuzetnog značaja. Tkivna kateterizacija u okviru studije kardiomagnetnom rezonancom može pružiti značajne informacije, koje odlično koreliraju sa kliničkim ishodima pacijenata.

Magnetna rezonanca srca predstavlja zlatni standard u ne-invazivnoj dijagnostici miokarditisa. Kod pacijenata sa prethodnom COVID-19 infekcijom i postojećim kardiovaskularnim simptomima, mogu se registrovati tipični znaci miokarditisa na magnetnoj rezonanci srca, uključujući postojanje edema miokarda, nekroze i miokardne fibroze, odnosno ožiljka. Takođe, određenim novim, sofisticiranim sekvencama u sklopu kardiomagnetne rezonance, moguće je registrovati diskretne promene, koje mogu ukazivati na inflamaciju miokarda, bez jasno vidljivih promena na standardnim sekvencama.

Sveobuhvatna kardiološka dijagnostika kod ovih pacijenata je od neprocenjivog značaja jer, pored moguće miokardne inflamacije uzrokovane direktnim ili indirektnim delovanjem virusa, mogu se dijagnostikovati i mnogobrojna, prethodno neotkrivena kardiološka oboljenja, koja mogu biti odgovorna za postojanje tegoba. Zahvatanje perikarda zabeleženo je u značajnom procentu pacijenata sa kardiovaskularnim tegobama nakon COVID-19 infekcije, uglavnom u subakutnoj ili rekonvalescentnoj fazi, i može se javiti zajedno sa inflamatornim procesom u miokardu ili izolovano.

Ključne reči: COVID-19, kardiomagnetna rezonanca, srčana slabost, miokarditis, bolesti perikarda

Medicinski fakutet, Univerzitet u Beogradu
Kliničko bolnički centar „Bežanijska kosa", Beograd

KORONARNA BOLEST U AKUTNOJ FAZI COVID-19 I POST-COVID PERIODU

Aleksandra Đoković

Dokazano je da je SARS-CoV-2 infekcija kod pacijenata sa prethodnim kardiovaskularnim oboljenjem povezana sa većim brojem neželjenih događaja i povećanim mortalitetom. Međutim, pokazalo se da rizik od oštećenja miokarda i kardiovaskularnih komplikacija postoji i kod bolesnika bez prethodne dijagnoze ovog oboljenja. Prevalenca miokardnog oštećenja u COVID-19 kreće se od 7-36%. Miokardno oštećenje u COVID-19 je multifaktorijalno i nastaje kao posledica hipoksije, mikro/makrovaskularne tromboze, akutnog miokarditisa, u uslovima razvoja stresom indukovane kardiomiopatije, ventrikularnih ili supraventrikularnih poremećaja ritma, citokinske oluje ili usled razvoja šoknog stanja različite etologije. Sistemski multi-inflamatorni odgovor u COVID-19 ima štetan efekat na endotel, čini ga disfunkcionalnim odnosno protrombogenim te je akutni koronarni sindrom (AKS) u COVID-19 delom posledica tromboze koronarnih arterija a delom nesklada između potreba tkiva za kiseonikom i smanjenog snabdevanja/hipoksije usled respiratorne insuficijencije. Patogeneza akutnog koronarnog sindroma/miokardnog oštećenja u COVID-19 nam je sada jasna ali je u uslovima pandemije bilo teško odrediti kada je miokardna povreda manifestacija koronarne bolesti koja zahteva hitan tretman a kada bi se ista definisala kao tip 2 infarkta miokarda. Karakteristike anginoznog bola, težina COVID-19 infekcije, vrednosti hsTnT, ehokardiografski pregled su bili osnovni postulati u dijagnozi akutnog koronarnog sindroma i u COVID-19 a kateterizacija srca sa selektivnom koronarografijom neophodna radi pravilnog lečenja svih bolesnika sa STEMI/NSTEMI i COVID-19. Specifičnost AKS u COVID-19 ogledala se i u činjenici da je značajno veći procenat bolesnika imao infarkt miokarda bez opstrukcije koronarnih arterija (40%) nego što je to slučaj u opštoj populaciji. Konačno, i nakon akutne faze (u post-COVID-19 periodu) isti patogenetski mehanizmi doprinose progresiji i destabilizaciji koronarne bolesti. Pokazano je da pacijenti koji su preboleli COVID-19 imaju trostruko veći rizik za razvoj velikih neželjenih kardiovaskularnih događaja u periodu od pet meseci nakon otpusta u poređenju sa kontrolnom grupom a incidenca AKS, miokardnog infarkta je značajno veća u odnosu na kohortu bez COVID-19.

Ključne reči: COVID-19, post-COVID, koronarna bolest

Kliničko bolnički centar "Bežanijska kosa", Beograd

GASTROINTESTINALNE MANIFESTACIJE COVID-19 INFEKCIJE

Marija Branković

Prvi slučajevi COVID-19 kod ljudi izazvani SARS-CoV-2 zabeleženi su u decembru 2019. godine u Vuhanu, gradu u Kini, nakon čega je ovaj virus izazvao pandemiju 21. veka. Put prenošenja je uglavnom respiratornim kapljicama i zato je najčešća manifestacija bolesti COVID-19 virusna upala pluća. Najčešći prijavljeni simptomi bili su temperatura, kašalj i umor, dok su glavni faktori rizika za razvoj teškog COVID-19 koji zahteva bolničko lečenje: poodmaklo doba, komorbiditeti (naročito kardiovaskularne bolesti i dijabetes melitus) i gojaznost.

Pored toga, manje uobičajeni, ali podjednako klinički važni simptomi ove infekcije uključuju simptome gastrointestinalnog trakta kao što su dijareja, bol u stomaku, povraćanje i gubitak apetita. Sada je poznato da je receptor angiotenzin-konvertujućeg enzima 2 (ACE2) ključan za ulazak virusa u ćeliju i oni se identifikuju u alveolarnim ćelijama tipa 2 u plućima, ali i u ćelijama žlezda želuca i enterocitima u ileum i debelo crevo. Kada SARS-CoV-2 uđe u enterocite, to dovodi do malapsorpcije, neuravnotežene crevne sekrecije i aktiviranja enteričkog nervnog sistema, što dovodi do dijareje. Štaviše, uzorci stolice se obično ne koriste za dijagnozu COVID-19, iako je poznato da je SARS-CoV-2 RNK prisutna u stolici pacijenata i ovi uzorci mogu ostati pozitivni duže u poređenju sa brisevima nazofarinksa. Zbog toga je fekalno - oralni prenos ovog virusa moguć i ovaj način prenošenja može se desiti čak i nakon uklanjanja virusa iz respiratornog trakta.

