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THE VOICE OF HEALTH: FINDING A CURE FOR THE CLIMATE CHANGE MALADY

GLAS ZDRAVLJA U PRONALAZENJU LEKA ZA KLIMATSKE PROMENE

Marija JEVTIĆ

Introduction

Being healthy, rather than simply being not being ill, means living in a state of complete psychological, physical, and social well-being. This also confirms the fact that the individual health is not fully attainable as an absolute category.

According to the American public health expert, C.E.A. Winslow, public health is the art and science of disease prevention, lifespan extension, and physical health improvement. He focused on addressing and mitigating the causes of illness. From this viewpoint, we can view effective public health measures as being those that take place through organized societal efforts which include: environmental rehabilitation, infection control within the community, and hygiene education. The organization of health care services that provide early diagnosis, preventive care, and the development of social supports that improve the standard of living, all help make it possible for individuals to protect their health [1].

The World Health Organization (WHO) simplifies this definition by stating that public health is the art and science of disease prevention, lifespan extension, and health improvement through organized efforts by society [1].

According to the American Medical Association, public health is what society does to ensure the conditions that are necessary for people to be healthy. These efforts include a range of educational, economic, social and environmental initiatives.

Therefore, all definitions of individual health and public health, at their foundation, support physical wellbeing and a safe living environment, as well as efforts by individuals, population and society as a whole, that are supposed to provide/improve the working and living conditions.

One of the primary defining elements of an environment is the climate of a certain area. In mod-

ern times, the challenge of climate change and its influence on health and quality of life affects us all.

The global population is unstoppably nearing nine billion residents. However, living conditions in certain areas of our planet have not been adapted, either naturally or through human intervention, to sustain these numbers. As a result, different challenges emerge, including social, economic, and religious ones. It is also important to emphasize that, as human beings (*Homo sapiens*), we are homeothermic organisms. If our populations are widely spread out across the planet, we have very limited capacity to adapt to the external environment. This adaptive factor is of significance to human interaction with the environment, climate changes and the influence on morbidity, mortality and health systems as well.

Some Facts about Climate

The climate of an area is defined on the basis of average values, extreme and other statistical meteorological parameters throughout an interval of time - months, years, centuries. According to a more recent definition of climate, the climate is a dynamic system in which there are mutual influencing factors: atmosphere, oceans, ice and snow cover, processes on the ground (lithosphere) and biosphere - including those caused by humans and their activities. Each of these components in the climate system exhibits its own dynamics, on which other components exert influence and as such, cause changes to them [2].

This more recent, modern definition of climate had resulted from the precise need to explain changes which are visible and which have been recognized and felt on an individual level in the previous several decades (**Figure 1**) [3].

South-Eastern Europe is an area with continental climate having clear transitions between seasons,

Abbreviations

WHO – World Health Organization

and climate changes are quite obvious. Consequences are very noticeably felt and they are expected to be even more pronounced in the coming period.

Hygiene is defined as a health science which studies external environmental factors (biological, physical, social) and their effect on the health of individuals and populations. It also tends to define the measures and activities that lessen the effect of negative factors and increase the effects of positive factors in the external environment (individual effects or combined effects) [4].

Climate as a factor in the external environment is seen as positive, for example facilitating healing centers situated in favorable climatic areas, such as medical centers adjacent to thermal hot springs, climatic areas that are suitable for rest and vacations where people can enjoy the benefits of the sun, as well as other environmental benefits. However, much of what was previously seen as a recommendation has been brought into question in recent decades precisely because of evidenced changes in climate.

Climate changes have become an increasingly destructive process at a much faster rate than predicted. Climate change induced by greenhouse gas emissions caused by different human activities including high energy production and consumption is the biggest challenge faced by global health during the 21st century for the decision-makers in most diverse countries [5, 6].

Climate change, chemical contamination, water and air pollution are all exacerbating diseases worldwide [6].

Climate Change, Environment, Urbanization, Energy, and Sustainability

If our planet Earth were to be viewed as an organism, it could be said to have become “highly febrile”. It is nearly impossible to lower the temperature of the planet and difficult to even slow down its further increase. Human activities directed to both industrial and economic development as well as material gain alongside the completely absent or insufficient concern about their influence on the environment, have led to a reaction by the planet. Earth, with its delicate balance having been endangered, reacts with a spectrum of symptoms and presents clinical features of an illness which is becoming chronic in character. This malady is manifested through: floods, hurricanes, tsunamis, as well as other strong winds, heavy rains and all the more pronounced changes in temperatures and unstable weather in the restricted areas.

In addition to these physical manifestations, there are changes in biodiversity and the number of endangered species on the planet rises. There is an extreme increase in areas affected by drought, and many animal species move on looking for another habitat.

It is also essential to mention that people have created a “new form” of environment through urbanization and the concentration of populations into

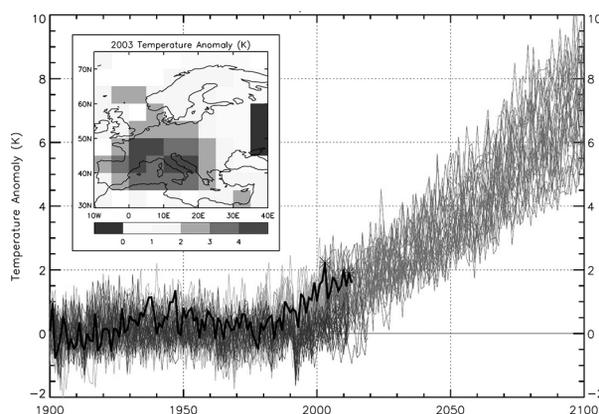


Figure 1. Variation of summer temperatures across Europe relative to the pre-industrial period [Source: Met Office, 2014]

Slika 1. Varijacije letnjih temperatura u Evropi u poređenju sa pre-industrijskim periodom [Izvor: Met Office, 2014]

big cities. There is a significant cause and effect relationship between urbanization and climate change. Cities are the greatest causes of climate change, and the human population in cities is the most subjected to the health-damaging consequences [7, 8].

Due to climate change, the use of water resources and water supply is also damaged and endangered, in the sense of both quality and quantity. On one hand, there are droughts and the absence of water and on the other hand, there are floods and threats to infrastructure, material damage and increased risk for the spread of infection. All of these elements, as well as their relation to the intensification of migration, represent huge challenges and add strong arguments to the cause of climate change reduction and mitigation. Their resolution requires engagement that increases preparedness for and resilience to climate changes. However, they represent another strong argument for actions in the field of the mitigation of the climate changes [9].

The development of infrastructure, provision of necessary energy sources, and economic possibilities which include job availability, make urban settings attractive living environments for individuals and large populations. However, at the same time, there is a new increasing set of risks that are significant to human health. Urban settings are as much the source of the problem as they are the place to solve them.

It is predicted that 70% of the human population will live in urban settings by the year 2050. Urban health has become a new area of focus for health care. One of the most important goals related to urban health is the maintenance and improvement of infrastructure. This ought to occur simultaneously with the reduction of causes of climate change and the preservation of the health of the population. Dealing with the urbanization-related challenges influenced by climate change has become increasingly interesting to numerous experts who seek to ensure secure future for the generations ahead of us. Those involved in finding solutions understand the interdependence of the need for energy to

be provided from renewable resources, the sustainability of all systems (particularly health and education), as well as the increase of their resilience.

According to the WHO, and other stakeholder organizations, cleaner energy systems, promoting the safe use of public transportation, and active movement (cycling or walking) could reduce carbon emissions, and reduce the burden of household air pollution [10, 11].

Urbanization trends, population growth and migration mean that the number of people exposed to high temperature extremes will increase, which has major implications for public health planning. Urban areas will expand: by 2030, urban land cover is projected to triple compared to its extent in the year 2000. The number of people exposed to the risks of climate change is intensified by social factors: the distribution of population density caused by urbanization, and changes in population demographics related to aging [10, 12].

Today, cities contribute to more than 60% of greenhouse gas emissions. Urbanization is responsible for 75% of energy consumption and a similar portion of all waste. Populations in cities are especially vulnerable to the consequences of climate change such as heat waves, increasing levels of air pollution, and rising sea levels in coastal areas [13].

Population health and climate change are in a state of mutual dependence with macroeconomics, energy policy, and urbanization. There is also a significant demographic factor.

It is very important to underline that environmental sustainability is a central concern of the Sustainable Development Goals and is addressed in goals for water and sanitation, energy, cities and climate change. Sustainable Development Goal 13 underlines that we should take an urgent action to combat climate change and its impacts. Climate change is one of the major health challenges of the future and its mitigation is a prerequisite for sustainable development. Climate change is related to many of these goals, affecting, for example, water resources, food production, desertification, air pollution, and therefore, human health [14].

Climate Change, Global Health, and the Health of Population

“The climate change factory” in its full capacity produces direct and indirect “by-products of climate changes” resulting in numerous consequences which affect individual health, the health of the population as a whole and the environment. This represents not only a challenge for public health, but also for health care systems and health professionals.

Human activities have significantly contributed to climate change. Its consequences are a reflection of the health of Planet Earth itself and they intensify the need for the increase in resiliency, and adaptation capability. We are in need of creative solutions that go above and beyond the necessary action required to mitigate climate change.

Indirect effects of climate change include consequences faced by the population such as air pollution,

increasing vector disease, food insecurity, undernutrition, mental illness, climate displacement and migration. For example, according to the WHO, nearly 7 million people die annually from air pollution. Much of this is due to the same unsustainable transport, construction, and home energy production sources that contribute to climate change, directly or indirectly [15, 16].

A sudden and uneven demographic growth in the population number causes migration which is additionally intensified due to climate change (as well as due to wars, economic upheaval, etc.). For these reasons, climate changes and migration are priorities that can be viewed as separate but yet similar and partly interconnected processes [17, 18].

According to the WHO, rising temperatures and variable precipitation are likely to decrease the production of staple foods in many of the poorest regions. This will increase the prevalence of malnutrition and undernutrition, which currently cause 3.1 million deaths every year [10, 16].

Based on some non-optimistic assessments, catastrophes due to climate change are inescapable; however, their arrival is gradual. This is primarily relevant to changes that affect agriculture and food production. Agriculture and provision of sufficient quantities of safe food and clean water are huge present and future challenges [19].

According to the WHO, climatic conditions, strongly influence water-borne diseases and diseases transmitted through insects, snails or other cold blooded animals. Changes in climate are likely to lengthen the transmission seasons of significant vector-borne diseases and alter their geographic range. Malaria is also strongly influenced by climate and kills more than 600,000 people every year – mainly African children under the age of 5. Besides, studies suggest that climate change is likely to continue to increase the exposure to the dengue virus [10, 17].

Lack of safe water can compromise hygiene and increase the risk of diarrheal disease, which kills approximately 760,000 children under 5 years of age every year. In extreme cases, water scarcity and drought lead to famine. By the late 21st century, climate change is likely to increase the frequency and intensity of drought at both regional and global levels [10, 20, 21].

Research on the influence of climate change on mental health suggests their connection with the development of post-traumatic stress. Serious anxiety disorders are correlated to acute disasters such as earthquakes, floods, fires, and hurricanes. Traumatic exposure can cause reactions ranging from general somatic and mental disorders with difficult recovery to serious psychopathology, increased aggression, as well as suicide. Climate change is associated with increasingly longer and harder periods of extreme heat and/or drought. These situations can permanently drive people from their homes, making them displaced persons at a higher risk of developing depression and trauma due to irreversible losses. It is assessed that by 2050 there could be 150 million displaced persons due to floods, erosion, and agricultural degradation [22].

According to available data, the WHO has concluded that climate change is expected to cause approximately 250,000 additional deaths per year between 2030 and 2050; 38,000 deaths of elderly people due to their suffering resulting from heat exposure, 48,000 and 60,000 deaths caused by diarrhea and malaria, respectively and 95,000 due to childhood undernutrition. Some human population categories are more vulnerable than others (the poor, children, elderly, people with disabilities or those with pre-existing medical conditions) [10].

Climate Change, Health Care System, and Role of Health Care Professionals

Climate changes are not only associated with the population health condition and the frequency of individual illnesses, but also with the ability of the health care system to address related consequences. It is especially significant to consider the potential influence of climate change on the organization of the health care itself, the work of individual branches of clinical medicine, and also on planning aspects related to the provision of health care. More equipment and consumables, better preparedness, smart organization, and efforts to increase the future resiliency of the health sector are necessary steps in dealing with climate change [23, 24].

The health systems are significant participants in the total energy balance. Insisting on the renewable energy sources and on the diversification of the energy sources also relates to the infrastructure in health care, and not only to the economy and habitation. Responsible leaders within the health care sector are devoted to green energy and carbon footprint reduction. Such care and concern for environmental factors also plays a role in raising health care standards and improving the quality of care for the patient.

Current regulations regarding the observation of policies and requirements related to energy efficiency are also applicable to the health care sector. Health care institutions to be built in the future must be highly advanced when it comes to their energy efficiency measures.

Within the health care system itself, it is not enough only to think about adapting to climate change and increasing our preparedness to respond to newly occurring needs at the same time. A meaningful action must be undertaken to reduce the greenhouse gas (GHG) footprint - and thus establish mitigation as a strategic direction.

The knowledge and skill of medical professionals, especially specialists such as surgeons and anesthesiologists can be of benefit only if proper infrastructural conditions are present. Elements such as energy sources, microclimate, and water supply are crucial for front-line health care providers such as primary care physicians who practice in the areas that are heavily burdened by climate change. The continuous increase of the resiliency of the health care system as a whole can support doctors in treating patients whose health is negatively affected by climate change.

It is necessary to rethink priorities and needs at individual and professional levels within the health sector. The patients' safety and care must remain the main goal, but we must also include advocacy of environmental health, sustainable healthcare, and high standards in energy efficiency [23].

The agreement [COP 21 - Climate Summit 2016] to keep global warming below 2°C above pre-industrial levels is important not only politically and economically, but also when it comes to public health, and it encourages the following:

- actions and measures that will limit climate change and decrease risks to the global health sector to be as low as possible,
- financing and supporting measures for the adjustment of climate change, and public health initiatives to decrease risks resulting from extreme weather,
- actions by which health is improved alongside contributions made to decrease climate change, which decreases the incidence of individual malignant diseases, respiratory and cardiovascular diseases [caused by air pollution],
- increasing awareness among health care professionals and within the general population about climate change health risks, and the benefits of decarbonisation,
- development and implementation of measures for limiting climate change, health protection at the workplace, and within society,
- actions for decreasing the environmental and climate footprint of health care institutions and the health care system itself, alongside the improvement of health care services.

The health sector should contribute to the improvement of health and living conditions of populations living in polluted areas, and reducing its climate footprint is one of the ways to do so. The WHO suggests several elements of a climate-friendly hospital: energy efficiency, green building design, green energy generation, environmentally-friendly transportation, adequate food, waste and water policy [24].

Conclusion

The voice of health is calling for a cure to the climate change malady. Health care professionals have the unique ability to reach both individual patients and influential institutions. Across the sector, physicians, nurses, paramedics and other health care providers are seen as leaders in their communities. Their efforts to educate patients, advocate within their workplaces, and shape policy can cause tremendous momentum leading to meaningful solutions to the climate change malady affecting our Earth. Efforts to adapt to and mitigate climate change directly contribute to resiliency throughout the health care sector. Scientific and professional achievements in medicine, patients' satisfaction with the health care services provided, and the working conditions of health professionals all directly depend on our ability to treat and cure the climate change malady.

Health professionals represent great leadership potential when it comes to reducing the patients' vul-

nerability to climate change, and promoting health while reducing carbon emissions. To fulfill this potential, the public health sector requires support and assistance in the capacity-building efforts [10].

Climate change is a challenge for the educational system in general, but also for the education of health care professionals. The educational process is essential for changing the mindset of the whole population and especially that of health professionals. Health professionals can take a leadership role in addressing climate change and increasing health literacy related to climate change. Within their curricula for all health professionals, medical schools should include topics related to environmental health, climate change and climate change mitigation [23].

Recommended actions within health care facilities include: educating hospital staff about climate change issues; reviewing facility procurement practices, and following sustainable practices whenever possible; auditing, measuring, monitoring, and reducing the climate footprint of healthcare facilities; recognizing potential co-benefits of climate mitigation activities; identifying the ways by which sustainability practices can be incorporated into accreditation standards [23, 34].