Digestivni simptomi se često posmatraju kao prva manifestacija infekcije COVID-19. Stoga, svaki pacijent sa novonastalim simptomima gastrointestinalnog trakta, posebno imunokompromitovani pacijenti, treba da se testira na COVID-19 u kontekstu globalne pandemije koja je u toku. COVID-19 je sistemska bolest sa višestrukim oštećenjem organa i gastrointestinalni trakt nije pošteđen.

Ključne reči: COVID-19, gastrointestinalne manifestacije

Medicinski fakultet, Univerzitet u Beogradu
Kliničko bolnički centar „Bežanijska kosa", Beograd

TRANSLACIONI ZNAČAJ LIPIDOMIKE U MODELIMA ISHEMIJSKO-REPERFUZIJSKIH OŠTEĆENJA ORGANA

Zoran Todorović

Lipidomika je deo metabolomike koja je usmerena na male molekule relativne mase ispod 1500. Poslednjih godina postaje sve očiglednija ključna uloga lipidoma u patogenezi i terapiji kardiovaskularnih događaja. Na primer, ishemijsko-reperfuzijsko oštećenje (IR) može pokrenuti oksidativni stres koji dovodi do štetnih promena u membranskim lipidima, uz neželjeno nakupljanje masnih kiselina koje dovodi do lipotoksičnosti. Analiza lipida pruža dodatni uvid u patogenezu IR poremećaja i otkriva nove mete za dejstvo lekova. Terapijski pristup reperfuzijskoj lipotoksičnosti uključuje smanjenje prekomernog nakupljanja masnih kiselina, odnosno uticaj na njihov transport u masno tkivo i/ili inhibiciju štetnih efekata masnih kiselina na oštećenje i smrt ćelija. Posljednja opcija uključuje korištenje PPAR agonista i lekova koji modulišu transport masnih kiselina preko karnitina u unutrašnjost mitohondrija ili preusmeravanje dugolančanih masnih kiselina u peroksizome. Takođe, polinezasićene masne kiseline igraju ulogu u povećanju reaktivnosti trombocita i nastanku velikih štetnih kardiovaskularnih događaja (MACE). Stalni porast incidence kardiovaskularnih bolesti naglašava važnost istraživanja povezivanja lipida i funkcije trombocita. Konkretno, *rebound* fenomen koji prati prestanak uzimanja klopidogrela kod pacijenata koji primaju dvojnu antitrombocitnu terapiju povezan je s promenama u lipidnom profilu. Naša dugogodišnja istraživanja naglašavaju važnost smanjenih vrijednosti HDL-a za rizik od ovakvog *rebound* efekta i nastanka tromboembolijskih događaja. Lipidi su inače heterogena grupa molekula, a njihovi signalni molekuli se ne akumuliraju već formiraju po potrebi u ćeliji. S druge strane, egzozomi prenose lipidne signale između ćelija, a profil takvih promena može se pratiti lipidomikom. Promene u lipidnom profilu su specifične za organ i mogu ukazivati na nove mete za dejstvo lekova.

Ključne reči: lipidomika, ishemijsko-reperfuzijsko oštećenje, funkcija trombocita

Medicinski fakultet, Univerzitet u Beogradu

Klinika za infektivne i tropske bolesti, Univerzitetski klinički centar Srbije, Beograd

INFEKTOLOŠKI OSVRT NA PANDEMIJU COVID-19

Miloš Korać

Epidemija koronavirusne infekcije (SARS-CoV-2), izbila je 31. decembra 2019. u Vuhanu (Kina) i ubrzo se proširila po celom svetu. Prema podacima SZO, do 1. septembra 2022. bilo je više od 598 miliona zaraženih virusom i 6,46 miliona umrlih. Virus se prenosi kapljičnim putem, a izvor infekcije je zaražena osoba. Najčešći simptomi COVID-19 su povišena temperatura, bolovi u mišićima, malaksalost, gubitak čula ukusa i mirisa i kašalj. Bolest se može komplikovati pneumonijom i respiratornom insuficijencijom. Smrtnost je najveća kod starijih ljudi sa komorbiditetima.

Tokom pandemije smo se suočili sa brojnim izazovima u dijagnostici i terapiji. Na samom početku postojao je problem u dijagnostici zbog nedovoljnog broja testova ili njihove neadekvatne osetljivosti. Ubrzo je utvrđeno da postoje laboratorijske analize koje mogu da se koriste za

procenu težine bolesti (krvna slika, zapaljenski parametri, koagulacioni status, srčani markeri, enzimi jetre, gasne analize itd.). U tom smislu je veoma važna i radiološka dijagnostika: ne samo da CT pregledom grudnog koša može da se utvrdi stadijum bolesti, već i kod pacijenata kod kojih nije dokazana infekcija, karakterističan CT nalaz ("ground glass" promene na plućima) ukazuje na COVID-19. U početku je mortalitet bio visok, ali kako se vremenom došlo do odgovarajućih saznanja o patogenezi bolesti, počeli su da se koriste lekovi koji utiču na tok bolesti (kortikosteroidi, antikoagulantna terapija), a potom su stigli i antivirusni lekovi i vakcine. Iako su antivirusni lekovi uticali na ublažavanje kliničke slike COVID-19, nijedan nije pokazao efikasnost u smanjenju mortaliteta.

Infektolozi su tokom ove epidemije imali dvostruku ulogu, ne samo da leče svoje pacijente sa COVID-19, već su radili i kao konsultanti u drugim klinikama i zdravstvenim ustanovama. Uprkos tome, od marta 2020. do marta 2022. godine u prijemno- trijažnom centru Klinike za infektivne i tropske bolesti pregledno je 143 819 pacijenata, a hospitalno je lečeno 5342.

Ključne reči: COVID-19, dijagnoza, terapija

Medicinski fakultet, Univerzitet u Beogradu
Kliničko bolnički centar "Bežanijska kosa", Beograd

DIJABETES MELITUS I COVID-19

Jelica Bjekić-Macut

Nedavna analiza preko 1,3 miliona laboratorijski potvrđenih slučajeva COVID-19 u Sjedinjenim američkim državama je pokazala da su kod ovih pacijenata najčešći komorbiditeti bile kardiovaskularne bolesti (32%), dijabetes (30%) i hronične bolesti pluća (18%). Od navedenog broja potvrđenih slučajeva, 14% je bilo hospitalizovano, 2% je bilo primljeno u Jedinice intenzivnog lečenja (JIL) i 5% je umrlo. Hospitalizacije su bile 6 puta češće kod bolesnika sa postojećim komorbiditetima (45,4%) u odnosu na one bez prethodno registrovanih bolesti (7,6%). Štaviše, ukoliko je pacijent sa dijabetesom imao ozbiljnu pridruženu bolest kao što je hronično srčano oboljenje, imao je veći rizik od ozbiljnih komplikacija od COVID-19. Konačno, bolesnici sa dijabetesom nemaju veće šanse da se zaraze već imaju veću verovatnoću od ozbiljnih komplikacija od COVID-19. Primećeno je u brojnim studijama širom sveta da je veliki udeo obolelih sa dijabetesom, a koji je razvio tešku formu COVID-19, bivao primljen u JIL i imao veću šansu da ravije akutni respiratorni distres sindrom (ARDS) uz produženu hospitalizaciju. Primećeno je da hiperglikemija na prijemu u bolnicu kod bolesnika koji ranije nisu imali verifikovan dijabetes, predstavlja faktor rizika za razvoj ozbiljnih formi bolesti. Dijabetes i posledična hiperglikemija su bile udružene sa formom bolesti nazvanim "dijabetesna pluća" koja se karakterišu promenama plućnog volumena i difuzije uzrokujući subkliničko plućno remodelovanje. Takođe, smatra se da dijabetesna pluća mogu biti delom urokovana gojaznošću i metaboličkim sindromom, a da sistemska inflamacija i trombocitna disfunkcija mogu biti udružene sa hiperglikemijskom plućnom mikroangiopatijom što sve može voditi lošem ishodu COVID-19 u takvih bolesnika. Glikemijska kontrola pre infekcije COVID-19 je važna za dalji tok bolesti. Naime, bolesnici sa dijabetesom i HbA1c 6% pre infekcije COVID-19 imali su 29% manji rizik za razvoj teških formi bolesti. Lečenje dijabetesa u COVID-19 podrazumeva optimalizaciju postojećih terapijskih režima ili uvođenje adekvatne terapije.

Ključne reči: COVID-19, komorbiditeti, hiperglikemija, dijabetes

Medicinski fakutet, Univerzitet u Beogradu
Kliničko bolnički centar „Bežanijska kosa", Beograd

KORISNI EFEKTI I POTENCIJALNI RIZICI PRIMENE GLUKOKORTIKOIDNIH HORMONA U LEČENJU PACIJENATA SA COVID-19

Svetlana Jelić

Broj protokola za lečenje COVID-19, koji je definisan i kod nas i u svetu, od prve pojave ove bolesti, krajem 2019. godine, ilustruje sva naša lutanja, ali i brojna saznanja, koja smo stekli. Glukokortikoidni hormoni su grupa lekova, uključenih u svaki od ovih protokola, zahvaljujući svojim dobro poznatim antinflamatornim efektima. Njihova manje poznata proinflamatorna dejstva i međuigra ovih, naizgled, suprotstavljenih efekata, od značaja su u pripremi imunološkog odgovora, ali i u sprečavanju prekomernog odgovora (npr. „citokinske oluje u COVID-19).

Klinički povoljni ishodi primene glukokortikoidnih hormona, pak, zapaženi su isključivo kod pacijenata sa teškom COVID-19 infekcijom i onih, koji su bili kritično oboleli. To su uglavnom bili bolesnici kojima je bila potrebna mehanička ventilacija ili neinvazivna kiseonična podrška. Rezultati studije RECOVERY i naknadne meta - analize sedam studija, koja je uključila i ovu, su kod ovih bolesnika pokazali da primena glukokortikoidnih hormona redukuje mortalitet unutar 28 dana, smanjuje rizik za nastanak potrebe za mehaničkom ventilacijom i skraćuje hospitalizaciju. Nema, međutim, dokaza da glukokortikoidna terapija ima bilo kakav pozitivan efekat kod pacijenata sa lakim i umereno teškim oblicima COVID-19. Naprotiv, rezultati ukazuju na potencijalne rizike i štetne efekte ove terapije kod ovih bolesnika. Statistički značajni ozbiljni neželjeni efekti ove terapije kod pacijenata sa COVID-19, koji se izdvajaju u meta-analizama, su hiperglikemija i hipernatremija.

Iako nam je pandemija COVID-19 pružila rezultate primene glukokortikoidnih hormona kod velikog broja bolesnika, otvorila je ponovo i brojna kontroverzna pitanja. To je, prvenstveno, određivanje optimalnog vremena za započinjanje ove terapije, izbor preparata, dužina primene, ali i uticaj na kasni mortalitet u post-COVID periodu.

Cilj ovog predavanja je pokušaj sistematizovanja korisnih efekata i potencijalnih rizika primene glukokortikoidnih hormona u lečenju pacijenata sa COVID-19, što bi moglo da posluži kao dobar model za njihovu efikasniju i bezbedniju primenu i u drugim indikacijama.

Ključne reči: COVID-19, glukokortikoidni hormoni

Medicinski fakultet, Univerzitet u Beogradu
Kliničko bolnički centar "Bežanijska kosa", Beograd

LIMFOPROLIFERATIVNA OBOLJENJA I COVID-19

Olivera Marković

Bolesnici sa limfoproliferativnim (LPO) oboljenjima imaju visok rizik za razvoj teških i životno ugrožavajućih infekcija, zbog imunodeficijencije uzrokovane samom bolešću, kao i zbog imunosupresivne terapije. Isto tako, infekcija izazvana SARS-CoV-2 kod bolesnika sa LPO vodi često teškim oblicima bolesti i visokom mortalitetu. Prema rezultatima do sada objavljenih studija ukupna stopa smrtnosti kod bolesnika sa LPO-a i SARS-Cov2 infekcijom je preko 20% i veća je među pacijentima sa koji zahtevaju hospitalizaciju. Najveće stope morbiditeta i mortaliteta zabeležene su kod pacijenata koji su bili stariji, koji su imali relapsnu/refraktornu bolest, komorbiditete kao što su hipertenzija i dijabetes, i prognozu preživljavanja za malignu bolest manju od 12 meseci u vreme postavljanja dijagnoze SARS-Cov2 infekcije. Pri tome, rezultati pokazuju da je rizik od smrtnosti heterogen i da se ne može predvideti isključivo na osnovu pojedinih faktora rizika kao što su starost pacijenta i težina osnovne bolesti. Visokoj smrtnosti doprinosi i nemogućnost adekvatnog i pravoremenog lečenja bolesnika tokom SARS-Cov-2 infekcije i stoga su od strane nacionalnih i internacionalnih hematoloških udruženja donate preporuke za lečenje bolesnika sa LPO u slovima kovid-19 pandemije. Rezultati lečenja (prognostički faktori i mortalitet) naših bolesnika sa LPO koji će biti detaljno prikazani su u saglasnosti sa rezultatima objavljenih studija.