The health sector as a significant consumer of energy, and simultaneously a source of greenhouse gas emissions, can achieve significant economic and health benefits from the implementation of sus-

tainability strategies to reduce energy use. Improving ventilation in health care settings can reduce airborne disease cross-infection (by monitoring these components the performance and energy efficiency could be improved).

The health sector should react to the challenge of climate change by taking a concrete leadership role in mitigation efforts, beginning with its own policies and practices. Health professionals can and must play a leadership role in mitigating climate change, and in helping societies adapt to climate change and the health risk it poses. There is a great potential for health care providers, hospitals, public health systems and the decision makers that govern them to lead us towards an economy based on clean, renewable, efficient and healthy energy. The education process is essential for changing the mindset of the entire population, but especially that of all health professionals.

Mitigating the climate impact of health care facilities is an essential part of this process. By taking action to move us towards low carbon health care systems, health professionals can lead by being the example to the others. Their voices are able to inspire, motivate, and educate interconnected groups of people of all ages, from patients to policy makers. Rethinking and reinventing the public health system to respond properly to climate change is an important priority and an opportunity for all health professionals to lead us towards better healthcare in the future.

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ORIGINAL STUDIES

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SEMIOLOGY OF PATHOLOGICAL CONDITIONS IN PATIENTS INDICATED FOR STEREOTACTIC BIOPSY

SEMIOLOGIJA KOD PACIJENATA INDIKOVANIH ZA STEREOTAKSIČNU BIOPSIJU

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Summary

Introduction. Brain tumors produce symptoms and signs which are often non-specific, and therefore they may occur for more than a few months prior to diagnosis. The aim of this study was to determine the frequency of referent signs and symptoms among patients referred for stereotactic brain biopsy. **Material and Methods.** In this study, we retrospectively analyzed medical history of 65 patients (67.7% males and 32.3% females) between the ages of 16 and 81 years. The following symptoms and signs were included in the analysis: organic brain syndrome, lateralization of crossed pyramidal tract, cranial nerve dysfunction, speech disorders, cerebellar-vestibular syndrome, nausea, vomiting, headache, the occurrence of at least one epileptic seizure and respondents' physical weakness. **Results.** Physical weakness was the most frequent symptom to be recognized (76.9%), whereas pyramidal neurological lateralization was the most commonly recognized sign (58.5%). There was a significant correlation between the course of disease and physical weakness ($\rho = -0.34$, $p = 0.005$), as well as the course of disease and lateralization of the pyramidal tract ($\rho = 0.65$, $p = 0.00$). No significant correlation was found between other clinical signs and symptoms. **Conclusion.** An accurate diagnosis and early recognition of signs and symptoms may be useful in determining indications for stereotactic brain biopsy.

Key words: Image-Guided Biopsy; Stereotaxic Techniques; Brain Neoplasms; Signs and Symptoms; Early Detection of Cancer

Introduction

Brain tumors account for less than 2% of all tumors. Nearly 20,000 people in the United States are diagnosed with malignant brain tumors each year, and approximately two-thirds of them have fatal outcome [1, 2]. In Europe, the incidence rate of brain tumors ranges from 4.5 to 11.2 cases per 100,000 men and from 1.6 to 8.5 per 100,000 women [3]. According to the data of Central Serbia

Sažetak

Uvod. Tumori mozga izazivaju nespecifične simptome i znakove koji se mogu ispoljiti i više od nekoliko meseci pre postavljanja dijagnoze. Cilj ovog istraživanja bio je utvrđivanje učestalosti referentnih znakova i simptoma kod pacijenata indikovanih za stereotaksičnu biopsiju mozga. **Materijal i metode.** Istraživanje je sprovedeno kao retrospektivna studija. Analizirana je medicinska dokumentacija 65 bolesnika (67,7% muškaraca i 32,3% žena) starosti od 16 do 81 godinu. Analizirani su sledeći simptomi i znaci: organski moždani sindrom, piramidna lateralizacija, disfunkcija kranijalnih živaca, poremećaji govora, cerebralno-vestibularni sindrom, mučnina, povraćanje, glavobolja, pojava barem jednog epileptičkog napada ili fizičke slabosti. **Rezultati.** Fizička slabost je najčešće prepoznat simptom (76,9%), dok je piramidna lateralizacija najprepoznatljiviji znak (58,5%). Pokazana je značajna korelacija između trajanja bolesti i telesne slabosti ($\rho = -0,34$, $p = 0,005$), kao i toka bolesti i lateralizacije piramidnog trakta ($\rho = 0,65$, $p = 0,00$). Nema signifikantne korelacije između ostalih kliničkih znakova i simptoma. **Zaključak.** Tačna dijagnoza i rano prepoznavanje znakova i simptoma mogu biti korisni za određivanje indikacije za stereotaksičnu biopsiju mozga.

Ključne reči: biopsija vodena slikom; stereotaksične tehnike; tumori mozga; znaci i simptomi; rana detekcija kancera

Cancer Registry for the same incidence rate there were 11.7 cases per men and 9.2 per women [4]. Despite the relatively low survival rate as compared to the overall tumor rate (2.3%), brain tumors may become fatal because they may disrupt the function of unaffected brain structures, most frequently due to compression of tumor adjacent regions [3, 5]. Although many advances have been made in the field of early detection of brain tumors, presentation with symptoms and clinical signs of tumor may

still last for more than a few months before the tumor is diagnosed [6]. The most frequent clinical presentations develop as a result of compression and invasion of surrounding brain structure either through vascular compression or elevated intracranial pressure, and therefore brain tumor symptoms tend to present with combination of generalized and focal neurologic deficits [7]. Previous studies related to clinical presentations of tumors in children and adults were dependent on tumor location, its size and growth rate [7–9].

The most common presenting clinical signs and symptoms among patients with brain tumors were headache in 30–50% of cases, focal neurological deficits in 40–60% of cases [7], seizures occurred in about 30%–50% of cases [6, 7], as well as non-specific clinical presentations such as physical weakness and psycho-organic changes. However, these clinical presentations may also occur in other brain lesions such as brain abscess or non-cancerous changes [10, 11], and therefore there is a delay in diagnosis and treatment in many patients whose first presenting symptoms are not correctly diagnosed until other clinical symptoms and signs develop. Stereotactic biopsy for brain tumors and tumor-like lesions is indicated for such patients. The aim of this study was to determine the frequency of referent clinical signs and symptoms in the patients with stereotactic biopsy-proved lesions according to the type and location of the lesion, as well as the course of the disease and respondents' age.

Material and Methods

We performed a retrospective analysis of the data obtained from medical history, surgical protocol and pathohistological examination of the biopsied tissue in the patients who were treated at Clinical Center of Vojvodina, Clinic for Neurosurgery in the period from 1/1/2009 to 30/7/2009. Informed consent was obtained prior to participation in the research by Clinic for Neurosurgery, Clinical Center of Vojvodina, as well as by the Ethics Committee of the Clinical Center of Vojvodina for the implementation of this research. We analyzed the initial signs and symptoms, diagnosis, age, gender, pathohistological examination of the biopsied tissue and location of lesions using medical history of 65 patients. The following symptoms and clinical signs were included in the analysis: organic brain syndrome, lateralization of crossed pyramidal tract, cranial nerve dysfunction, cerebellar-vestibular syndrome, nausea, vomiting, headache, the occurrence of at least one epileptic seizure, as well as physical weakness of respondents. The order in which symptoms and clinical signs develop was not specified in the available documentation and accordingly, this information could not be included in the analysis. In terms of location, lesions were classified into two groups: a group of cerebral cortical lesions and a group of structural lesions in deep brain structures. Based on the type of lesion, brain tumors were classified whether they belonged to a group of primary brain tumors, whether they were

benign or malignant tumors, and whether they belonged to the group of gliomas. The respondents were divided into three age groups: 1–54 years, 55–66 years and over 67 years.

Out of 65 respondents included in this retrospective study, 41 were men (67.7%) and 21 were women (32.3%), their age ranging from 16 to 81 years, the mean age being 59.1 years (Mean = 62 years, SD = 12.91). The sample included only those respondents whose records were available, and who were indicated for computed tomography-guided stereotactic biopsy of intracranial lesions that required pathohistological and microbiological diagnosis. The following indications were included: deep positioned lesions (deep-seated lesion) localized in a surgically inaccessible locations, the patients at higher risk for invasive open surgical biopsy, cystic abscess with suspected lesions or granulomatous infection, multifocal lesions, lesions which appear to have better clinical outcomes if minimally invasive procedures were done after a diagnosis of lymphoma or teratoma, as well as the patients who are often not referred for invasive surgical approach and longer sedation due to their age and comorbidity.

The retrospective analysis of available documentation showed that 61 out of 65 respondents referred for stereotactic intervention had tumor-like lesions and they underwent tissue biopsy, while the other four patients underwent biopsies without findings in the diagnosis of tumor changes.

In this study, measures of descriptive statistics were used arithmetic mean, standard deviation, attributive frequency features (n) and percentage (%). Nonparametric measures, such as Spearman's correlation coefficient, were also used to determine the correlation between the ordinal and numerical variables. In addition, nonparametric χ^2 square test was used to measure differences in frequency distributions of attributive features. In all analyses, differences were interpreted as statistically significant if the p value was less than 0.05 ($p < 0.05$).

Results

Based on the pathohistological findings, the structure of the respondents was as follows: 29 patients were diagnosed with glioblastoma multiforme, which was the most prevalent diagnosis in this respondent group with 44.6%. In our study malignancy-associated lesions were found in 45 patients (69.2%), while benign lesions were found in 16 (24.6%) and non-cancerous lesions occurred in 4 patients (6.2%). In relation to the primary and secondary brain tumors, the total of 56 cases (86.2%) was diagnosed with a primary tumor, 5 with a secondary tumor (7.7%) and 4 with non-cancerous lesions (6.2%). The highest percentage of respondents was diagnosed with glioma (76.9%) (glioblastoma multiforme in 44.6%, anaplastic astrocytoma in 16.9%, astrocytoma grade II in 10.8%, astrocytoma grade I in 1.5%, ependymoma grade II in 1.5% and oligodendroglioma

in 1.5%), while the percentage of other lesions was 23.1%.

Based on the location of biopsied lesion, the brain lesion was located on the surface of the brain in most cases. Out of 50 patients (76.9%) who had superficial lesions of the brain, 15 patients had the right hemisphere lesions (23.1%), 29 patients had the left hemisphere lesions (44.6%), 6 patients had lesions on both sides (9.2%), whereas 15 patients had lesions of the deep structures of the brain (23.1%).

As for the symptoms, the most frequent ones were weakness (76.9%), organic brain syndrome (47.7%), headache (43.1%) and/or nausea (13.8%).

The most common presenting clinical signs are pyramidal neurological lateralization (58.5%), speech disorders (40%), cranial nerve dysfunction (35.4%), cerebellar-vestibular syndrome (20.0%) incidence of epileptic seizure (13.8%), vomiting (12.3%).

The frequency of referent symptoms and clinical signs among patients with stereotactic biopsy-proved lesions was evaluated according to the lesion location. Although one symptom and/or clinical sign cannot be solely attributed to one location or the type of change, nausea and vomiting are more frequently observed in the patients whose surface structures of the brain were affected, while other symptoms and signs showed no significant difference (**Table 1**).

In relation to the type of lesion, the frequency of clinical signs and symptoms was highest among the patients with primary tumors, whereas the absence of nausea, vomiting, cerebellar syndrome was observed in the patients with secondary tumors, and only one patient was recorded with organic brain syndrome, headache, seizure and speech disorders. Physical weakness and pyramidal neurological lateralization were observed in most respondents who had primary and secondary tumors (**Table 2**).

Spearman's rank correlation coefficient was used to evaluate whether there was a correlation between the course of acute, subacute, or chronic manifestations of the disease that may become indicated for stereotactic brain biopsy, and the occurrence of the first disease-related events. A statistically significant correlation was obtained between the course of the disease and pyramidal neurological lateralization, where the strong, positive correlation $\rho = 0.65$, $p = 0.00$ was found, and between the course of disease and physical weakness, where the moderately strong, negative correlation $\rho = -0.34$, $p = 0.005$ was obtained. Other variables were not significantly correlated. Using χ^2 test, we assessed the course of disease (acute, subacute and chronic). Further, there was a statistically significant difference ($\chi^2 = 4.63$, $p = 0.03$) among the respondents with the pyramidal neurological lateralization in relation to the disease course of the respondents with this clinical sign. The comparison of grouped frequency distributions showed that the highest percentage of respondents with the acute course of disease had pyramidal neurological lateralization (77.3%), followed by the respondents in subacute phase (51.7%) and chronic phase (42.9%). Furthermore, χ^2 test showed a statistically significant difference in physical weakness compared to the course of disease ($\chi^2 = 7.67$, $p = 0.02$). In addition, the highest percentage of respondents with self-reported physical weakness was in the group of those who were in the acute course of the disease (95.5%), followed by the respondents in the subacute course of disease (72.4%) and chronic disease (57.1%).

Moreover, by examining the correlation between the respondents' age and presentation of clinical signs and symptoms we found that there was a medium strong positive correlation between the respondent's age and epileptic seizure ($\rho = 0.34$, p

Table 1. Frequency of referent clinical signs and symptoms based on location of lesion
Tabela 1. Učestalost kliničkih simptoma i znakova u odnosu na lokalizaciju lezije

Clinical signs and symptoms <i>Klinički znaci i simptomi</i>	Group of cerebral cortical lesions <i>Kortikalne moždane lezije</i> <i>N = 50</i>		Group of structural lesions in deep brain structures/ <i>Lezije u dubokim</i> <i>moždanim strukturama N = 15</i>	
	N	%	N	%
Organic brain syndrome/ <i>Moždani sindrom</i>	26	52%	5	33.33%
Pyramidal neurological lateralization <i>Piramidna neurološka lateralizacija</i>	30	60%	8	53.33%
Cranial nerve dysfunction <i>Lezija kranijalnih nerava</i>	17	34%	6	40%
Cerebellar syndrome <i>Cerebelarna simptomatologija</i>	10	20%	3	20%
Headache/ <i>Glavobolja</i>	21	41%	7	46.67%
Nausea/ <i>Mučnina</i>	8	16%	1	6.67%
Vomiting/ <i>Povraćanje</i>	8	16%	0	0%
Speech problems <i>Problemi sa govorom</i>	21	42%	5	33.33%
Epileptic seizure/ <i>Epileptični napad</i>	7	14%	2	13.33%
Physical weakness/ <i>Fizička slabost</i>	38	76%	12	80%

= 0.00), as well as a weak negative correlation with acute or chronic brain syndrome ($\rho = -0.29$, $p = 0.01$).

By means of the χ^2 test, we assessed the differences among the patients regarding the age (divided into three groups of 16 to 54 years, 55 to 66 and 67 to 88 years), and the occurrence of symptoms and clinical signs. Among the observed respondent groups, a statistically significant difference ($\chi^2 = 8.45$, $p < 0.01$) was obtained only in the patients who had an epileptic seizure, while for those with organic brain syndrome the threshold value of 0.05 was obtained. According to the grouped frequency distributions, epileptic seizure was most frequent in the patients under 55 years of age (31.6%), and the organic brain syndrome in the patients over 67 years of age (61.9%), while for those between the ages of 56 and 66 years, the percentage was 48%. No statistically significant difference was found for other symptoms and clinical signs.

Discussion

Tumor that grows intracranially may lead to brain compression or infiltration. Meningiomas are the most common benign brain tumors in people over 45 years of age and biopsies are often not necessary due to the very nature of the tumor [1]. Glial tumors are the most common brain tumors and account for 77% of all primary brain tumors [12]. Glioblastomas represent about 30% of all brain tumors [13], and in the sample studied, the most malignant glioblastoma multiforme occurred in 45% of patients. If we take into account the age of our respondents, their mean age being 62 years, then the frequency of this type of tumor can be also associated with a higher incidence of its occurrence in elderly respondents [12, 14, 15].