Poseban problem kod bolesnika sa LPO predstavlja nedekvatan postvakcinalni humoralni imunološki odgovor nakon primene SARS-Cov-2 vakcine, naročito u grupi bolesnika koji su dobijali anti-CD20 terapiju u prethodnih godinu dana. Medjutim, pokazano je da je i pored slabijeg imunološkog odgovora na vakcinu, smrtnost vakcinisanih pacijenata sa LPO značajno manja u odnosu na nevakcinisane bolesnike. Imajući u vidu smanjen kapacitet imunološkog odgovora, naročito kod bolesnika kod kojih je hemioterapija u toku, važnu ulogu u zaštiti bolesnika sa LPO od SARS-Cov-2 infekcije igra preekspozicijska i postekspozicijska profilaksa primenom neutrališućih antitela.

Ključne reči: COVID-19, limfoproliferativna oboljenja, imunološki odgovor, vakcine

Kliničko bolnički centar "Bežanijska kosa", Beograd

POREMEĆAJI HEMOSTAZE U COVID 19 INFEKCIJI

Stanisavljević Nataša

Kod COVID-19 pacijenata prisutna je stečena koagulopatija sa pratećim inflamatornim sindromom, hiperkoagulacijom i poremećajem na nivou endotela uzrokovanih ne samo aktivnošću virusa već prisustvom hipoksije i sepse. Sa jedne strane, postoji opasnost od tromboze, ali je optimalna strategija tromboprofilakse kontraverza zbog ograničenog poznavanja uticaja COVID-19 na hemostazu. Indikacija za terapijsku dozu antikoagulantne terapije je dokazana duboka venska tromboza/plućna embolija koja se nalazi kod 25-75% hospitalizovanih pacijenata u jedinicama intenzivne nege kao i prisustvo klasičnih indikacija (mehanička srčana valvula, prethodno ponavljane tromboze kod dokazane trombofilije itd.). Sa druge strane, kod COVID 19 pacijenata prijavljene su i komplikacije u vidu krvarenja što se objašnjava remećenjem imunološke hemostaze, aktiviranjem renin-angiotenzin-aldosteron ose, endotelnom disfunkcijom itd. Trombocitopenija je registovana kod 22,9% od 6892 pacijenta u sistematskoj analizi 58 studija. Kod čak 70% umrlih u jedinicama intenzivne nege uočena je koagulopatija koja podsećana na diseminovanu intravaskularnu koagulaciju i sepsom indukovanu koagulopatiju pa je u nekoliko studija prijavljena i stopa (većinom intacerebralnih) krvarenja od oko 20%.

Veliko krvarenje se češće javlja između druge i treće nedelje od prijema, dok je trombotični događaj češći u prvoj nedelji hospitalizacije. Nakon hiperinflamatorne faze, d dimer i fibrinogen počinju da padaju i to je prelomna faza kada počinje da raste rizik za krvarenje (uz mogući pad broja trombocita) i tada je pravi trenutak za korekciju antikoagulantne terapije. U obzir treba uzeti i individualne faktore rizika tipa komorbiditeta, težinu COVID 19 infekcije, prisustvo mogućih komplikacija tipa sepse i ostalo.

Koliko je pitanje hemostaze u COVID 19 kompleksno i individualno orijentisano predstavljamo u primeru slučaja pacijenta starog 74 godine hospitalizovanog zbog COVID pneumonije skor 10/25 koji je lečen prema Nacionalnom vodiču. Devetog dana hospitalizacije uočen je značajan pad broja trombocita sa HIT 4T skorom 5 i pozitivnim PF4/HIT testom pa je preveden na fondaparin. Dva dana nakon toga dolazi do masivnog retroperitonealnog krvarenja sa urađenom embolizacijom i pacijent je otpušten 36og dana na dalje kućno lečenje.

Ključne reči: hemostaza, tromboza, krvarenje

Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu

Kliničko bolnički centar „Bežanijska kosa“, Beograd

IZAZOVI U RADU EPIDEMIOLOŠKE SLUŽBE KBC „BEŽANIJSKA KOSA” TOKOM KOVID I NE-KOVID REŽIMA ZA VREME PANDEMIJE

Ljiljana Marković Denić

Tokom pandemije kovid 19 oboljenja, osoblje za prevenciji i suzbijanju (PIS) bolničkih infekcija (BI), odnosno Tim za BI i Komisija za BI su u prvoj liniji u zaštiti javnog zdravlja u svim zdravstvenim ustanovama.

Tim i Komisija za BI KBC „Bežanijska kosa” susreli su se sa nizom izazova tokom pandemije kovid 19. Izazovi su bili različiti, ali ne manje značajni tokom 15 meseci ne-kovid režima rada bolnice (od marta 2020. kada je dijagnostikovan prvi kovid 19 slučaj u Srbiji, do danas, sa dva prelaska u kovid režim) u odnosu na kovid režim rada tokom 15 meseci u 2020/21/22. godine. Prvi deo ne-kovid režima rada omogućio je opsežnu teorijsku i praktičnu obuku zaposlenih o nošenju lične zaštitne opreme (LZO). Ali, poseban izazov u tom periodu bilo je pravovremeno prepoznavanje pacijenata koji su bili u inkubaciji kovid 19 oboljenja, a bez simptoma bolesti i neprepoznati na prijemu, s obzirom na nepostojanje brzih antigenskih testova u tom periodu. Posledično, trijaža na prijemu, izolacija kontakata i srečavanje nastajanje epidemije zahtevali su timski rad osoblja za nadzor nad BI i osoblja odeljenja bolnice. U drugom periodu ne-kovid ražima rada, svim pacijentima se na prijemu uzimaju antigenski testovi, što olakšava adekvatnu trijažu. Posebne preporuke usvojene su za testiranje i izolaciju pacijente koji su tokom hospitalizacije bili u kontaktu sa obolelim od kovid 19. Tokom kovid režima rada bolnica je arhitektonski prilagođena putevima kretanja zelena-crvena-zelena zona. Posebna briga posvećena je zaštiti osoblja od zaražavanja SARS-CoV-2 virusom. Osim infekcija *C. difficle*, incidencija drugih BI nije bila značajnije povećana u kovid režimu rada. Međutim, porast rezistencije uočen je kod svih vodećih prouzrokovača BI.