A lot of the clinical signs and symptoms a patient may experience depend on the tumor location. The majority of tumors in the elderly are in the cerebral hemispheres [16]. Jennings and his associ-

ates stated that 76% of most commonly affected brain structures involve cortex lesions [17]. Similar data based on Vates research (2003) show that lesions which occur most frequently affect the superficial cortex [18]. In the present study, we found that brain lesions occurring most frequently affected superficial cerebral structures (77%), whereas the lesions affected the deep brain structure in 23% of cases. In more than 60% of cases, biopsied lesions involved superficial structures in the left brain hemisphere. According to our findings, the clinical signs and symptoms were correlated to tumor location [14, 19]; however, they were often nonspecific initially. Headaches are typically associated with brain tumors. Prevalence of headache ranges from 48% to 71% in unselected series [20], while the same author has found that nausea and vomiting occur in 46% – 60%, as well as that these symptoms are rarely presented with children and older adults. Stark et al. [21] reviewed the presence of clinical signs and symptoms among 478 patients, with the mean age of 60.42 years, who most commonly had symptoms of hemiparesis 41.3%, then neuropsychological changes 37.0%, while headache (nausea) vomiting occurred in slightly more than 30% of patients, and seizures in 23.0%. Babu et al. [22] also found that the occurrence of headache and nausea was most frequent, and unlike them, Jung et al. [13] reported seizures to be the initial presenting sign in 45.3% of patients; headache in 32.6% of patients, and other neurological symptoms such as hemiparesis in 19.8% of patients. The occurrence of non-specific symptoms such as physical weakness, headache, vomiting, and epileptic seizures were also reported in children [10].

As compared to these studies, our data show that the majority of respondents reported the occurrence of physical weakness, and pyramidal neurological lateralization was identified in more than half of the respondents, there was also a manifestation of spee-

Table 2. Frequency of referent clinical signs and symptoms based on the type of lesion

Tabela 2. Učestalost kliničkih simptoma i znakova u odnosu na tip lezije

Clinical signs and symptoms <i>Klinički znaci i simptomi</i>	Primary tumors N = 56		Secondary tumors N = 5		Other N = 4	
	<i>Primarni moždani tumori N = 56</i>		<i>Sekundarni moždani tumori N = 5</i>		<i>Drugo N = 4</i>	
	N	%	N	%	N	%
Organic brain syndrome/ <i>Moždani sindrom</i>	28	50%	1	20%	2	50%
Pyramidal neurological lateralization <i>Piramidna neurološka lateralizacija</i>	34	60.71%	3	60%	1	25%
Cranial nerve dysfunction/ <i>Lezija kranijalnih nerava</i>	21	37.50%	2	40%	0	0%
Cerebellar syndrome/ <i>Cerebelarna simptomatologija</i>	13	23.21%	0	0%	0	0%
Headache/ <i>Glavobolja</i>	26	46.42%	1	20%	1	25%
Nausea/ <i>Mučnina</i>	8	14.28%	0	0%	1	25%
Vomiting/ <i>Povraćanje</i>	8	14.28%	0	0%	0	0%
Speech problems/ <i>Problemi sa govorom</i>	24	42.85%	1	20%	1	25%
Epileptic seizure/ <i>Epileptični napad</i>	8	14.28%	1	20%	0	0%
Physical weakness/ <i>Fizička slabost</i>	44	78.57%	4	80%	2	50%

ch disorders in 40% of the sample, which would correspond to the results of the previous studies [12, 13, 22]. A slightly lower frequency in comparison to previous research was found in the presentation of epileptic seizures (13.8%). A review of literature shows that seizures, based on tumor location, may occur in 30–60% of patients [7, 23]. In addition, seizures occur in 20% of patients with supratentorial brain tumors, and in 70% of patients with primary parenchymal tumors, whereas 40% of the patients with metastatic brain tumors will have a seizure in the course of disease [6]. There was no statistically significant correlation between the type of change, location of lesion and presentation of symptoms i.e. clinical signs. This means that most brain lesions include symptoms and clinical signs that are frequently not attributable to one specific clinical sign and symptom, but rather constitute a group of signs and symptoms that together indicate the nature of the disease. The clinical picture of brain lesions is the result of their mass, surrounding edema, as well as infiltration and destruction of brain tissue. Regardless of the histology of the lesion, the diagnosis most often indicates physical weakness, neurological signs, headache, and partial or generalized seizures. Another explanation is that different parts of the brain control different functions and thus symptoms depend on which part of the brain is affected. The diagnosis of tumor can be suspected if the symptoms develop over a short period of time (i.e. less than 6 months) [20, 21]. Although there is no exact pattern which clearly connects the course of disease with the diagnosis, the largest number of the respondents in this study was in the subacute phase of the disease. It was found that the highest percentage of respondents with a pyramidal neurological lateralization and physical weakness was in the group of those who were in the acute course of the disease. Physical weakness and pyramidal neurological lateralization showed the strongest correlation with the course of the disease, because it is usually an indication for computed tomography scanning of endocranium, after which working diagnosis is determined. Among the most common symptoms were motor and sensory deficits [19] and there were various reports on the patients who underwent brain biopsy because the initial diagnosis of central nervous system tumor depended on brain magnetic resonance imaging combined with stereotactic brain biopsy [19, 24, 25]. Initial symptoms of incidental presentation and seizures had a longer overall survival than did headache or other neurological symptoms [22].

The incidence of primary brain tumors among all tumors increases with age so in patients between the ages of 75 and 85 years, it ranges from 7 to 23.4% [16]. The highest incidence of glioblastomas and astrocytomas is among individuals aged 65–74 [12]. Evidence observation also includes the presen-

tation of age-related clinical signs and symptoms. The first recording supports seizure presentations as the main clinical sign in the patients from the youngest age group, which occurs in one third of the cases presenting in this age group. An increased risk of brain tumors appears to be more related to a history of epileptic seizures, but it is difficult to determine whether these seizures are the result of the early development of tumors or tumor caused by many years of epileptic seizures [12]. Different authors suggest that seizures may occur in brain tumor patients of median age [26]. In addition, some researchers suggest that overlapping or dual pathology is possible in tumor-like lesions of the brain, such as glial tumors and focal cortical dysplasia, thus reflecting neurobiological source of epileptic seizures [27]. Unlike previous research, we obtained data on the presentation of organic brain syndrome in respondents over 67 years of age, which was also shown in the previous studies, in which physical weakness, depression and psycho organic changes in respondents over 67 years of age were recognized as the main symptoms of brain tumors [28].

Conclusion

In this study, we showed clinical signs and symptoms in the patients referred for stereotactic brain biopsy as compared to the location of lesion, the course of disease, and the age of patients. The study also showed that the most commonly seen symptom in the study group was physical weakness, while the most common clinical sign was pyramidal neurological lateralization. Moreover, there was a statistically significant correlation between disease progression and physical weakness, as well as disease progression and pyramidal neurological lateralization. Results did, however, show that there was no statistically significant correlation between other clinical signs and symptoms. The analysis of the age-related differences across the respondent age groups showed the largest number of seizures in the youngest group of respondents (up to 54 years of age), and the largest number of acute or chronic brain syndrome in the oldest group of respondents (67 years and over). There was a statistically significant difference among the respondent groups in terms of the time elapsed between the onset of clinical signs and symptoms of physical weakness, with the largest number of these symptoms present in the group who developed symptoms during the acute phase (1–21 days). Limitations of this study refer to the fact that the sequence of symptoms and clinical signs was not viewed in their exact chronological order so it can be useful to conduct a further research which should include these issues. Thus, accurate and timely assessment of symptoms and clinical signs may help in determining the indications for stereotactic brain biopsy.

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COMPLETENESS OF CIRCLE OF WILLIS IN ASYMPTOMATIC AND SYMPTOMATIC EXTRACRANIAL CAROTID DISEASE

KOMPLETNOST VILISOVOG POLIGONA KOD EKSTRAKRANIJALNE KAROTIDNE BOLESTI BEZ SIMPTOMA I SA SIMPTOMIMA

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Summary

Introduction. This research has been aimed at determining whether incomplete Circle of Willis in patients with significant extracranial carotid stenosis is associated with a higher incidence of neurological symptomatology and/or ischemic cerebral lesions. **Material and Methods.** The research was conducted as a prospective study which comprised 211 patients who underwent surgical treatment of extracranial carotid disease at the Department of Vascular Surgery in Novi Sad and 102 patients in the control group. Each patient underwent preoperative magnetic resonance imaging and magnetic resonance angiography with visualization of cerebral parenchyma, extracranial and intracranial cerebral circulation. Assessment of Circle of Willis morphology was performed by 3D time-of-flight magnetic resonance angiogram sequence analysis. The patients were divided into two groups: group I – the patients with complete Circle of Willis and group II – the patients with incomplete Circle of Willis i.e. with the disruption of anterior and/or ipsilateral posterior circulation - regarding the side of significant carotid stenosis. **Results.** Out of 211 patients who were operated during a two-year period, 133 had the complete Circle of Willis, while 78 patients had the incomplete Circle of Willis. Out of 111 patients with symptomatic carotid disease or silent cerebral infarction, 52.5% (58) had the complete Circle of Willis and 47.5% (53) had the incomplete Circle of Willis. It was shown to be statistically different ($P = 0.0146$) in relation with the asymptomatic group of patients (100), where the frequency of the complete Circle of Willis was 75% (75) while the insufficiency of anterior or ipsilateral posterior collateralization was found in 25% (25). In the control group there were significantly fewer cases of developed collateral flow and the complete Circle of Willis (41%) compared to the operated patients with extracranial carotid stenosis (63%) ($P = 0.0003$). **Conclusion.** Incompleteness of Circle of Willis is associated with more frequent occurrence of neurological symptomatology or ischemic lesions of brain parenchyma in operated patients with significant extracranial carotid stenosis. The control group without extracranial carotid stenosis had less developed collaterals of Circle of Willis compared to extracranial carotid patients.

Key words: Circle of Willis; Carotid Artery Diseases; Carotid Stenosis; Magnetic Resonance Imaging; Brain Ischemia; Brain Infarction; Signs and Symptoms

Sažetak

Uvod. Cilj ovog istraživanja bio je utvrditi da li je nekompletnost Vilisovog poligona (*Circle of Willis*) kod pacijenata sa značajnom ekstrakranijalnom karotidnom stenozom udružena sa češćim pojavljivanjem neuroloških simptoma i/ili ishemijskih moždanih lezija. **Materijal i metode.** Istraživanje je sprovedeno kao prospektivna studija i uključilo je 211 pacijenata koji su hirurški tretirani zbog ekstrakranijalne karotidne bolesti na Klinici za vaskularnu hirurgiju u Novom Sadu i 102 pacijenata u kontrolnoj grupi. Kod svih ispitanika preoperativno je rađena magnetna rezonancija i magnetno rezonantna angiografija za vizualizaciju moždanog parenhima, ekstrakranijalne i intrakranijalne moždane cirkulacije. Procena morfologije Vilisovog poligona izvršena je analizom *3D time-of-flight magnetic resonance angiogram sequence*. Pacijenti su bili podeljeni u dve grupe: 1. grupa – pacijenti sa kompletnim Vilisovim poligonom i 2. grupa – pacijenti sa nekompletnim Vilisovim poligonom, odnosno prekidom prednje i/ili ipsilateralne zadnje kolateralne. **Rezultati.** Tokom perioda od dve godine, operisano je 211 bolesnika sa ekstrakranijalnom karotidnom bolesti, od kojih je 133 imalo kompletan Vilisov poligon, dok je 78 pacijenata je imalo nekompletan Vilisov poligon. Od 111 pacijenata sa simptomatskom karotidnom bolesti ili „nemim cerebralnim infarkt“, 52,5% (58) je imalo kompletan Vilisov poligon i 47,5% (53) nekompletan Vilisov poligon. To se pokazalo statistički različito ($P = 0,0146$) u odnosu na grupu pacijenata bez simptoma (100), u kojoj je zastupljenost kompletnog Vilisovog poligona iznosila 75% a nekompletnog Vilisovog poligona u 25%. U kontrolnoj grupi bilo je značajno manje slučajeva razvijenog kolateralnog protoka unutar Vilisovog poligona (41%) u odnosu na bolesnike sa ekstrakranijalnom karotidnom stenozom (63%) ($p = 0,0003$). **Zaključak.** Nekompletnost Vilisovog poligona je povezana sa češćom pojavom neurološke simptomatologije ili ishemijskih lezija moždanog parenhima kod operisanih bolesnika sa značajnom ekstrakranijalnom karotidnom stenozom. Kontrolna grupa bez ekstrakranijalne karotidne stenozе imala je manje razvijen kolateralni protok unutar Vilisovog poligona u odnosu na operisane pacijente.

Ključne reči: Vilisov poligon; bolesti karotidnih arterija; karotidna stenozа; magnetna rezonanca; ishemijska mozga; infarkcija mozga; znaci i simptomi

Abbreviations

CoW	– circle of Willis
ICA	– internal carotid artery
ACA	– anterior cerebral artery
AcomA	– anterior communicating artery
ACP	– posterior cerebral artery
MRI	– magnetic resonance imaging
MRA	– magnetic resonance angiography
DUS	– duplex ultrasonography

Introduction

Circle of Willis (CoW) is the most significant collateral pathway in the presence of extracranial carotid disease. Collateralization with the opposite internal carotid artery (ICA) is conducted via anterior collateral segment of CoW (made of A1 segments of anterior cerebral artery – ACA and anterior communicating artery – AcomA). Collateralization with posterior cerebral circulation is achieved by posterior collateral segment of CoW, (made by P1 segments of posterior cerebral artery – ACP and posterior communicating artery – AcomP). Hypoplasia or occlusion of arteries forming the aforementioned collateral segments are common as variations of incomplete CoW are presented in one third to one half of population [1, 2]. An incomplete CoW becomes clinically significant in the setting of inadequate blood inflow in extracranial cerebrovascular disease [3] (**Figure 1**).

The blood flow through anterior and posterior segment of CoW increases in significant stenosis of extracranial segment of ICA due to a decreased inflow. Such a development of collateral flow depends on the patency of anterior and ipsilateral posterior collateral arterial pathway. Insufficient collateralization results in a decreased flow in the cerebral arteries, which increases the risk of neurological symptoms and cerebrovascular insult [4]. By recognizing the importance of collateral flow and finding patients at the highest risk of stroke we are able to treat such patients on time, before a disabling cerebrovascular event occurs [5].

Magnetic resonance angiography (MRA) has a significant role in examining CoW. It is a low risk procedure enabling *in vivo* studies which provide information on the patency and diameter of arteries, as well as on the functional morphology, and indirectly on hemodynamic changes of CoW [6–8].

This research has been aimed at determining whether an incomplete CoW (hypoplasia or occlusion of anterior or posterior collateral segment) is associated with neurological symptoms or ischemic lesion of brain parenchyma in the patients with significant extracranial carotid stenosis.

Material and Methods

The research was conducted as a prospective study comprising 211 patients who underwent surgical treatment of extracranial carotid disease at the Department of Vascular Surgery in Novi Sad, in the period from September 1st, 2013 to September 1st,

2014. Neurological examination was preoperatively performed on each patient by a qualified neurologist. The degree of stenosis was determined by duplex ultrasonography (DUS) according to the NASCET criteria using 5MHz linear transducer. Each patient underwent preoperative magnetic resonance imaging (MRI) and MRA examination on standardized magnetic resonance (MR) device GEHC Signa HDt 1.5T at the Center of Radiology, Clinical Center of Vojvodina. We analyzed two sequences: T2 sequence for visualization of cerebral parenchyma; 3D TOF sequence for the assessment of CoW morphology. Only the patients with unilateral carotid disease and no vertebral and basilar artery stenosis or occlusion were included. The control group consisted of 102 patients whose indications for MRI/MRA examination were other than extracranial cerebrovascular disease. The same sequences of MRI/MRA were analyzed in this group of patients by using the data base of Center of Radiology, Clinical Center of Vojvodina. This study was approved by the Ethics Committee of Clinical Center of Vojvodina in Novi Sad, Serbia (No 145/2013/2).

The selected participants were grouped according to the following criteria:

- The groups of the asymptomatic and symptomatic patients were formed regarding symptoms of extracranial carotid disease. “Pseudo asymptomatic patients” (“silent brain infarction” larger than 1 cm) were assigned to the symptomatic patient group.

- Regarding the CoW completeness the patients were assigned to the group of patients with complete CoW and the group of patients with incomplete CoW (occlusion or hypoplasia (less than 2 mm of diameter on 3D TOF MRA finding) of arteries forming anterior and/or ipsilateral posterior collateral segment regarding the side of significant carotid stenosis) as it is shown in **Figure 1**.

Results

Out of 211 patients who were operated during the observed period, 133 were males and 78 were females, between the ages of 49 and 81 years (mean age being 69.3 years).

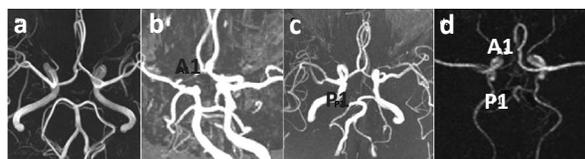


Figure 1. Clinically significant types of CoW: a. complete CoW; incomplete CoW presented by: b. interruption of anterior collaterals c. interruption of posterior collaterals; d. interruption of both anterior and posterior collaterals

Slika 1. Klinički značajni tipovi Vilisovog prstena: a. kompletan Vilisov prsten; nekompletan Vilisov prsten sa: b. prekidom prednjih kolateralala c. prekidom zadnjih kolateralala d. prekidom i prednjih i zadnjih kolateralala

A hundred (47.3%) asymptomatic patients and 111 (52.7%) patients with symptomatic carotid stenosis or ischemic cerebral parenchymal lesion greater than 1 cm („silent brain infarction“) underwent surgery.

The total number of operated patients with the complete and with the incomplete CoW was 133 (63%) and 78 (37%), respectively. In the group of asymptomatic patients, the complete CoW was observed in 75% (75) of patients, while the disruption of anterior or ipsilateral posterior collateralization was found in 25% (25) of patients. Out of 111 patients with symptomatic carotid disease or silent brain infarction, 52.5% (58 patients) had the complete CoW, and 47.5% (53 patients) had the incomplete CoW. In the control group, 41% (42 patients) had the complete CoW and 59% (60 patients) had the incomplete CoW.

The difference in the occurrence of complete and incomplete CoW was shown to be statistically different between the patients with extracranial carotid disease and the control group of patients, there were more complete CoW in the group of patients with extracranial carotid disease ($P = 0.0003$ OR 2.4359 95% CI:1.5022 to 3.9498 z stat. 3.610)

The difference in the occurrence of complete and incomplete CoW was shown to be statistically different between the asymptomatic and symptomatic patients with extracranial carotid disease, there were more complete CoW in asymptomatic group of patients ($P = 0.0146$ OR 0.4906 95% CI: 0.2770 to 0.8688 z stat. 2.442) (Table 1).

Discussion

The results of this study have shown that based on 3D TOF MRA findings, the frequency of CoW variety with complete anterior and posterior collateral segment in the patients with carotid disease is 63%, which is higher compared to the control group of patients free of extracranial carotid stenosis (41%). According to literature data, the frequency of complete CoW in the age-matched general population is about 35–50%. The causes of incompleteness of CoW are hypoplasia or aplasia of arteries forming it and with progression of atherosclerotic disease, stenosis and occlusion occur. That can be confirmed by 3D TOF MRA analysis of diameter and patency of CoW collaterals in patients of different age [9]. In the patients with regular flow in the carotid and vertebral arteries, the collaterals of CoW are usually inactive,

which can be confirmed by imaging methods and transcranial Doppler (TCD), with a high level of correlation. This correlation is explained by the fact that MRA 3D TOF sequence register flowing of the blood (speed of blood less than 5 cm/s is virtually not registered) providing not only morphological but also functional findings on CoW [10].

As already stated, in about one third of general population at certain age the CoW collaterals are completely developed, and in such persons a decreased flow in one carotid artery (e.g. occlusion or ligation) would be accompanied by a less severe hemodynamic disorder, and therefore a lower risk of significant neurological deficiency. In the remaining two thirds of population, CoW is a reserve whose activation depends on the potential of arteries to increase the flow (an important factor is affection of collaterals by atherosclerotic process), as the extracranial occlusive carotid disease gradually progresses. It has been proven that in the patients with significant extracranial carotid stenosis there is not only the collateral blood flow, but the collaterals have greater diameter as well, which indicates the capability of CoW adaptation on altered hemodynamics due to carotid stenosis or occlusion, which is called remodeling [11]. In case of unilateral carotid occlusive disease, the anterior collateral segment (ACA1, AcomA) made of arteries with constant diameter is crucial, while in case of bilateral occlusive carotid disease the posterior collateralization (ACP1, AcomP) develops, with the inflow from the vertebro-basilar arterial system. A more frequent occurrence of complete CoW in patients with extracranial carotid stenosis undergoing surgical treatment can be explained by two mechanisms: one is the gradual stimulation of CoW arteries to develop collateral flow due to decreased inflow, and the other one is “natural selection” as the patients with developed CoW collateralization tend to have mild neurological damage, and are therefore better qualified for the surgical treatment.

Considering the importance of collateral circulation in extracranial carotid disease, a compelling correlation between ischemic cerebral lesions or neurological symptoms and incompleteness of CoW would be expected. However, not all surveys have confirmed this correlation. To the contrary, certain studies have not proven a statistically significant difference in the occurrence of incomplete CoW in the patients with symptomatic carotid stenosis [11]. On the other hand, different studies have shown that the

Table 1. Frequency of complete and incomplete CoW in operated patients with asymptomatic and symptomatic extracranial carotid disease and control group.

Tabela 1. Učestalost kompletnog i nekompletnog Vilisovog prstena kod operisanih pacijenata sa asimptomatskom i simptomatskom karotidnom bolesti i kod kontrolne grupe ispitanika

	All operated Svi operisani	Asymptomatic Asimptomatski	Symptomatic Simptomatski	Control group Kontrolna grupa
All/Svi	211	100 (47%)	111 (53%)	102
Complete CoW/Kompletan Vilisov prsten	133 (63%)	75 (75%)	58 (52,5%)	42 (41%)
Incomplete CoW/Nekompletan Vilisov prsten	78 (37%)	25 (25%)	53 (47,5%)	60 (59%)

occurrence of ischemic lesions, especially hemodynamic “watershed” ischemic lesions is connected to the smaller diameter of anterior and posterior collaterals and their occlusion [12]. Moreover, rare randomized controlled studies have shown a protective effect of complete CoW in the symptomatic carotid patients on medicament treatment, as well as in surgically treated patients perioperatively and during the two-year follow up period [13]. According to certain authors, the disruption of anterior collaterals is an isolated risk factor for brain ischemia development, even in the absence of extracranial carotid disease (A1 hypoplasia syndrome), [14] while the disruption in the posterior collaterals has an impact on hemodynamics only in the presence of a carotid occlusive disease [15].

In our study, we have found the significant statistical correlation between neurological deficit or silent brain infarction and interruption in anterior or ipsilateral posterior collaterals of CoW in the patients with extracranial carotid stenosis undergoing surgical treatment. A high degree of statistical significance is a little surprising considering previous studies, and initial elimination of patients with severe neurological deficit, large ischemic areas and extensive changes on intracranial segments of ICA and cerebral arteries, in which even more frequent interruption of CoW collateralization is expected.

The shortcoming of this study and of similar studies as well lies in fact that CoW is presented with numerous variations and even more numerous classifications, which makes the assessment of CoW morphology more complicated. Such detailed classifications have little clinical usage, especially when analyzed in terms of extracranial carotid disease. We used complete/incomplete CoW classification, disregarding further divisions (i.e. on the anterior or posterior collateral segment incompleteness) as it was recently proposed by SMART

study group [16]. However, this study did not prove completely the importance of complete CoW in prevention of ischemic stroke in asymptomatic carotid patients. However, in more recent study the complete CoW proved to be an independent predictor of good outcome after ischemic stroke [17].

It can be concluded that an incomplete CoW is a risk factor for neurological symptoms and cerebral ischemia in the patients with significant ICA stenosis, i.e. it contributes to their more frequent occurrence. The patients with interrupted anterior or posterior CoW collaterals who have not developed ischemic cerebral lesions or neurological symptoms are of special interest. Such asymptomatic patients accounted for 25% of participants in our study, and 12% of total number of treated patients. If we assume that those are asymptomatic patients with the increased risk for development of neurological symptoms, their timely treatment would probably have a significant impact on primary prevention of cerebrovascular infarction. Thus, these patients would have the most benefit from surgical treatment. Such an assumption emphasizes the surgical perspective of role of CoW in carotid disease, considering that previous studies have mostly been based on choice of surgical technique and intraoperative protection of cerebral ischemia in relation to morphology of CoW [18].

Conclusion

Incompleteness of circle of Willis is associated with a more frequent occurrence of neurological symptomatology or ischemic lesions of brain parenchyma in the operated patients with significant extracranial carotid stenosis

The control group without extracranial carotid stenosis had less developed collaterals of circle of Willis compared to the patients with extracranial carotid disease.

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THE PREVALENCE OF STRESS AND BURNOUT SYNDROME IN HOSPITAL DOCTORS AND FAMILY PHYSICIANS

ZASTUPLJENOST STRESA I SINDROMA SAGOREVANJA NA POSLU KOD LEKARA U BOLNICAMA I PORODIČNIH LEKARA

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Summary

Introduction. Burnout syndrome is the result of chronic emotional stress. It is characterized by high levels of emotional exhaustion and depersonalization, and reduced level of personal accomplishment. The aim of this study was to determine the level of stress and risk for burnout syndrome in doctors employed in health centers and hospitals, and to investigate the impact of socio-demographic characteristics on the level of stress and the occurrence of burnout syndrome. **Material and Methods.** A cross-sectional study was conducted in the period from October 1 to December 31, 2015 in three health centers and in the University Clinical Center of the Republic of Srpska. The survey was anonymous. A socio-demographic questionnaire and a questionnaire for self-assessment of the level of stress and Maslach Burnout Inventory were used as research instruments. Out of 151 doctors included in the study, 49% were family physicians, and 51% were hospital doctors. **Results.** The analysis of responses to questionnaires for self-assessment of stress level revealed that 51.7% of participants had high levels of stress (52.7% of family physicians, 50.6% of doctors working in hospital). A high degree of emotional exhaustion was found in 27.2% of participants (29.7% of family physicians, 24.6% of doctors working in hospital), high depersonalization was found in 23.8% of participants (25.7% of family physicians, 22.1% of doctors working in hospital), a low level of personal accomplishment was found in 39.7% of participants (37.8% of family physicians, 41.6% of doctors working in hospital). No statistically significant difference regarding stress degree, emotional exhaustion and depersonalization and personal accomplishment was found between hospital doctors and family physicians. The physicians aged over 45 years had a significantly ($p = 0.030$) higher level of emotional exhaustion than their younger colleagues. **Conclusion.** This study found that there was a high risk of burnout syndrome in physicians in the Republic of Srpska. Although the exposure to professional stress was higher in family physicians than in hospital doctors, the obtained difference was not statistically significant.

Key words: Burnout, Professional; Stress, Psychological; Physicians; Family; Risk Factors; Surveys and Questionnaires; Self-Assessment

Sažetak

Uvod. Sindrom sagorevanja na poslu je posledica hroničnog emocionalnog stresa, a karakteriše ga visok nivo emocionalne iscrpljenosti i depersonalizacije, kao i smanjen nivo lične ispunjenosti. Cilj ovog rada je da se utvrdi nivo stresa i rizik za obolevanje od sindroma sagorevanja na poslu kod lekara zaposlenih u domovima zdravlja i bolnici, te da se ispita uticaj sociodemografskih karakteristika na nivo stresa i nastanak sindroma sagorevanja. **Materijal i metode.** Studija preseka je sprovedena u periodu od 1. oktobra do 31. decembra 2015. godine u tri doma zdravlja i Univerzitetском kliničkom centru Republike Srpske. Anketiranje je bilo anonimno. Kao instrumenti istraživanja korišteni su sociodemografski upitnik, upitnik za samoprocenu nivoa stresa i *Maslach Burnout Inventory*. U studiji je učestvovao 151 lekar. Lekari porodične medicine su činili 49% ispitanika, a bolnički lekari 51%. **Rezultati.** Analizom odgovora iz upitnika za samoprocenu nivoa stresa nađeno je da je 51,7% imalo visok nivo stresa (52,7% porodičnih lekara, 50,6% lekara u bolnici). Visok stepen emocionalne iscrpljenosti je pronađen kod 27,2% ispitanika (29,7% porodičnih lekara, 24,6% lekara u bolnici), visok stepen depersonalizacije kod 23,8% ispitanika (25,7% porodičnih lekara, 22,1% lekara u bolnici), a nizak stepen lične ispunjenosti kod 39,7% ispitanika (37,8% porodičnih lekara, 41,6% lekara u bolnici). Statistički značajna razlika u pogledu stepena stresa, emocionalne iscrpljenosti i depersonalizacije i lične ispunjenosti nije pronađena između bolničkih i lekara porodične medicine. Lekari starosti preko 45 godina imali su statistički značajno ($p = 0,030$) viši nivo emocionalne iscrpljenosti u odnosu na mlađe ispitanike. **Zaključak.** Ovo istraživanje pokazalo je da postoji visok rizik od nastanka sindroma sagorevanja kod lekara u Republici Srpskoj. Premda je izloženost profesionalnom stresu viša kod lekara porodične medicine, nego kod bolničkih lekara, dobijena razlika nije statistički značajna.

Ključne reči: sindrom izgaranja na poslu; stres, psihološki; lekari; porodični lekari; faktori rizika; ankete i upitnici; samoprocena

Abbreviations

RS – Republic of Srpska
 MBI – Maslach-Burnout Inventory

Introduction

Burnout syndrome is the result of chronic emotional stress experienced by employees; it is characterized by high levels of emotional exhaustion and depersonalization and low levels of personal accomplishment [1]. It is most common among employed persons whose job requires direct contacts with other people [2].

Prolonged exposure to stress is usually the main cause of emotional exhaustion, which is manifested by reduced enthusiasm for work, a sense of helplessness, failure, and fatigue. Depersonalization is described as indifferent approach to patients and negative attitude towards colleagues and profession. Inefficiency, alienation or loss of will for personal achievements are the characteristics of a person who has lost the sense of responsibility for his/her job [3, 4].

The syndrome is recognized worldwide as one of the major causes of psychosocial problems affecting the quality of life of employees in different professions, and the most prevalent one in employees in healthcare, education, and service occupations [5, 6].

Burnout syndrome manifestations are the symptoms of extreme emotional exhaustion, apathy, cynicism and depersonalization, and a strong sense of low self-esteem. The result is a lack of motivation for professional activity, development of mental disorders, primarily depression, and generally reduced quality of life. Physical symptoms of burnout syndrome could be manifested as different problems: insomnia, changes in appetite, fatigue, frequent colds and flu, headaches, gastrointestinal disorders. Psychosocial problems are mostly manifested as mood swings, cynicism and reduced concentration, which negatively affects the quality of work [7, 8]. Common consequences of burnout syndrome are increased consumption of alcohol and drugs, which further adversely affects the quality of work and quality of life [9].

Numerous studies have shown a high prevalence of burnout syndrome among practicing doctors. The results showed that one-third of physicians had symptoms of burnout syndrome during their career [10]. According to research conducted in the United States, 47% of doctors had burnout experience, which was a considerably higher percentage than in the general population [11]. Research in Italy, conducted on a sample of 470 health care workers (220 doctors and 250 nurses) showed a high incidence of stress and risk of developing the burnout syndrome [12]. Studies conducted in Canada and Switzerland have shown that doctors were highly susceptible to develop burnout syndrome [13, 14].

There are limited data about exposure to stress and risk for burnout syndrome among the physicians in the Republic of Srpska (RS). Therefore, the aim of this study was to determine the level of stress and risk for burnout syndrome among doctors

employed in primary health care centers and hospitals in RS, and to investigate the impact of socio-demographic characteristics on the stress level and development of burnout syndrome.

Material and Methods

The research was conducted in the period from October 1 to December 31 in three primary health care centers (Prijedor, Doboj and Laktaši) and in the University Clinical Center of the Republic of Srpska (UCCRS) in Banja Luka. A cross-sectional study was done.

The participants in primary health care centers were family doctors, in UCCRS the participants were doctors from the Department of Anesthesiology, Department of Psychiatry, and the Department of Internal Medicine. The researchers distributed the questionnaires to all doctors working in primary health care centers and hospitals where the study was conducted.

Out of 198 distributed questionnaires, 151 questionnaires were completed and returned (the response rate being 76.26%).

The Ethical Committee of the University Clinical Center of the Republic of Srpska in Banja Luka gave written consent for conducting research, while the consent for conducting research in primary health care centers was obtained from the managers of these institutions.

The Questionnaires and Measurements

The survey was anonymous. A socio-demographic questionnaire, questionnaire for self-assessment of the level of stress (Gyrdin, Everly, Dusek) [15] and Maslach Burnout Inventory were used as research instruments [16, 17].