Multidisciplinarni pristup, timski rad, pravovremena pripema stručnih preporuka za različite komponente PIS-a, kontinuirana edukacija osoblja i pružanje pravovremenih informacija pacijentima, efikasno snabdevanje neophodnim sredstvima za dezinfekciju površina i higijenu ruku i LZO, kao i elektornska infrastruktura u praćenju pacijenata omogućili su adekvatnu i pravovremenu primenu svih mera prevencije i kontrole koje se primenjuju u našoj zemlji i svetu u cilju zaštite pacijenata i osoblja.

Ključne reči: COVID-19, epidemiološka služba, bolničke infekcije, prevencija, lična zaštitna oprema, trijaža

MINI SIMPOZIJUM
SAVREMENI IZAZOVI U BIOETICI

Medicinski fakultet, Univerzitet u Beogradu
Kliničko bolnički centar „Bežanijska kosa", Beograd

ZNAČAJ EDUKACIJE IZ KLINIČKE ETIKE U RADU SA KRITIČNO OBOLELIM PACIJENTIMA

Zoran Todorović

Pojam medicinske etike datira iz antičke Grčke, značajne promene doživeo u periodu srednjeg veka pod uticajem hrišćanstva, a njegovom nazivu je kumovao engleski lekar i etičar Tomas Persival (Thomas Percival) početkom XIX veka. Savremeno shvatanje medicinske etike presudno je determinisano tokom poslednjih pola veka nastankom bioetike i definisanjem temeljnih etičkih principa Američke i Evropske škole. Poslednjih trideset godina postala je neminovnost da se uvede klinička etika u kurikulume medicinskih fakulteta. Pri tome, neke oblasti kliničke etike su se i samostalno razvijale, recimo neuroetika u neuronaukama i kliničkoj medicini na Medicinskom fakultetu Univerziteta u Beogradu. Rad sa kritično obolelim pacijentima je poseban izazov za kliničku etiku ne samo zato što je reč o vulnerabilnim subjektima. Možemo govoriti o izazovima u svakodnevnoj kliničkoj praksi i u kliničkim ispitivanjima, ali je uvek teško poštovati u potpunosti osnovne etičke principe, a posebno autonomiju, ali i ne dovesti ih u međusobnu koliziju. Važno je reći da se u radu sa kritično obolelima, osim individualne etike, javlja i aspekt kolektivne etike o kome treba posebno voditi računa. Takođe, važno je i pitanje individualne i kolektivne odgovornosti medicinskih radnika u donošenju ključnih odluka za život i zdravlje kritično obolelih pacijenata. Rad sa takvim pacijentima predstavlja izazovno okruženje u kome se stvara izuzetan pritisak na pripadnike medicinske struke koji se može ublažiti, ako ne i izbeći definisanjem striktnih pravila i sprovođenjem programa edukacije iz kliničke etike (npr. kroz kratke obrazovne cikluse). Ostaje otvoreno pitanje kako pretočiti definisane osnovne kompetence u svakodnevnu medicinsku praksu.

Ključne reči: klinička etika, kritično oboleli, vulnerabilnost, autonomija

Institut za farmakologiju, kliničku farmakologiju i toksikologiju, Medicinski fakultet, Univerzitet u Beogradu

INFORMISANA SAGLASNOST – ISTRAŽIVAČKI ASPEKTI I ETIČKE DILEME

Miroslav Radenković

Informisana saglasnost predstavlja postupak dobijanja pismene saglasnosti za učešće u kliničkom istraživanju od potencijalnog učesnika kliničke studije nakon što je u potpunosti obavešten o ciljevima istraživanja, protokolu istraživanja, kao i predvidljivim koristima, ali i potencijalnim rizicima istraživačkog postupka. Mogući nedostatak razumevanja, prepreke u komunikaciji, kulturološke razlike i različiti drugi faktori uvek zahtevaju dodatnu pažnju u dobijanju validnog informisanog pristanka, posebno ukoliko se radi o placebo-kontrolisanom ispitivanju. Tokom ovog procesa, relevantna etička komisija je odgovorna da planirano istraživanje bude sprovedeno u potpunom skladu sa predloženim protokolom, usvojenom metodologijom i najvišim etičkim standardima, pri čemu je neophodno da se autonomija ispitanika u donošenju odluka u potpunosti zaštiti.

Dobijanje informisanog pristanka od učesnika u kliničkim istraživanjima je od suštinskog značaja jer promoviše njihovu sveukupnu dobrobit i obezbeđuje njihova prava. Ovo dalje ukazuje da se uvek moraju poštovati osnovni etički principi u istraživanjima na ljudima, kao što su autonomija, činjenje dobra, ne nanošenja zla, kao i jednakosti u postupcima. Shodno tome, uvek treba imati na umu tri suštinska standarda za dobijanje informisanog pristanka, a to je da učesnik mora imati očuvan kapacitet za donošenje odluka, mora biti adekvatno informisan i ni pod kakvim neadekvatnim pritiskom u toku donošenja odluke.

Informisani pristanak uvek treba posmatrati kao postupak koji je mnogo više od potpisa učesnika istraživanja na pravnom dokumentu, zatim kao kontinuirani dinamički proces, ali nikako ne kao potpuno izolovani događaj tokom kliničke studije. U ovom procesu neophodno je usvojiti inovativne multimedijske strategije u komunikaciji kako bi se dodatno poboljšalo razumevanje informacija o kliničkom ispitivanju među učesnicima. Poboljšanje efikasnosti procesa informisanog pristanka je jedno od ključnih pitanja zdravstvene zaštite u celini, što podrazumeva i dalji razvoj međunarodnih etičkih standarda za odgovorno sprovođenje kliničkih studija.

Ključne reči: informisana saglasnost, kliničko istraživanje, etika, autonomija.

Medicinski fakultet, Univerzitet u Beogradu
Univerzitetska dečja klinika, Beograd

ETIČKE PERSPEKTIVE PEDIJATRIJSKE PALIJATIVNE NEGE U SRBIJI

Vera Zdravković

Pedijatrijska palijativna nega je usmerena na poboljšanje života dece, koja su kritično obolela ili imaju neizlečivu bolest. Cilj palijativne nege je da proceni njihove potrebe i da omogući lečenje koje koje će smanjiti fizičku i psihološku patnju dece, kao i da poboljša kvalitet života i adap-

taciju podrodice na bolest i tugovanje. Palijativna nega treba da pomogne da deca, lekari i zdravstveni radnici donose odluke i omogući koordinisanje nege između svih osoba koje su uključene u nju. Preporuke za organizaciju pedijatrijske palijativne nege u Srbiji obezbedile su analizu svih aspekata njene organizacije u našem zdravstvenom sistemu. Predlažemo edukaciju etičkih konsultanata koji će pružati podršku porodici, detetu i zdravstvenim radnicima. Neophodni su ukoliko postoje neslaganja oko planiranog lečenja, primene preporučenih terapija, kao i prava deteta da bude informisano o svojoj bolesti. Svako dete zaslužuje da zna istinu, koja je prilagođena njegovom uzrastu i da se saglasi sa lečenjem u skladu sa svojom kompetentošću i kapacitetom donošenja odluka. U komunikaciji i procesu donošenja odluka treba da učestvuje cela porodica, po predloženom algoritmu.

Ključne reči: etika, deca, palijativna nega, intenzivna nega i terapija

Institute for Immunobiology and Human Genetics, Medical Faculty in Skopje

IMPLEMENTING ETHICS IN GENETIC/ GENOMIC RESEARCH IN REPUBLIC OF NORTH MACEDONIA

Aleksandar Petlichkovski

Major advancements in the field of molecular diagnostics, combined with personalized treatment strategies, have led to better understanding of molecular mechanism of different disease and conditions in the past decade. The new technologies allow identification of gene alterations that are targetable at molecular level and thus provide actionable information which help clinicians to choose the treatment strategy. Genomic medicine refers to medical interventions that employ the information encoded in an individual's genetic material to amend medical interventions, such as drug prescription and preventive medical testing, and guide lifestyle decision-making, aimed to improve the overall quality of life. This is especially true for the developed world.

While genomic medicine initiatives in developed countries have been driven by countrywide strategies, whereas the use of genomics and implementation of genomic medicine practices in emerging economies has been much more targeted to specific local needs or opportunities. Emerging economies face specific challenges with respect to the support of genomics research. Most developing countries lack the qualified personnel, infrastructure, and research centers that could disseminate the new knowledge by training and educating young scientists, medical students, and clinicians. When taken into account that around 85% of the world's population lives in developing/resource-limited countries, it becomes apparent that the issue of implementing genomic medicine practices in these settings is crucial. These countries are all in desperate need of more effective and precise health care systems that will help all patients get a better diagnosis, more targeted treatment, and, most importantly, shift from a disease-centered to a prevention-focused system.

The clinical implementation and general use of genomics technologies in the developing world faces many different challenges, like the lack of genomic laboratory infrastructure and a coordinated effort to impart the necessary knowledge, skills, and attitudes on the part of the healthcare workforce to successfully implement genomic medicine.

Key Words: Genomic medicine, developing countries, ethics in genetic research

Institut za medicinsku fiziologiju „Rihard Burijan", Medicinski fakultet, Univerzitet u Beogradu

TRANSLACIONA ISTRAŽIVANJA: ETIČKI I NAUČNI IZAZOVI

Dragan Hrnčić, Olivera Stanojlović

Translaciono istraživanje bi se moglo definisati na nekoliko načina, ali sledeća definicija bi mogla biti korisna za razumevanje prirode ove vrste istraživanja: „Translaciono istraživanje podstiče višesmernu integraciju osnovnih istraživanja, istraživanja usmerenih ka pacijentima i populacionih istraživanja, sa dugoročnim ciljom poboljšanja javnog zdravlja". U stvari, trebalo bi da bude jasno da translaciona istraživanja transformišu otkrića različito orijentisanih studija u novi klinički armamentarijum. Pored toga, translaciona istraživanja angažuju i društvenu zajednicu, podrazumevaju blisku saradnju sa industrijom, državnim organima i kreatorima zdravstvenih i naučnih politika. Često ova istraživanja integrišu i niz naučnih disciplina van biomedicinske oblasti, posebno onih vezanih za biomedicinske tehnologije, biomedicinsko inženjerstvo, digitalnu medicinu, veštačku inteligenciju, mašinsko učenje i druge. Stoga su translaciona istraživanja u biomedicini proces koji se suočava sa brojnim etičkim izazovima i koji zahteva pažljiv etički monitoring sa mnogo specifičnosti. Česta su etička pitanja vezana za alokaciju finasiranja. Naime, translaciona istraživanja zahtevaju značajna finansijska sredstva koja moraju biti pravedno raspoređena. Pošto su završni koraci u translacionom istraživanju usko povezani sa saradnjom sa industrijom, sukob interesa na institucionalnom nivou je značajno pitanje u ovoj vrsti istraživanja. Dakle, imajući u vidu jedinstvene karakteristike translacionih istraživanja, potrebno je primeniti integrisani etički pogled na translacijski kontinuum. Poseban naglasak treba staviti na etička pitanja i izazove koji se mogu pojaviti tokom svake faze i jaza. Svi akteri i zainteresovane strane u areni translacionog istraživanja moraju biti proći adekvatnu obuku o osnovnim konceptima bioetike. Edukacija u oblasti bioetike je od vitalnog značaja za sprečavanje bilo koje vrste neakademskog ponašanja i kršenja etičkih načela dobre naučne prakse u translacionom istraživanju.