The socio-demographic questionnaire included data on gender, age, place of employment, length of service, marital status, number of children in the family, and education.

The questionnaire for self-assessment of the stress level contained ten questions and included four main factors of overburden (chronic lack of time, excessive responsibility, lack of support and exaggerated expectations of oneself and one's surroundings). The participants could provide the following answers to the offered questions: nearly always (4 points), often (3 points), rarely (2 points), and nearly never (1 point). The total score was the sum and the maximum score was 40. The participants with score between 25 and 40 points were in a state of high stress level, while the participants with the highest total score of less than 25 had stress within normal limits.

The original version of the questionnaire Maslach Burnout Inventory consists of 22 "closed" questions with the following answers: never (0 point), several times a year (1 point), once a month (2 points), several times a month (3 points), once a week (4 points), several times a week (5 points) and daily (6 points). All questions are divided into three sub-scales which are used as indicators for assessing the degree of emo-

tional exhaustion, depersonalization and personal satisfaction. The first sub-scale, which measures the degree of emotional exhaustion, highlights the excessive demands addressed to service providers. The second sub-scale measures the presence of depersonalization characterized by a negative relationship between donors and recipients of services. The third sub-scale measures the level of personal accomplishment. The estimation of emotional exhaustion is based on the answers for 9 questions, and the maximum score is 54 (the sum of points < 17 indicates a low, 18-29 indicates a moderate, and > 30 indicates a high level of emotional exhaustion). Depersonalization is tested using 5 questions and the maximum score is 30 (the sum of points < 5 indicates a low, 6-11 a moderate, > 12 a high level of depersonalization), and personal accomplishment is assessed using the answers for the 8 questions; the maximum score is 48 (the sum of points < 33 indicates a high, 34-39 a moderate, > 40 low level of personal satisfaction).

Statistical analysis was released using the SPSS software package. Descriptive analysis in the form of frequency and percentage was used to check the sample and response to each question individually. The comparison of categorical variables was done by χ^2 test. The level of statistical significance was 5% ($p < 0.05$).

Results

Out of 151 physicians included in the study sample, 99 were females (65.6%) and 52 were males (34.4%). The average age of all participants was 41.09 ± 9.7 years. The average age of the participants in primary health care centers was 37.9 ± 9.3 years, while the average age of hospital doctors participating in the study was 44.17 ± 9.2 years. According to their age, the participants were divided into three groups: doctors under 35 years of age (34.4%), those between 36 and 45 years of age (31.8%) and doctors over 45 years of age (33.8%). According to the working place, roughly the same number of the participants was employed in primary health care centers (49.0%) and in hospitals (51.0%). Regarding the institution where the participants were employed, the distribution was as following: 30 medical doctors (MDs) (19.9%) were affiliated with the Primary Health Care Center in Prijedor, 26 MDs (17.2%) with the Primary Health Care Center in Dobo, 18 MDs (11.9%) with the Primary Health Care Center in Laktaši, 33 MDs (21.9%) with the Department of Anesthesiology, 28 (18.5%) MDs worked at the Department of Internal Medicine and 16 MDs (10.6%) worked at the Department of Psychiatry. Most participants were married, and the lowest number of them was widows/widowers. The majority of the participants had no children, and the lowest number of them had three or more children. Regarding the education level, most of them (total 86; 57.9%) were specialists, and the lowest number of the participants was in residency (total 20; 13.2%). As for the length of service, the participants were divided into three groups for the purpose of statistical data analysis. The first group in-

cluded doctors with the length of service up to 10 years, the second group included doctors with a length of service from 11 to 20 years, and the third group included doctors with 21 or more years of service, the average length of service being 14.05 ± 9.9 years. Hospital doctors had an average length of service of 17.6 ± 10.4 years, while the doctors working in primary health care had an average length of service of 10.4 ± 7.9 years (**Table 1**).

By analyzing the results of the questionnaire for self-assessment of stress level, it is evident that more than half of the participants (total 78; 51.7%) had a high stress level; 52.7% of them were primary care physicians, and 50.6% of them were hospital doctors. The results obtained from the questionnaire Maslach Burnout Inventory (MBI) have shown that 27.2% of the participants (29.7% primary care physicians, and 24.6% hospital doctors) had a high level of emotional exhaustion; 23.8% of the participants (25.7% primary care physicians, and 22.1% hospital doctors) had a high degree of depersonalization; 39.7% of the participants (37.8% primary care physicians, and 41.6% hospital doctors) had a low level of personal accomplishment (**Tables 2 and 3**).

We analyzed the results obtained for the stress level and for all three components of burnout syndrome according to working place. Statistical analysis of the results obtained from the questionnaire for self-assessment of the stress level and from the MBI questionnaire did not show any significant difference even in the incident stress or the components of burnout syndrome between the primary care physicians and hospital doctors. Although not statistically significant, the primary care physicians had a higher stress level, higher degrees of emotional exhaustion and depersonalization, and a lower degree of personal accomplishment than the hospital doctors.

A low stress level was found in 48.3% of participants, while 51.7% of them had a high stress level. Regarding the institution where the participants were employed, there was no significant difference ($p = 0.101$) for the stress level. Although not statistically significant, the highest stress level was reported by the doctors working in the Primary Health Care Center in Prijedor (66.7%) and at the Department of Internal Medicine (60.7%), while the lowest stress level was found among physicians employed in the Primary Health Care Center in Laktaši (27.8%). High levels of emotional exhaustion were found in 27.2% of the participants. There was no significant difference ($p = 0.133$) in the level of emotional exhaustion regarding the institution where the participants were employed. The highest percentage of doctors with a high degree of emotional exhaustion was found among those affiliated with the Primary Health Care Center in Prijedor (36.7%), and the lowest percentage was among those employed at the Department of Psychiatry (18.8%). 23.8% of the participants had a high level of depersonalization. Regarding the level of depersonalization, a statistically significant difference was found among the participants in relation to the institution

Table 1. Socio-demographic data of participants
Tabela 1. Sociodemografski podaci ispitanika

Variable <i>Varijabla</i>	Primary Health Centers <i>Domovi zdravlja</i> n = 74 N (%)	Hospital <i>Bolnica</i> n = 77 N (%)	Total <i>Ukupno</i> n = 151 N (%)
Gender/ <i>Pol</i>			
Male/ <i>Muški</i>	13 (17.57)	39 (50.65)	52 (34.4)
Female/ <i>Ženski</i>	61 (82.43)	38 (49.35)	99 (65.6)
Age/ <i>Starost</i>			
Years/ <i>Godine</i>			
< 36	32 (43.24)	20 (25.97)	52 (34.4)
36 – 45	26 (35.14)	22 (28.57)	48 (31.8)
> 45	16 (21.62)	35 (45.46)	51 (33.8)
Marital status/ <i>Bračno stanje</i>			
Married/ <i>U braku</i>	47 (63.51)	51 (66.23)	98 (64.9)
Single/ <i>Neoženjen/neudata</i>	24 (32.43)	16 (20.78)	40 (26.5)
Divorced/ <i>Razveden/Razvedena</i>	2 (2.7)	7 (9.09)	9 (6.0)
Widowed/ <i>Udovac/udovica</i>	1 (1.35)	3 (3.9)	4 (2.6)
Number of children in family/ <i>Broj dece u porodici</i>			
Childless/ <i>Bez dece</i>	35 (47.29)	23 (29.87)	58 (38.4)
One child/ <i>Jedno dete</i>	15 (20.27)	26 (33.77)	41 (27.2)
Two children/ <i>Dvoje dece</i>	22 (29.73)	23 (29.87)	45 (29.8)
Three or more children/ <i>Troje ili više dece</i>	2 (2.7)	5 (6.49)	7 (4.6)
Education level/ <i>Obrazovni nivo</i>			
General practitioner/ <i>Lekar opšte prakse</i>	22 (29.73)	1 (1.3)	23 (15.2)
Resident/ <i>Na specijalizaciji</i>	6 (8.11)	14 (18.19)	20 (13.2)
Specialist/ <i>Specijalista</i>	46 (62.16)	40 (51.95)	86 (57.0)
Subspecialist/ <i>Supspecijalista</i>		22 (28.56)	22 (14.6)
Length of service/ <i>Radni vek</i>			
Years/ <i>Godine</i>			
< 11	42 (56.76)	26 (33.77)	68 (45.0)
11 – 20	22 (29.73)	23 (29.87)	45 (29.8)
> 20	10 (13.51)	28 (36.36)	38 (25.2)

where they were employed ($p = 0.017$), the highest level of depersonalization being among physicians employed in the Primary Health Care Center in Prijedor (40%), and the lowest percentage of physicians with a high level of depersonalization were employed in the Department of Psychiatry (6.2%). 39.7% of the

participants had a low level of personal accomplishment. Regarding the institution where the participants were employed, a statistically significant difference was found ($p = 0.037$) for the level of personal accomplishment; the highest percentage of low level of personal accomplishment was observed

Table 2. Summarized results on the level of stress, emotional exhaustion, depersonalization, and personal accomplishment ($n = 151$)**Tabela 2.** Sumarni rezultati nivoa stresa i sve tri komponente sindroma sagorevanja na poslu u grupi svih ispitanika ($n = 151$)

Variable <i>Varijabla</i>	Level <i>Stepen</i>	Number of participants <i>Broj ispitanika</i>	Percent of participants <i>Procenat ispitanika (%)</i>
Stress <i>Stres</i>	Low/ <i>Nizak</i>	73	48.3
	High/ <i>Visok</i>	78	51.7
Emotional exhaustion <i>Emocionalna iscrpljenost</i>	Low/ <i>Niska</i>	59	39.1
	Moderate/ <i>Umerena</i>	51	33.7
	High/ <i>Visoka</i>	41	27.2
Depersonalization <i>Depersonalizacija</i>	Low/ <i>Niska</i>	71	47.1
	Moderate/ <i>Umerena</i>	44	29.1
	High/ <i>Visoka</i>	36	23.8
Personal accomplishment <i>Lična ispunjenost</i>	High/ <i>Visoka</i>	57	37.7
	Moderate/ <i>Umerena</i>	34	22.6
	Low/ <i>Niska</i>	60	39.7

Table 3. Results on the level of stress, emotional exhaustion, depersonalization, and personal accomplishment in relation to employment (n = 151)**Tabela 3.** Nivo stresa, emocionalne iscrpljenosti, depersonalizacije i stepena lične ispunjenosti u odnosu na zaposlenje (n = 151)

Variable Varijabla	Level Stepen	Employment/Zaposlenje		Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	P*
		Primary Health Center Dom zdravlja N (%)	Hospital Bolnica N (%)		
Stress Stres	Low/Nizak	35 (47.3)	38 (49.4)	0.064	0.464
	High/Visok	39 (52.7)	39 (50.6)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	30 (40.6)	29 (37.7)	1.138	0.566
	Moderate/Umerena	22 (29.7)	29 (37.7)		
	High/Visoka	22 (29.7)	19 (24.6)		
Depersonalization Depersonalizacija	Low/Niska	31 (41.9)	40 (51.9)	1.557	0.459
	Moderate/Umerena	24 (32.4)	20 (26.0)		
	High/Visoka	19 (25.7)	17 (22.1)		
Personal accomplishment Lična ispunjenost	High/Visoka	30 (40.5)	27 (35.1)	0.483	0.786
	Moderate/Umerena	16 (21.7)	18 (23.3)		
	Low/Niska	28 (37.8)	32 (41.6)		

*Statistically significant at $p < 0.05$

among the physicians employed in the Primary Health Care Center in Prijedor (60%), and the highest percentage of the participants with a high level of personal accomplishment were employed in the Primary Health Care Center in Laktaši (61.1%), at the Department of Psychiatry (56.2%) and the Department of Internal Medicine (53.6%) (**Table 4**).

Regarding the gender, there was no significant difference in the stress level and components of burnout syndrome between male and female doctors.

Although not statistically significant, women having a high stress level and high degree of emotional exhaustion were more numerous than men, whereas more men had high levels of depersonalization and low personal accomplishment than women. The analysis of results obtained regarding the age has shown a statistically significant difference in the level of emotional exhaustion ($p = 0.030$) among the participants of different age. The largest number of respondents with a high degree of emotional exhaustion

Table 4. Results on the level of stress, emotional exhaustion, depersonalization, and personal accomplishment in relation to institutions (n = 151)**Tabela 4.** Nivo stresa, emocionalne iscrpljenosti, depersonalizacije i stepena lične ispunjenosti u odnosu ustanovu u kojoj ispitanici rade (n = 151)

Variable Varijabla	Level Stepen	Primary Health Centers, Clinics/Domovi zdravlja, Klinike						Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		Primary Health Center Prijedor Dom zdravlja Prijedor N (%)	Primary Health Center Doboj Dom zdravlja Doboj N (%)	Primary Health Center Laktaši Dom zdravlja Laktaši N (%)	Department of Psychiatry Klinika za psihijatriju N (%)	Department of Anesthesiology Klinika za anesteziiju N (%)	Department of Internal Medicine Interna klinika N (%)		
Stress Stres	Low/Nizak	10 (33.3)	12 (46.2)	13 (72.2)	10 (62.5)	17 (51.5)	11 (39.3)	9.203	0.101
	High/Visok	20 (66.7)	14 (53.8)	5 (27.8)	6 (37.5)	16 (48.5)	17 (60.7)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	19 (33.3)	9 (34.6)	11 (61.1)	8 (50.0)	8 (24.2)	13 (46.4)	14.985	0.133
	Moderate/Umerena	9 (30.0)	10 (38.5)	3 (16.7)	5 (31.2)	18 (54.5)	6 (21.4)		
	High/Visoka	11 (36.7)	7 (26.9)	4 (22.2)	3 (18.8)	7 (21.2)	9 (32.2)		
Depersonalization Depersonalizacija	Low/Niska	8 (26.7)	10 (38.5)	13 (72.2)	12 (75.0)	12 (36.4)	16 (57.1)	21.643	0.017
	Moderate/Umerena	10 (33.3)	11 (42.3)	3 (16.7)	3 (18.8)	12 (36.4)	5 (17.9)		
	High/Visoka	12 (40.0)	5 (19.2)	2 (11.1)	1 (6.2)	9 (27.3)	7 (25.0)		
Personal accomplishment Lična ispunjenost	Low/Niska	18 (60.0)	8 (30.8)	4 (22.2)	4 (25.0)	14 (42.4)	9 (32.1)	19.268	0.037
	Moderate/Umerena	6 (20.0)	7 (26.9)	3 (16.7)	3 (18.8)	11 (33.3)	4 (14.3)		
	High/Visoka	6 (20.0)	11 (42.3)	11 (61.1)	9 (56.2)	8 (24.2)	15 (53.6)		

* Statistically significant at $p < 0.05$

Table 5. Results on the level of stress, emotional exhaustion, depersonalization and personal accomplishment in relation to gender, age, and length of service (n = 151)**Tabela 5.** Nivo stresa, emocionalne iscrpljenosti, depersonalizacije i lične ispunjenosti u odnosu na pol, starost i dužinu radnog staža (n = 151)

Variable Varijabla	Level Stepen	Gender/Pol		Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		Male/Muški N (%)	Female/Ženski N (%)		
Stress Stres	Low/Nizak	29 (55.8)	44 (44.4)	0.231	0.125
	High/Visok	23 (44.2)	55 (55.6)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	23 (44.2)	36 (36.4)	1.053	0.591
	Moderate/Umerena	17 (32.7)	34 (34.3)		
	High/Visoka	12 (23.1)	29 (29.3)		
Depersonalization Depersonalizacija	Low/Niska	25 (48.1)	46 (46.5)	0.197	0.906
	Moderate/Umerena	14 (26.9)	30 (30.3)		
	High/Visoka	13 (25.0)	23 (23.2)		
Personal accomplishment Lična ispunjenost	High/Visoka	16 (30.8)	41 (41.4)	1.857	0.395
	Moderate/Umerena	12 (23.0)	22 (22.2)		
	Low/Niska	24 (46.2)	36 (36.4)		

Variable Varijabla	Level Stepen	Age/Dob			Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		< 35 N (%)	36 to 45 N (%)	≥45 N (%)		
Stress Stres	Low/Nizak	23 (44.2)	23 (47.9)	27 (52.9)	0.787	0.675
	High/Visok	29 (55.8)	25 (52.1)	24 (47.1)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	22 (42.3)	17 (35.4)	20 (39.2)	10.688	0.030
	Moderate/Umerena	20 (38.5)	21 (43.8)	10 (19.6)		
	High/Visoka	10 (19.2)	10 (20.8)	21 (41.2)		
Depersonalization Depersonalizacija	Low/Niska	20 (38.5)	23 (47.9)	28 (54.9)	4.211	0.378
	Moderate/Umerena	20 (38.4)	12 (25.0)	12 (23.5)		
	High/Visoka	12 (23.1)	13 (27.1)	11 (21.6)		
Personal accomplishment Lična ispunjenost	High/Visoka	23 (44.2)	17 (35.4)	17 (33.3)	2.682	0.612
	Moderate/Umerena	11 (21.2)	13 (27.1)	10 (19.5)		
	Low/Niska	18 (34.6)	18 (37.5)	24 (47.2)		

Variable Varijabla	Level Stepen	Length of service/Dužina radnog staža			Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		< 10 years godina N (%)	11 – 20 years/godina N (%)	≥21 years godina N (%)		
Stress Stres	Low/Nizak	31 (45.6)	21 (46.7)	21 (55.3)	0.986	0.611
	High/Visok	37 (54.4)	24 (53.3)	17 (44.7)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	28 (41.2)	17 (37.8)	14 (36.8)	8.513	0.074
	Moderate/Umerena	28 (41.2)	15 (33.3)	8 (21.1)		
	High/Visoka	12 (17.6)	13 (28.9)	16 (42.1)		
Depersonalization Depersonalizacija	Low/Niska	27 (39.7)	21 (46.6)	23 (60.5)	5.476	0.242
	Moderate/Umerena	25 (36.8)	12 (26.7)	7 (18.4)		
	High/Visoka	16 (23.5)	12 (26.7)	8 (21.1)		
Personal accomplishment Lična ispunjenost	High/Visoka	27 (39.7)	19 (42.2)	11 (28.9)	2.020	0.732
	Moderate/Umerena	16 (23.5)	9 (20.0)	9 (23.7)		
	Low/Niska	25 (36.8)	17 (37.8)	18 (47.4)		

* Statistically significant at p<0.05

were doctors over 45 years of age (41.2%), while a similar percentage of physicians with high levels of emotional exhaustion was observed among the participants up to 35 years of age and between the age of 36 and 45. The highest percentage (42.3%) of the participants who had a low level of emotional exhaustion was among the physicians under 35 years of age. As for the length of service, there was no significant difference in the stress level, emotional exha-

ustion, and the level of personal satisfaction. The highest stress levels were observed among doctors with the length of service up to 10 years (54.4%), the highest percentage of doctors with a high degree of emotional exhaustion was found among those with the length of service \geq 21 years (42.1%), the highest level of depersonalization was seen among doctors with the length of service from 11 to 20 years (27.7%), while the lowest level of personal accom-

Table 6. Results on the level of stress, emotional exhaustion, depersonalization and personal accomplishment in relation to marital status and number of children in family (n = 151)**Tabela 6.** Nivo stresa, emocionalne iscrpljenosti, depersonalizacije i lične ispunjenosti u odnosu na bračni status i broj dece u porodici (n = 151)

Variable Varijabla	Level Stepen	Marital status/Bračni status				Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		Married/ Oženjen/ N (%)	Single/ Neoženjen/ne- udata N (%)	Divorced/ Razveden/ razvedena N (%)	Widowed/Udo- vac/udovica N (%)		
Stress Stres	Low/Nizak	43 (43.9)	20 (50.0)	7 (77.8)	3 (75.0)	5.087	0.166
	High/Visok	55 (56.1)	20 (50.0)	2 (22.2)	1 (25.0)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska	35 (35.7)	15 (37.5)	6 (66.7)	3 (75.0)	6.605	0.359
	Moderate/Umerena	35 (35.7)	15 (37.5)	1 (11.1)	0 (0.0)		
	High/Visoka	28 (28.6)	10 (25.0)	2 (22.2)	1 (25.0)		
Depersonalization Depersonalizacija	Low/Niska	49 (50.0)	14 (35.0)	4 (44.4)	4 (100.0)	12.499	0.052
	Moderate/Umerena	27 (27.6)	12 (30.0)	5 (55.6)	0 (0.0)		
	High/Visoka	22 (22.4)	14 (35.0)	0 (0.0)	0 (0.0)		
Personal accomplishment Lična ispunjenost	High/Visoka	28 (28.6)	23 (57.5)	4 (44.4)	2 (50.0)	12.238	0.057
	Moderate/Umerena	24 (24.5)	8 (20.0)	2 (22.2)	0 (0.0)		
	Low/Niska	46 (46.9)	9 (22.5)	3 (33.4)	2 (50.0)		

Variable Varijabla	Level Stepen	Number of children in family/Broj dece u porodici				Pearson Chi-Square Pearsonov hi kvadrat χ^2 test	p*
		Childless Bez dece N (%)	One child Jedno dete N (%)	Two children Dvoje dece N (%)	Three or more children/Troje i više dece - N (%)		
Stress Stres	Low/Nizak	28 (48.3)	17 (41.5)	25 (55.6)	3 (42.9)	1.799	0.615
	High/Visok	30 (51.7)	24 (58.5)	20 (44.4)	4 (57.1)		
Emotional exhaustion Emocionalna iscrpljenost	Low/Niska					2.119	0.908
	Moderate/Umerena	21 (36.2)	16 (39.0)	19 (42.2)	3 (42.9)		
	High/Visoka	22 (37.9)	14 (34.2)	14 (31.1)	1 (14.2)		
Depersonalization Depersonalizacija	Low/Niska	15 (25.9)	11 (26.8)	12 (26.7)	3 (42.9)	9.336	0.156
	Moderate/Umerena	24 (41.4)	20 (48.8)	24 (53.4)	3 (42.8)		
	High/Visoka	15 (25.8)	17 (41.4)	10 (22.2)	2 (28.6)		
Personal accomplishment Lična ispunjenost	High/Visoka	19 (32.8)	4 (9.8)	11 (24.4)	2 (28.6)	13.194	0.040
	Moderate/Umerena	30 (51.7)	8 (19.5)	16 (35.6)	3 (42.9)		
	Low/Niska	11 (19.0)	13 (31.7)	10 (22.2)	0 (0.0)		
		17 (29.3)	20 (48.8)	19 (42.2)	4 (57.1)		

* Statistically significant at $p < 0.05$

plishment (47.4%) was observed among the physicians with the greatest length of service ≥ 21 years (Table 5).

Regarding the education level, there was no significant difference in the stress level and all three components of burnout syndrome. The highest percentage of physicians with high levels of stress was in the group of doctors-residents (75.0%); the highest percentage (36.4%) of the participants with a high degree of emotional exhaustion was among doctors sub-specialists; the highest percentage (30.4%) with a high degree of depersonalization was among general practitioners; and the highest percentage of the participants with low levels of personal accomplishment was among doctors subspecialists (59.1%).

Regarding the marital status, there was no significant difference in the stress level and all three components of burnout syndrome. However, the highest percentage of physicians with a high stress level (56.1%) and a high level of emotional exhaustion (28.6%) was married, and the largest percentage of physicians with high levels of depersonalization (35.0%) were

single. As for the number of children in the family, the participants with one child had a statistically significant ($p = 0.040$) higher level of personal accomplishment. Although not statistically significant, the highest level of stress (58.5%) was observed among the participants with one child in the family, the highest percentage (42.9%) with a high degree of emotional exhaustion was found among those with three or more children, and the highest percentage of participants with a high degree of depersonalization (32.8%) was seen among the doctors without children (Table 6).

Discussion

The results of our study showed that just over a half of participants - 78 (51.7%) had a high level of stress, 27.2% of participants had a high degree of emotional exhaustion, 23.8% of participants had a high degree of depersonalization, and 39.7% of participants had a low level of personal accomplishment. No significant differences regarding gender, place of

employment, length of service and marital status were found among the participants from this study sample. The doctors over 45 years of age had a significantly ($p = 0.030$) higher levels of emotional exhaustion than the younger ones and regarding the number of children in the family, the doctors with one child had a statistically significant ($p = 0.040$) highest level of personal accomplishment. Although not statistically significant, the doctors working in health centers had a higher level of stress, emotional exhaustion and depersonalization, a lower degree of personal fulfillment in relation to the doctors employed in hospital.

Results of a study conducted in Brazil are similar to the results of our research. The study involved 191 doctors in primary health care; 43% of participants had a high level of emotional exhaustion, 17% of them had a high level of depersonalization, and 32% of participants had a low level of personal accomplishment [18]. A research on the presence of burnout syndrome was conducted at the hospital in Rijeka; 286 hospital doctors were included. Results of this study showed that the physicians in Rijeka had a higher percentage of emotional exhaustion (43.6%), a greater degree of depersonalization (33.5%) and a higher percentage of low level of personal accomplishment (49.1%) compared to the physicians in our study [19].

A survey conducted in 2010 among 259 doctors in primary health care in the Republic of Srpska showed that 75.3% of participants had a high stress level, 46% of participants had high level of emotional exhaustion, 31.3% of participants had high level of depersonalization, and 22.2% of them had a low level of personal accomplishment [20]. The results of the same survey showed that elderly doctors and doctors with longer service had a significantly higher level of stress and emotional exhaustion in relation to younger doctors and shorter service. Also, we noted in our study that statistically significant highest level of emotional exhaustion was among doctors aged over 45. Our research has shown that surveyed physicians in a lower percentage had high stress levels, but it was also significantly higher percentage of doctors with low levels of personal accomplishment.

Numerous studies were conducted all over the world to estimate the presence of burnout syndrome among family doctors. Results of the research conducted by O'Dea and his associates in Ireland showed that 52.7% of family doctors had a high degree of emotional exhaustion, 31.6% of them had high level of depersonalization and 16.3% had low level of personal accomplishment, while 6.6% of the surveyed doctors had a positive score in all three subscales [21]. Similar results were obtained from the research in Denmark, conducted by Torppa and associates. This research has shown that emotional exhaustion was common among family doctors in Denmark and it was associated with older age, increasing along the length of service, due to the working overload and because of fear of medical errors [22]. Results of research in Denmark showed that the percentage of family doctors suffering from burnout syndrome has been increasing, and that this number in

2012 increased to 5.3% compared to 2.8% noted in 2004 [23]. Results of this study showed that there was no correlation between risk of developing burnout syndrome and older age and length of service.

Research conducted in Colombia, involving 106 family doctors, showed a high overall risk of burnout syndrome among family doctors [24]. Kotb and colleagues in their study, which included 171 doctors, demonstrated that hospital doctors suffered significantly more from burnout than family doctors [25]. In our research, family doctors have higher stress levels and all three components of burnout syndrome in relation to the hospital doctors, but not significantly.

Results of this study showed different results regarding the institution in which doctors were employed. Therefore, the highest stress level was found among doctors working in the Primary Health Care Center in Prijedor, while the lowest stress level was noted among doctors employed in the Primary Health Care Center in Laktaši. The lowest level of emotional exhaustion was noted among the doctors employed in the Primary Health Care Center in Laktaši, at the Department of Psychiatry, and the highest level was noted among doctors in the Primary Health Care Center in Prijedor, at the Department of Internal Medicine. The highest percentage of physicians with a high degree of depersonalization was noted among doctors in the Primary Health Care Center in Prijedor, and the lowest percentage was noted among physicians employed at the Department of Psychiatry. The highest percentage of physicians with high levels of personal accomplishment were employed in the Primary Health Care Center in Laktaši and at the Department of Psychiatry, while the lowest level of personal accomplishment was found among the doctor working in Primary Health Care Center in Prijedor. Results of this study showed that, in comparison to other doctors, psychiatrists were at lower risk of developing burnout syndrome, while Ferrari and colleagues [26] in their research showed that even doctors, psychiatry residents, were at moderate risk of developing burnout syndrome. The results of this study showed that the most important risk factors for developing burnout and working overload were symptoms of depression and low satisfaction in the workplace. The survey conducted by Tanner and his associates included 763 hospital doctors of different specialties. The results showed that some specialties were more exposed to stress than others, and the highest level of stress was found in internal medicine specialists [27]. Besides, the results of this study showed a high percentage (60.7%) of doctors employed at the Department of Internal Medicine with high stress levels. A survey conducted in Serbia [28], which included 30 general practitioners and 30 psychiatrists, showed a high risk of developing burnout syndrome in both groups of doctors. The exposure to professional stress was slightly higher among the general practitioners than among psychiatrists, but this difference was not statistically significant, that being similar to the results of our research.

The influence of marital status and number of children on the risk of developing burnout syndrome was the subject of much research. Research results for 57 residents of family medicine in the Republic of Srpska showed that there were correlations between gender, marital status and number of children on the occurrence of burnout syndrome [29]; we also have the same results in our research. The research conducted by Martini's et al. [30] did not show that parenting affected the occurrence of burnout syndrome among doctors specializing in family medicine, but Lemkau [31] found that parenthood led to a lower level of depersonalization.

An extensive research conducted in Italy included 182 general practitioners and 148 hospital doctors [32]. The symptoms of emotional exhaustion were observed in 27.5% of the participants (32.4% of general practitioners and 21.2% of hospital physicians). The high degree of depersonalization was noted in 25.6% of the participants (27.4% general practitioners and 22.6% hospital physicians), a low level of personal accomplishment was seen in 12.8% of physicians (13.1% general practitioners, and 12.3% hospital doctors). There were no significant differences on any sub-scale of burnout syndrome between these two groups of doctors. Our results are similar to the results of research conducted in Italy, except in our study a significantly higher percentage of physicians having a low level of personal accomplishment was observed.

The most important risk factors for burnout syndrome development listed in the literature are younger age, male gender, marital status (single) and a few years of work experience [33, 34]. The results of our study showed that gender, marital status and length of service did not have an impact on morbidity of burnout syndrome, while the older age significantly influenced the risk of developing the syndrome.

Self-help and self-care are not a part of the professional training of doctors and generally has a very low place on the priority list of doctors. In

Switzerland, 21% of doctors in primary health care did not have a family doctor, and 90% of them were treated by themselves (self-medication) [35]. The study conducted by Cumbria et al. showed that as many as 62.9% of family doctors in Croatia did not have their chosen doctor, but they treated themselves [36]. The doctor deals with problems of his/her patients, so there is little time to deal with one's personal problems.

Our findings can be explained by the characteristics of working in family medicine. Family doctors have direct contact with patients during working hours; they are burdened with a large number of patients with chronic diseases, their social and other problems that they are not always able to solve. Family doctors are commonly expected by their patients to give much more than they could give them, thus the physicians are often led to a state of chronic stress. Family doctors are additionally burdened with extensive administration; they have lower income and "lower" status in relation to the doctors employed in hospitals. Our results and other studies [37] indicate the need to educate physicians about prevention and methods for coping with stress and burnout syndrome.

Conclusion

Findings from our study are similar to those published in the world literature regarding the level of stress and the risk of developing burnout syndrome among physicians. Although not statistically significant, doctors working in health centers had a higher level of stress, emotional exhaustion and depersonalization, a lower degree of personal fulfillment in relation to the doctors employed in the hospital. The age and number of children in the family have a significant impact on the risk of developing burnout syndrome, while gender, length of service, place of employment, education and marital status did not significantly influence the level of stress and burnout syndrome.

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CONTEMPORARY PRINCIPLES OF SUICIDE PREVENTION

SAVREMENI PRINCIPI PREVENCIJE SAMOUBISTVA

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Summary

Introduction. Suicide remains a significant public health problem worldwide. This study is aimed at analyzing and presenting contemporary methods in suicide prevention in the world as well as at identifying specific risk groups and risk factors in order to explain their importance in suicide prevention. **Material and Methods.** The literature search covered electronic databases PubMed, Web of Science and Scopus. In order to select the relevant articles, the authors searched for the combination of key-words which included the following medical subject heading terms (suicide or suicide ideation or attempted) and (prevention or risk factors) and (man or elders or mental disorders). Data analysis covered meta-analyses, systematic reviews and original scientific papers with different characteristics of suicide preventions, risk factors and risk groups. **Results.** Worldwide evidence-based interventions for suicide prevention are divided in universal, selective and indicated interventions. Restricted approach to various methods of committing suicide as well as pharmacotherapy contributes to a lower suicide rate. Suicide risk factors can be categorized as proximal and distal. The following groups are at highest risk of committing suicide: males, older persons and persons with registered psychiatric disorders. **Conclusion.** There is a lot of evidence that suicide is preventable. It is known that only 28 countries in the world have national suicide prevention strategies and Serbia is not one of them.