Ključne reči: translaciona istraživanja, nauka, bioetika, edukacija

Institut za epidemiologiju, Medicinski fakutet, Univerzitet u Beogradu

VAKCINACIJA PROTIV COVID-19 - ETIČKI IZAZOVI I KAKO IH PREVAZIĆI

Tatjana Gazibara

Vakcinacija protiv infekcije COVID-19 je jedna od mera koje su imale za cilj suzbijanje pandemije. Širom sveta zabeležen je različit odziv na vakcinaciju. U Srbiji, vakcinacija je dobrovoljna, a građani mogu samostalno odabrati jednu od 4 dostupne vakcine. Obuhvat vakcinacijom je prvih nekoliko meseci rastao, da bi zatim stagnirao. Jedan od mogućih pristupa u naporima da se poveća obuhvat vakcinacijom je bilo i uvođenje novčane naknade, ali u naučnoj javnosti još uvek ima puno dilema o etičkoj dimenziji ovakve strategije. Tako je u prestižnom stručnom medicinskom časopisu Lanset ova strategija okarakterisna kao neetična pri čemu je glavni argument za ovakvu tvrdnju bio taj da novac menja percepciju - zbog koje se ljudi mogu izložiti većem riziku kojem se inače ne bi izložili da se ne nudi novčana nagrada (tzv. neopravdani podsticaj). Još jedan argument protiv novčane stimulacije vakcinacije je bio i taj da se ovakvim pristupom ljudi iz siromašnijih društvenih slojeva stavljaju u poziciju koju teško mogu da odbiju, pa su samim tim primorani da se vakcinišu i protiv svojih ubeđenja. U ovom predavanju, objasniće se da neopravdani podsticaj, koji može biti etički problem u kliničkim istraživanjima na ljudima, nije primenljiv na vakcinaciju stanovništva koja je odobrena od strane regulatornih tela (kako nacionalnih tako i međunarodnih). Slično tome, nije reč ni o primoravanju na vakcinaciju zato što je iznos novčane naknade u visini jedne dnevnice nekvalifikovanog radnika (koja je inače norma za finansijsku kompenzaciju u kliničkim istraživanjima na ljudima), pa samim tim nije „isuviše dobra da bi se odbila".

Ključne reči: COVID-19, vakcinacija, novčana nagrada, etika.

Institut za medicinsku i kliničku biohemiju, Medicinski fakutet, Univerzitet u Beogradu

DESET GODINA EDUKACIJE IZ BIOETIKE NA MEDICINSKOM FAKULTETU UNIVERZITETA U BEOGRADU

Ivanka Marković

Medicinski fakultet Univerziteta u Beogradu (MFUB) i Medicinski fakultet Maunt Sajnaj iz Njujorka, SAD (Icahn School of Medicine at Mount Sinai - ISMMS) imaju desetogodišnju saradnju u edukaciji u oblasti istraživačke etike, kroz dva projekta koja je finansirala Fogarti fondacija Nacionalnog instituta za zdravlje SAD. Saradnja je počela 2012. godine, zajedničkim projektom „Edukacija o o istraživačkoj etici u regionu Balkana i crnomorskim zemljama". Zahvaljujući ovom petogodišnjem projektu, 33 polaznika iz balkanskih zemalja završili su jednogodišnju edukaciju u oblasti istraživačke etike i dobili sertifikat obe institucije. Saradnja je nastavljena kroz projekat „Uvođenje master akademskih studija iz istraživačke etike na Medicinskom fakultetu Univerziteta u Beogradu". Tokom projekta, nastavu na svim predmetima zajedno su planirali i realizovali nastavnici sa MFUB i ISMMS, a sertifikat o završenom programu iz bioetike steklo je osam polaznika iz Srbije i Bugarske. Ovo iskustvo u zajedničkoj pripremi i izvođenju nastave poslužilo je kao osnova za razvoj programa Master akademskih studija iz bioetike na Medicinskom fakultetu Univerziteta u Beogradu. Program MAS iz Bioetike je dobio nacionalnu akreditaciju u junu 2021. godine, a prva generacija od osam master studenata upisana je u školskoj 2021/2022. godini.

Program MAS iz Bioetike ima za cilj da studentima omogući sticanje ekspertize u oblasti bioetike i obezbedi stalno usklađivanje istraživačke prakse u našoj sredini sa međunarodnim etičkim standardima u istraživanja na oglednim životinjama i u humanoj populaciji. Program se oslanja na znanja i iskustva naših nastavnika, od kojih su četvoro završili dvogodišnji program studije iz bioetike univerzita Clarkson-ISMMS i stekli zvanje Mastera iz bioetike, ali i na ogromne on-line resurse razvijene tokom prethodnih 10 godina. Kao jedini program ove vrste u regionu, program MAS iz Bioetike je prilagođen potrebama edukacije o istraživačkoj etici u regionu Balkana, i dragocen resurs za kliničare, istraživače i članove etičkih komisija. Uz to, ovaj program daje snažnu podršku našoj naučnoj zajednici u pravcu jačanja pouzdanosti i etičnosti u sprovođenju istraživanja.

Ključne reči: bioetika; edukacija; obrazovne potrebe; istraživači

Katedra humanističkih nauka, Medicinski fakultet, Univerzitet u Beogradu

ISTRAŽIVANJE POTREBA ZA EDUKACIJOM IZ BIOETIKE NA MEDICINSKIM FAKULTETIMA U SRBIJI

Vida Jeremić Stojković

Kao deo procesa osnivanja Master programa iz Bioetike na Medicinskom fakultetu Univerziteta u Beogradu, ova studija predstavlja procenu obrazovnih potreba istraživača u Srbiji sa ciljem usklađivanja nastavnog plana i programa. Primenjen je kombinovani, eksploratorni dizajn koji sjedninjuje kvalitativnu i kvantitativnu metodologiju prikupljanja podataka. Prvu fazu je činilo preliminarno kvalitativno istraživanje kojim su se kroz intervjue i fokus grupe identifikovale ključne teme na osnovu kojih je konstruisan upitnik za drugu fazu – studiju preseka, koja je obuhvatila lekare-istraživače sa medicinskih fakulte-

ta u Beogradu, Novom Sadu i Kragujevcu. Uzorak je činilo 154 ispitanika – istraživača. Iako je skoro polovina njih (48.1%) imalo edukaciju iz istraživačke etike, svega 10.3% je pohađalo edukaciju koja je trajala duže od mesec dana. Ispitanici su se osećali najmanje kompetentnim kad su u pitanju etičke dileme u vezi sa biobankama, međunarodnim i komercijalnim istraživanjima. Rezultati su pokazali da su istraživači u sva tri centra visoko motivisani da se dalje edukuju u oblasti istraživačke etike, a svega 5% ispitanika je smatralo da ne bi imali korsti od dodatne edukacije. Etičke dileme sa kojima se istraživači u Srbiji najčešće susreću su dileme u vezi sa autorstvom i publikovanjem (49%), informisanim pristankom (35.7%), i regrutovanjem ispitanika (34.4%). Najveći procenat ispitivanih istraživača pokazao je interesovanje za dodatnu edukaciju u vezi sa autorstvom i publikovanjem (50%), vulnerabilnim grupama (45.5%), komercijalnim (44.2%) i internacionalnim istraživanjima (41.6%) i regrutovanjem ispitanika (39%). S obzirom na ispoljenu visoku motivaciju za pohađanje dodatne edukacije iz istraživačke etike, Master program iz Bioetike predstavlja adekvatan odgovor na realne potrebe istraživača. Etička pitanja sa kojima se istraživači najčešće susreću, kao i pitanja u vezi sa kojim se osećaju najmanje kompetentno su upravo pitanja u vezi sa kojim pokazuju najveće interesovanje da se dodatno edukuju, što je važan rezultat za kreatore nastavnog plana i programa.