Key words: Suicide; Suicidal Ideation; Suicide, Attempted; Preventive Psychiatry; Accident Prevention; Risk Factors; Global Health; National Health Programs

Sažetak

Uvod. Samoubistvo je i dalje vodeći zdravstveni problem širom sveta. Cilj istraživanja bio je da se analiziraju savremeni principi prevencije samoubistva. Takođe, istraživanje je imalo za cilj da ukaže na specifične faktore rizika i grupe sa rizikom među osobama koje su počinile samoubistvo. **Materijal i metode.** Elektronska pretraga literature je izvršena u okviru indeksnih baza: PubMed – Medline, Web of Science i Scopus. Korišćena je kombinacija ključnih reči revidiranih u spisku medicinskih predmetnih naziva (MeSH) za odabir relevantnih članaka: (suicide or suicide ideation or attempted) i (prevention or risk factors) i (man or elders or mental disorders). Analiza je obuhvatila metaanalize, sistematske preglede i originalne naučne radove u kojima su prikazani faktori rizika i grupe sa rizikom za nastanak samoubistva. Takođe, analizirane su i karakteristike nacionalnih strategija prevencije samoubistva na svetskom nivou. **Rezultati.** Rezultati analiziranih metaanaliza i sistematskih pregleda ukazuju da su savremeni principi prevencije samoubistva zasnovani na univerzalnom, selektivnom i indikativnom pristupu. Ograničen pristup različitim metodama izvršenja samoubistva i farmakoterapija doprinose smanjenju stope samoubistva. Faktori rizika za izvršenje samoubistva mogu biti proksimalni i distalni. U grupe sa rizikom za izvršenje samoubistva spadaju: starije osobe, pripadnici muškog pola i osobe sa registrovanim mentalnim oboljenjima. **Zaključak.** Preventivne mere doprinose značajnom smanjenju stope samoubistva. U svetu 28 zemalja, među kojima nije Republika Srbija, ima nacionalnu strategiju prevencije samoubistva.

Ključne reči: samoubistvo; suicidalne ideje; pokušaj samoubistva; preventivna psihijatrija; prevencija nesreća; faktori rizika; globalno zdravlje; nacionalni programi zdravstvene zaštite

Abbreviations

WHO – World Health Organization

Introduction

The World Health Organization (WHO) multi-center study on suicidal behavior [1] has defined suicide as an act with a fatal outcome which the deceased, knowing or expecting a potentially fatal outcome, has initiated and carried out with the purpose of bringing about wanted changes. It represents a complex, dynamic and heterogeneous social phenomenon that is caused by several interacting factors, such as personal, social, psychological, cultural, biological and environmental ones [2].

Although the number of suicides has decreased since 2000 by 9%, it remains a significant public health problem worldwide. The WHO has reported that 804,000 suicides occurred globally in 2012. The estimated annual mortality is 11.4 suicides per 100,000 population (15.0 for males and 8.0 for females), which equates to one death every 40 s. Suicide rates vary widely within and between different geographic regions. The European Region is the second region in the world with the highest annual global age-standardized suicide rate of 13.8 per 100 000 population. In the European Region six European countries fall within the top 20 countries with the highest estimated suicide rates globally. For example, Lithuania has the fifth highest suicide rate globally at 28.2 per 100,000 and Kazakhstan has the tenth highest at 23.8 per 100,000. Of great concern is that suicide is the main cause of death in many European countries for the 15–29 age group [3, 4].

In Serbia, the total number of suicides exceeded 75,000 in the period from the early 1950s to the mid-2010s. Recent data from the Statistical Office of the Republic of Serbia estimated that the average age-standardized mortality rate was 17.4 suicides per 100,000 inhabitants in the whole country, that being above the world and European record [5]. Unfortunately, although the suicide rate in Serbia is high, there is no national strategy for preventing suicide. Recent studies reported the suicide mortality of Serbian population in different time periods related to age and sex [6–9]. The highest suicide rate was in Vojvodina region with 22.7 suicides per 100,000 inhabitants and the lowest was in South and East region of Serbia with 14.0 suicides per 100,000 inhabitants. The differences in suicide according to sex and age in Serbia followed the world trend. In the last two decades, 70.7% of the total number of suicides was committed by males and only 29.3% by females. In addition, 48.1% of those who committed suicide were at 60 years of age or over [5].

Previous studies [10–12] have reported that suicide is preventable according to strong evidence based on clinical trials and natural experiments of drug and psychotherapeutic interventions, improvements in patient identification and restricting access to means of committing suicide. Therefore, this study is aimed at analyzing and presenting contemporary methods in sui-

cide prevention worldwide as well as at identifying specific risk groups and risk factors in order to explain their importance in suicide prevention.

Material and Methods

The literature search covered electronic databases PubMed, Web of Science and Scopus. The authors searched for the key words which referred to the following medical subject heading terms: (suicide OR suicide ideation OR attempted) and (prevention OR risk factors) and (man OR elders OR mental disorders). A manual search involved reference lists from articles retrieved for possible inclusion. Database searches and hand searches were last conducted on July 31, 2016. Data analysis covered meta-analyses, systematic reviews and original scientific papers with different characteristics of suicide preventions, risk factors and risk groups.

Results and Discussion

Heterogeneity in study methodology and populations limited formal statistical analysis, thus we present a narrative synthesis of the results for the key domains of suicide prevention interventions, risk factors and risk groups.

Risk Factors and Risk Groups

Several risk factors act cumulatively to increase a person's vulnerability to suicidal behavior. Usually no single cause is sufficient to explain a suicidal act. In general, these factors can be categorized as state-dependent or proximal and trait-dependent or distal factors. The distal factors increase predisposition, whereas the proximal ones act as precipitants. Psychiatric and physical disorders, psychosocial crisis, availability of means and exposure to models are common proximal risk factors. On the other side, genetic loading, personality characteristics, restricted fetal growth and perinatal circumstances, early traumatic life events and neurobiological disturbances are recognized as distal risk factors [13]. The WHO reports a list of several risk factors that are interrelated [3, 4]. Moreover, they can contribute directly or even indirectly to suicidal behavior. They are divided into three big groups.

Health System and Societal Risk Factors

Stigma against seeking help for suicidal behaviors, problems of mental health or substance abuse, or other emotional stressors continues to exist in many societies and can be a substantial barrier to people receiving help that they need. Moreover, suicide risk increases significantly with different comorbidities [14]. Therefore, limited health care in different countries may contribute to higher suicide risk. Previous studies showed that adequate, prompt and accessible treatment for special risk groups (i.e. mental and substance use disorders) can reduce the risk of suicidal behavior [15–17].

Direct access or proximity to means of suicide significantly increases the risk of suicide. The most common means of suicide worldwide are self-poi-

soning with pesticides, firearm, and hanging [18, 19]. Restricting access to the means of suicide is effective in preventing suicide. Mann et al. [16] concluded that firearm control legislation was associated with reduced suicides involving this method. Moreover, several measures have been proposed to prevent suicide by pesticides which include reducing the toxicity of pesticides, reducing the access to pesticides by ratifying their safer storage and disposal, legislating to remove locally problematic pesticides from agricultural practice; enforcing regulations on the sale of pesticides, etc. [20].

Inappropriate media reporting practices can sensationalize suicide and increase the risk of “copycat” suicides (imitation of suicides) among vulnerable people. Additionally, exposure to models of suicide has been shown to increase the risk of suicidal behavior [21, 22]. Responsible reporting of suicide in the media has been shown to decrease suicide rates [16, 17]. Important aspects of responsible reporting include: avoiding detailed descriptions of suicidal acts, avoiding sensationalism and glamorization, using responsible language, minimizing the prominence of suicide reports, avoiding oversimplifications, educating the public about suicide and available treatments, and providing information on where to seek help [23].

Community and Relationship Risk Factors

The communities that people live in have an important association with suicide risk factors and it is related to different cultural, religious, legal and historical factors. Experiences of natural disaster, war and civil conflict can increase the risk of suicide because of the destructive impacts they have on social well-being, health, housing, employment and financial security [24]. Moreover, it has been reported that the stresses of acculturation and dislocation represent a significant suicide risk that has an impact on a number of vulnerable groups, including indigenous peoples, asylum-seekers, refugees, persons in detention centers, internally displaced people, and newly arrived migrants [25]. Additionally, discrimination against subgroups within the population can lead to the continued experience of stressful life events such as loss of freedom, rejection, stigmatization and violence that may evoke suicidal behavior and increase risk for suicide [26, 27]. Trauma or abuse increases emotional stresses and may trigger depression and suicidal behaviors in people who are already vulnerable [28].

Individual Risk Factors

Individual risk factors are related to the likelihood of a person developing suicidal behaviors. There are several individual risk factors that may increase the suicide risk. A prior suicide attempt is the single most important risk factor for suicide in the general population. Persons who have already attempted suicide have significantly higher risk for suicide in future [3, 4]. Another individual risk factor is the presence of mental disorders in persons who committed suicide. Previous psychological autopsy case-control studies

showed a strong relationship between suicide and psychiatric disorders. It has been reported that psychiatric disorders are present in about 80-90% of persons who kill themselves [29–31]. All substance use disorders increase the risk of suicide. Alcohol and other substance use disorders are found in 25–50% of all suicides, and suicide risk is further increased if alcohol or substance use is accompanied with other psychiatric disorders [32]. In addition, chronic pain and illness are important risk factors for suicidal behavior. Suicidal behavior has been found to be 2–3 times higher in those with chronic pain compared to the general population. All illnesses that are associated with pain, physical disability, neurodevelopmental impairment and distress increase the risk of suicide [33].

As mentioned above, several risk factors may contribute to suicidal behavior. Thus, several risk groups in the general population can be identified based on the analyzed data:

Males

According to the WHO report, significantly more men commit suicide than women. In 2012, male-to-female suicide ratio was higher in high-income countries compared to low- and middle-income countries (3.5 versus 1.6). Moreover, there are large differences between world regions, whereas male-to-female ratio is 4.1 in European Region [3, 4]. The differences in suicides between male and female gender in Serbia follow the world trend. In the last two decades, 70.7% of all suicides were committed by males and only 29.3% by females [5]. There are several explanations for this specific ratio. Basically, men are more impulsive and aggressive than women. Additionally, men choose more effective methods for suicide than women [3]. From the cultural aspect, since the society is less likely to accept suicide attempts done by men there are more deaths caused by suicide committed by men and their fewer suicide attempts than in female population [34]. Increased misuse of alcohol and psychoactive substances [35], suppression of emotion [36], and non-acceptance of medical care [37] contribute to higher suicide rate in males.

Old People

The WHO reports that with regard to age, suicide rates are lowest in persons under 15 years of age and highest in those aged 70 years or older for both men and women in almost all regions of the world [3]. In Serbia, 48.1% of person who committed suicide were aged 60 years or over [5]. The risk of suicide in old people increases with alcohol misuse [38], and higher number of diseases among them [39].

Psychiatric Disorders

According to a year-long research on suicide the patients with current psychiatric disorders top the list of those who commit suicide. Previous studies have reported that psychiatric disorders are present in about 80–90% of persons who kill themselves and contribute 47–74% to the population risk of suicide [29–31]. Harris & Barraclough [40] have reported

that the risk of suicide is increased 5 to 15-fold in persons with psychiatric disorders. Moreover, they claim that the functional psychiatric disorders (major depressive disorder, bipolar disorders, schizophrenia, etc.) pose a greater risk of committing suicide than organic psychiatric disorders (epilepsy and brain injury) [39]. In addition, previous meta-analyses showed that specific psychiatric disorders were associated with a higher risk of committing suicide. They reported that mood disorders (RR = 13.4), substance-related disorders (RR=5.2), personality disorders (RR=4.5) and psychotic disorders (RR=6.6) were the most common psychiatric disorders among the persons who committed suicide [41, 42].

Suicide Prevention Interventions

Despite the evidence that many deaths caused by suicide are preventable, often with low-cost interventions, suicide is too often a low priority for governments and policy-makers worldwide. In 2004, Sher [43] proposed three modes of suicide prevention. Namely, it has been stated that the ideal method of protection against suicide is primary prevention, i.e. reduction of number of new cases. In addition, the goal of secondary prevention is to decrease the likelihood of a suicide attempt in the high-risk patients. Furthermore, tertiary prevention is aimed at diminishing the consequences of suicide attempts.

World-wide evidence-based interventions for suicide prevention are divided into universal, selective and indicated interventions. Universal prevention strategies are designed to reach an entire population in an effort to maximize health and minimize suicide risk by removing barriers to care and increasing access to help, strengthening protective processes such as social support and altering the physical environment. Selective prevention strategies target vulnerable groups within a population based on characteristics such as age, sex, occupational status or family history. Indicated prevention strategies target specific vulnerable individuals within the population [3, 4].

Several reviews of the efficacy of different prevention practices have been published [16, 17]. One of the most comprehensive studies that are up-to date is the one conducted by Zalsman et al. [17]. Several aspects of suicide prevention interventions have been

analyzed in this systematic review. The authors have concluded that there is strong evidence that restricting access to lethal means is clearly linked to a decrease in suicide rates. They have reported that restricted access to the means of committing suicide include erection of barriers at sites popular for suicide by jumping, limiting pack sizes of analgesic and withdrawal of particularly toxic analgesics, restricting access to firearms in some countries, and withdrawal of more toxic pesticides in others. Furthermore, the authors analyzed the potential benefit of pharmacotherapy and psychotherapy. They have concluded that the anti-suicide effect of Clozapine and Lithium is confirmed but it might be less specific than thought before. Effective, pharmacological as well as psychological treatment of depression remains an important suicide and self-harm prevention strategy. Moreover, the authors have concluded that more research is needed to confirm the efficacy in suicide prevention in regard to the following public health approaches: gatekeeper training, media regulation, internet-based intervention, helplines, education of physicians and screening in primary-care population as healthcare strategies [17].

Conclusion

Evidence-based data suggest that several risk factors contribute to suicidal behavior, including societal, relationship and individual. Moreover, the most vulnerable risk groups are males, older persons and persons with registered psychiatric disorders. Analysis of previous studies indicates that the restriction of means and pharmacotherapy are effective in suicide prevention.

Although there is a lot of evidence that suicide is preventable, only 28 countries in the world are known to have national suicide prevention strategies today. Serbia, as a country with annual suicide rate above the world and European record, is not one of them.

It is well known that there is no way to predict those who will commit suicide. Thus, it is necessary to conduct more epidemiological studies which will help to recognize the population groups at risk of self-injuring and suicidal behavior. Based on data from other countries, the establishment of the national suicide strategy will improve suicide prevention in our country.