Ključne reči: bioetika; edukacija; obrazovne potrebe; istraživači

Icahn School of Medicine at Mount Sinai, New York, USA

MEDICAL ETHICS: AN UNCOMMON MORALITY

Rosamond Rhodes

Common morality has been the touchstone for addressing issues of medical ethics since the publication of Tom Beauchamp and James Childress's Principles of Biomedical Ethics in 1979. My presentation challenges that reigning view by demonstrating why the common morality accounts of medical ethics are unsuitable for the medical profession and inadequate for responding to the distinctive issues that arise in medical practice. First, I present a negative argument showing that common morality does not provide an account of medical ethics. I use vivid examples to show that some actions required or permitted by common morality are prohibited for medical professionals; some actions that are required or permitted by medical ethics are prohibited by common morality; some actions that are optional for people outside of medicine are strict duties for medical professionals. In sum, I illustrate that medical ethics and common morality incompatible. Second, I provide a positive argument to explain why common morality cannot yield the ethics of medicine and to demonstrate why the medical profession requires its own distinctive ethics. Taken together, my two arguments show that medical ethics is an autonomous field of morality because the duties of doctors cannot be deduced from the precepts of common morality.

I go on to explain medicine what it is that makes medicine a profession. As I see it, society grants professions distinctive specific powers, privileges, and immunities to be used in the interest of individuals and society. The grant of those unique rights entails society trusting that the rights will be used in a trustworthy way. From that perspective, I explain how the rights allowed to professions are limited by society and why the medical profession must strive to maintaining society's trust.

Key Words: medical ethics, uncommon morality, common morality, medical profession, trust

MINI SIMPOZIJUM
100 GODINA INSTITUTA ZA MEDICINSKU FIZIOLOGIJU „RIHARD BURIJAN“

Institut za medicinsku fiziologiju “Rihard Burijan”, Medicinski fakultet, Univerzitet u Beogradu

100 GODINA INSTITUTA ZA MEDICINSKU FIZIOLOGIJU "RIHARD BURIJAN"

Sanja Mazić, Dejan Nešić

Institut za medicinsku fiziologiju osnovan je 1921. godine kao Fiziološki zavod (kasnije Fiziološki institut). Osnivač Instituta za medicinsku fiziologiju bio je Rihard Burijan, (1871-1954), koji je na sednici Saveta Medicinskog fakulteta Univerziteta u Beogradu, 10. oktobra 1920. godine, izabran za redovnog profesora fiziologije a svoja prva predavanja održao je školske 1922/23 godine.

Danas, 101 godinu kasnije, nastavni rad u Institutu za medicinsku fiziologiju odvija se kroz: A. Katedru za osnovnu nastavu iz medicinske fiziologije (integrisane akademske studije), koja organizuje nastavu iz medicinske fiziologije na srpskom i engleskom jeziku, kao i na osnovnim akademskim studijama sestrinstva. Nastava iz medicinske fiziologije odvija se u dva semestra sa 268 časova teorijske, seminarske i praktične nastave, od čega 251 čas izvodi Katedra za medicinsku fiziologiju (112 časova teorijske nastave/25 metodskih jedinica, 34 časova seminarske nastave/17 seminara, 105 časova praktične nastave/27 vežbi). Tokom integrisanih akademskih studija medicine Katedra za medicinsku fiziologiju organizuje 10 izbornih modula, 7 izbornih modula se održavaju u III i IV semestru, i po jedan u VI, IX, i X semestru. B. Katedru za specijalističku nastavu iz Eksperimentalne fiziologije i patološke fiziologije (poslediplomska katedra), koja izvodi nastavu na specijalističkim akademskim studijama iz eksperimentalne fiziologije i patološke fiziologije (ranije i na specijalizaciji iz Kliničke fiziologije), C. Katedru za specijalizaciju iz Medicine sporta, koja izvodi nastavu kako na specijalizaciji iz Medicine sporta tako i na master akademskim studijama iz modula Fizička aktivnosti, zdravlje i terapija vežbanjem, D. Katedru za užu specijalizaciju iz Balneoklimatologije, E. Katedru za užu specijalizaciju iz Medicine bola, i F. Katedru za užu specijalizaciju iz Baromedicine. Nastava na doktorskim akademskim studijama na Katedri za medicinsku fiziologiju odvija se kroz dva modula: Fiziološke nauke i Primenjena istrazivanja u medicini sporta i motornim veštinama. Danas se na Katedri za medicinsku fiziologiju naučnoistraživački rad odvija u devet laboratorija, i to: Laboratoriju za kardiovaskularna istraživanja (rukovodilac, Prof. dr Dragan Đurić), Laboratoriju za neurofiziologiju (rukovodilac, Prof. dr Olivera Stanojlović), Laboratoriju za ćelijsku respiraciju (rukovodilac, Prof. dr Zvezdana Kojić), Laboratoriju za medicinu sporta i terapiju vežbanjem (rukovodilac, Prof. dr Sanja Mazić), Laboratoriju za neuroendokrinologiju i metabolizam (rukovodilac, Prof. dr Dejan Nešić), Laboratoriju za eksperimentalnu hiperbaričnu oksigenaciju (rukovodilac, Prof. dr Predrag Brkić), Laboratoriju za celularnu fiziologiju (rukovodilac, Prof. dr Igor Pantić), Laboratoriju za gastrointestinalnu fiziologiju (rukovodilac, Doc. dr Marija Stojanović).

Ključne reči: medicinska fiziologija, Rihard Burijan, 100 godina, jubilej.

Izdavač i vlasnik:

MEDICINSKI FAKULTET UNIVERZITETA U BEOGRADU

Uredništvo i administracija:

11105 Beograd, Dr Subotića br. 8, soba 311

Tehnički urednik:

Radević Vladimir

Lektor za engleski jezik:

doc. dr Danka Sinadinović

Tehnički sekretar:

Tijana Tošić

Grafički dizajn:

Prof. dr Slobodan Štetić
Fakultet pedagoških nauka u Jagodini Univerziteta u Kragujevcu