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CASE REPORTS

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Case report
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DYKE-DAVIDOFF-MASSON SYNDROME – TYPICAL IMAGING FEATURES

DAJK-DAVIDOV-MASONOV SINDROM – TIPIČNE RADIOLOŠKE KARAKTERISTIKE SINDROMA

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Summary

Introduction. Dyke-Davidoff-Masson syndrome is an uncommon neurological disorder clinically presented with seizures, various degrees of mental retardation, motor weakness and sometimes body asymmetry. Typical neuroimaging features include cerebral hemiatrophy with ipsilateral hyper pneumatization of paranasal sinuses. The purpose of this report was to present a rare cause of seizures revealed by magnetic resonance imaging. **Case Report.** We report a case of a 17-year-old boy admitted to hospital due to a severe headache. He had been treated because of partial epileptic seizures for six years. Neuropsychological examination revealed mild mental retardation, mild speech and reading difficulties and discrete right-sided hemiparesis. Typical magnetic resonance imaging features confirmed clinical suspicion of Dyke-Davidoff-Masson syndrome, revealing left frontal lobe atrophy, with consecutive widening of the left lateral ventricle frontal horn, thickening of the nearby frontal squama and hypertrophy of left frontal sinus. **Conclusion.** Magnetic resonance imaging is the key imaging modality that confirms clinical suspicion of Dyke-Davidoff-Masson syndrome based on a proper physical and neurological examination. **Key words:** Atrophy; Frontal Lobe; Craniofacial Abnormalities; Seizures; Intellectual Disability; Neuroimaging; Magnetic Resonance Imaging; Neurologic Examination

Introduction

Dyke-Davidoff-Masson syndrome (DDMS) is a rare neurologic condition clinically characterized by a different degree of mental retardation, facial or body asymmetry, hemiparesis or hemiplegia and epileptic seizures [1–3]. The syndrome was first reported in 1933. Using plain skull radiography and pneumoencephalography in the series of nine pa-

Sažetak

Uvod. Dajk-Davidov-Mejsonov sindrom (*Dyke-Davidoff-Masson*) redak je neurološki poremećaj koji se klinički ispoljava u formi epileptičkih napada, različitim stepenom nedovoljne mentalne razvijenosti, motornom slabošću i, ponekad, telesnom asimetrijom. Karakteristični radiološki nalaz uključuje cerebralnu hemiatrofiju sa istostranom hiperpneumatizacijom paranasalnih sinusa. Cilj rada bio je prikaz ovog sindroma kao retkog uzroka epileptičkih napada, dijagnostikovanog magnetno-rezonantnim pregledom. **Prikaz slučaja.** Sedamnaestogodišnji mladić je primljen u bolnicu zbog jake glavobolje. Tokom šest godina, lečen je od epilepsije koja se ispoljavala u formi parcijalnih napada. Neuropsihološkim pregledima ustanovljen je blag stepen nedovoljne mentalne razvijenosti, blaži poremećaji govora i tegobe sa čitanjem, te blaga desnostrana hemipareza. Tipični nalaz na magnetno-rezonantnom pregledu potvrdio je kliničku sumnju na Dajk-Davidov-Masonov sindrom, otkrivajući atrofiju levog frontalnog lobusa, sa posledničnim proširenjem frontalnog roga leve lateralne moždane komore, zadebljanjem susjednog dela skvame frontalne kosti i hipertrofijom levog frontalnog sinusa. **Zaključak.** Magnetno-rezonantni imidžing je ključna radiološka dijagnostička metoda koja potvrđuje kliničku sumnju na Dajk-Davidov-Masonov sindrom, zasnovanu na adekvatnom fizičkom i neurološkom pregledu.

Ključne reči: atrofija; frontalni rezanj; kraniofacijalne abnormalnosti; epileptički napadi; nedovoljna mentalna razvijenost; neuroimidžing; magnetna rezonanca; neurološki pregled

tients with the aforementioned symptoms, Dyke, Davidoff and Masson reported thickening of skull bones and asymmetry of lateral ventricles [3]. The development of more sophisticated diagnostic imaging modalities, such as computed tomography and, especially magnetic resonance imaging led to a more detailed evaluation of this condition. Classical imaging findings include hypoplasia of one brain hemisphere (hemiatrophy), often with reduced vol-

Abbreviations

DDMS	– Dyke-Davidoff-Masson syndrome
MRI	– magnetic resonance imaging
CSF	– cerebrospinal fluid
T2W FLAIR	– T2- weighted fluid attenuated inversion recovery
T1W	– T1- weighted
T2W	– T2- weighted

ume of a corresponding cranial fossa, and consecutive thickening of nearby bony structures and enlargement of equilateral paranasal sinuses, the frontal sinus being most often involved [1–3]. In more severe cases, hyperpneumatization of equilateral mastoid cells and elevation of a petrous ridge and orbital roof can be seen [3]. The purpose of this report was to present a rare cause of seizures revealed by magnetic resonance imaging (MRI).

Case Report

A 17-year-old boy was admitted to neurology department due to a sudden onset of severe frontal headache. Since the age of 11 he had been treated because of partial seizures manifested as short episodes of right arm tonic seizures, frequently accompanied with a stutter. He has had episodes of stutter ever since he was a little child. The seizures had not recurred since the introduction of the medications and the treatment ended two years ago. The parents gave information that the delivery had happened outside of a hospital and that the child had been resuscitated at birth.

Neuropsychological assessment revealed mild mental retardation, mild dyslexia and dyscalculia, as well as discrete right-sided hemiparesis. MRI was ordered.

Magnetic resonance imaging examination revealed a volume loss of the left frontal lobe with a gliosis of subcortical and deep frontal white matter and consequent widening of the extracerebral cerebrospinal fluid (CSF) spaces and the frontal horn of the left lateral ventricle (**Figure 1A**). Thickening of the squama of the frontal bone was evident as well as hyper-pneumatization of the left frontal sinus (**Figures 1B and 1C**). Mild enlargement of the left mastoid cells and discrete elevation of the left petrous ridge were also present (**Figures 2A and 2B**). The decreased volume of left anterior cranial fossa, with a shift of midline structures toward the left was evident (**Figure 1**).

Discussion

After the first report of the syndrome given by Dyke, Davidoff and Masson in 1933, Alpers and Dear defined two types of cerebral hemiatrophy in 1939, according to the probable etiology and the time of the insult [4]. In the primary or congenital type, an entire cerebral hemisphere is atrophic or hypoplastic while in the secondary or acquired type there is a localized volume loss of the brain parenchyma [1, 5]. In the primary type, a potential insult occurs in an

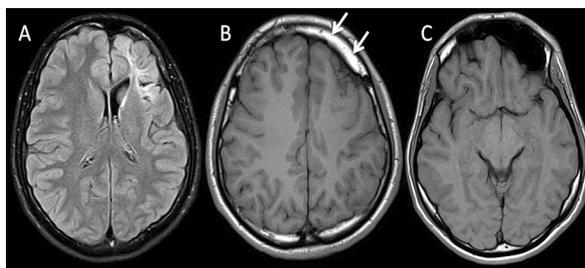


Figure 1. T2W FLAIR image in the axial plane (A) showing atrophy of the left frontal lobe with gliosis of subcortical and deep frontal white matter as well as “ex vacuo” widening of the extracerebral CSF spaces and frontal horn of the left lateral ventricle. Thickening of the squama of the frontal bone is evident on the T1W axial image (arrows in B) and shift of midline structures toward the left. T1W image in the axial plane (C) shows hyper-pneumatization of the left frontal sinus. Decreased volume of the left anterior cranial fossa is visible on all three images.

Slika 1. T2W FLAIR snimak u transverzalnoj ravni (A) pokazuje atrofiju levog frontalnog lobusa sa gliozom supkortiklane i duboke bele mase, kao i „ex vacuo“ proširenjem ekstracerebralnih likvorskih prostora i frontalnog roga leve lateralne moždane komore. Na T1W snimku u transverzalnoj ravni uočava se zadebljanje skvame frontalne kosti (strelica na slici B), kao i pomeranje struktura središnje linije ulevo. T1W snimak u transverzalnoj ravni (C) pokazuje hiperpneumatizaciju levog frontalnog sinusa. Smanjen volumen levog dela prednje lobanjske jame uočava se na sva tri snimka.

early pregnancy, causing a development of an entire brain hemisphere to slow down. There is no brain volume loss, but the brain never develops to the normal size, therefore this condition is known as hemihypoplasia or unilateral cerebral hypoplasia [6, 7]. The vast majority of the primary type is of an unknown origin (idiopathic) and the cerebrovascular origin in the early pregnancy is thought to be the most probable cause of the disorder.

In the secondary type, cerebral insults occur in the perinatal period or later and a possible cause could be either cerebrovascular insult, both ischemic or hemorrhagic, inflammatory, infectious process or head trauma [6]. Any of these factors can cause a delay in the development of the brain, most probably due to reduced perfusion and hypoxic-ischemic injury [7]. Recent fluorodeoxyglucose- positron emission tomography (FDG-PET) studies proved hypometabolism of the affected hemisphere [8, 9], whereas other studies have suggested that a reduced blood flow through carotid artery due to coarctation could be the cause of cerebral hemiatrophy [9, 10].

As the brain increases its volume during the development, it pushes the bony tables outwards and causes them to laminate. In case of retarded brain growth the bones and paranasal sinuses tend to invert its growth inwards, to enlarge and thus occupy the free intracranial space [6, 7, 11]. Therefore, the frontal sinus, ethmoid and mastoid cells equilateral to brain hemiatrophy get larger, the squama of the

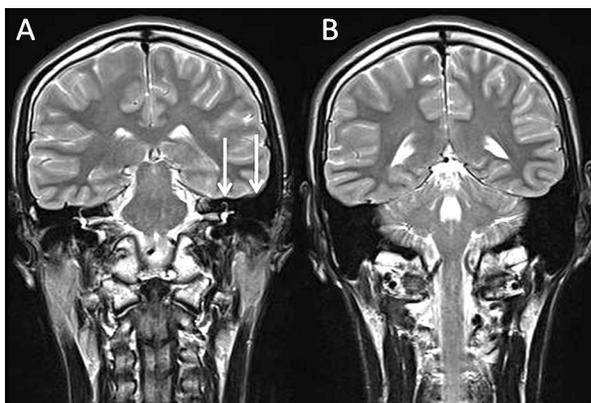


Figure 2. T2W images in coronal plane (A and B) showing mild enlargement of the left mastoid cells and discrete elevation of the left petrous ridge (arrows in A). *Slika 2.* T2W snimak u transverzalnoj ravni (A i B) pokazuje blago uvećanje mastoidnih ćelija s leve strane, kao i diskretnu elevaciju levog petroznog grebena (strelica na Slici A).

frontal bone becomes thicker and large sphenoid wing and petrous ridge elevate. The lateral ventricle and extracerebral CSF spaces also get larger *ex vacuo* due to the brain volume loss. Both genders and hemispheres may be affected, although there is a propensity for male and left hemisphere [1]. The frontal lobes are most commonly affected. Cross cerebellar atrophy

can be seen in patients with long-standing and extensive lesions, usually in the primary type of DDMS [1].

Conditions associated with cerebral hemiatrophy, such as Sturge-Weber syndrome, Rasmussen encephalitis, Linear nevus syndrome, Fishman syndrome, Silver-Russell syndrome and unilateral complete occlusion of the middle cerebral artery (MCA) could mimic DDMS on imaging. The clinical manifestation of this disorder may become evident at any time, depending on the time the insult occurred, and its severity. It most frequently becomes evident in the teenage or adolescent period. The clinical presentation may also be variable. A person most frequently experiences simple or complex partial seizures, varying degree of hemiparesis, cognitive disorder, language and learning disorders, depending upon the severity of the brain damage [1, 7, 12, 13].

Conclusion

Magnetic resonance imaging is the key imaging modality that confirms clinical suspicion of Duke–Davidoff–Masson syndrome based on a proper physical and neurological examination.

Prognosis is better if the onset of symptoms is after the age of 2 years with medically controllable seizures. In the case of a pharmacoresistant epilepsy, a hemispherectomy is a treatment of choice with a success rate of 85% in carefully selected cases.

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Case report
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THE CASE OF T-CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA PRESENTED AS TRANSFUSION DEPENDENT ANEMIA WITH SUSTAINED RESPONSE TO CYCLOSPORINE A THERAPY: CASE REPORT

T-ĆELIJSKA LEUKEMIJA VELIKIH GRANULISANIH LIMFOCITA SA KLINIČKOM SLIKOM TRANSFUZIONO ZAVISNE ANEMIJE I PROTRAHOVANIM TERAPIJSKIM ODGOVOROM NA CIKLOSPORIN A: PRIKAZ SLUČAJA

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Summary

Case report. A 41-year-old man presented with anemia, lymphocytosis and splenomegaly. T-cell large granular lymphocyte leukemia was diagnosed based on lymphocytosis of T-cell large granular lymphocytes, characteristic immunophenotype (CD3⁺, CD8⁺, CD16⁺, CD57⁺) of the lymphocytes and clonally rearranged T-cell receptor genes. Therapy indication was transfusion-dependent anemia. Initial cyclosporine therapy and low-dose oral methotrexate failed to control anemia and lymphocytosis. Yet, a complete clinical and hematological response (without molecular remission) was achieved and sustained when cyclosporine was reintroduced into the therapy. **Conclusion.** Our case confirms that cyclosporine therapy is effective in treating T-cell large granular lymphocyte leukemia and suggests that indefinite treatment may not be needed to maintain the response.

Key words: Leukemia, Large Granular Lymphocytic; Diagnosis; Lymphocytosis; Anemia; Cyclosporine; Treatment Outcome

Introduction

T-large granular lymphocyte (T-LGL) leukemia is a rare lymphoproliferative disorder that comprises 2%–5% of all T-cell/natural killer (NK)-cell malignancies [1, 2]. The diagnosis is suggested by flow cytometry and demonstrates an expansion of CD3⁺CD8⁺CD57⁺ T cells that is confirmed by T-cell receptor gene rearrangement studies [2–4]. In most patients, this is an indolent disorder with a median survival time >10 years [1, 2, 4]. Approximately two thirds of all patients with indolent T-LGL leukemia develop cytopenias, recurrent bacterial infections, autoimmune disorders, and/or splenomegaly over the course of their disease. Thus, more than half of these patients require treatment [3]. Immunosuppressive therapy, including single

Sažetak

Prikaz slučaja. Bolesnik star 41 godinu inicijalno je predstavljen anemijom, limfocitozom i splenomegalijom. Dijagnoza T-ćelijske leukemije velikih granuliranih limfocita postavljena je na osnovu prisustva limfocitoze velikih granuliranih limfocita (citomorfološki), karakterističnog imunofenotipa limfocita (CD3⁺, CD8⁺, CD16⁺, CD57⁺) i klonskog rearanžmana gena za T-ćelijski receptor. Glavna terapijska indikacija bila je transfuziono zavisna anemija. Inicijalno lečenje ciklosporinom kao i niskim dozama peroralnog metotreksata nije uspeo da kontroliše anemiju i limfocitozu. Međutim, ponovnim uvođenjem ciklosporina u terapiju postignut je kompletni klinički i hematološki odgovor (bez molekularne remisije). **Zaključak.** Naš slučaj potvrđuje da je ciklosporin delotvoran u terapiji leukemije velikih granuliranih limfocita i ukazuje da doživotna terapija radi održavanja terapijskog odgovora ne mora biti neophodna.

KLjučne reči: T-LGL leukemija; dijagnoza; limfocitoza; anemija; ciklosporin; ishod lečenja

agent corticosteroids, methotrexate, cyclophosphamide and cyclosporine (CsA), is effective in controlling symptoms and cytopenia [3, 4]. In this report, we discuss our own experience and report a complete response to CsA.

Case Report

A previously healthy 41-year-old man was admitted to our department for the investigation of symptomatic anemia. He did not have palpable peripheral lymphadenopathy, splenomegaly or hepatomegaly. His complete blood count showed anemia (hemoglobin (Hgb) of 80 g/l, erythroid indices: MCV 109.7 fl, MCHC 33.73 g/dl, RDW 19.6%) and lymphocytosis (white blood count - WBC) of 12.2 x 10⁹/L, with a differential count of 51% lymphocytes, total lymphocyte count:

Abbreviations

BM	– bone marrow
CsA	– cyclosporine
Hgb	– hemoglobin
T-LGL	– T-large granular lymphocyte
WBC	– white blood count

4.816 x 10⁹/l). The lymphocytes were small to intermediate with discrete but visible granules in cytoplasm (**Figure 1**). Other laboratory test results were as follows: reticulocytes 1x10⁻³/L, negative direct and indirect Coombs' test, liver enzymes, creatinine, blood urea nitrogen, and iron within the normal range. Hepatitis B surface antibody (HBsAg), anti hepatitis C virus (HCV), anti human immunodeficiency virus (HIV), Cytomegalo and Epstein-Barr virus were negative, whereas Mycoplasma pneumoniae and Adeno virus IgM were slightly positive. Bone marrow (BM) cytology showed moderate erythroid hypoplasia. The small to intermediate lymphocytic cells comprised 25% of the BM cells. Ultrasonography showed a slightly enlarged spleen. Treatment with corticosteroids was started (prednisone 20 mg/day). However, transfusions with erythrocytes were needed to address a persistent drop in Hgb to 67 g/L.

Subsequent diagnostic investigation excluded antinuclear, antimitochondrial, antismooth-muscle, antiparietal cell, antithyroid and anticardiac antibodies. Quantitative Igs were within the reference ranges. The Coombs direct (IgG and c3d) and indirect tests were positive. A 51Cr red cell survival study showed reduced survival times for erythrocytes (17 days). Flow cytometry of peripheral blood demonstrated a (CD3, TCR a/b, CD2, CD7, CD5, CD8, CD16, CD57, HLA DR)⁺ and (CD1a, CD4, TCR g/d)⁻ lymphocyte immunophenotype. A BM biopsy showed a moderate interstitial infiltration with CD3⁺, CD8⁺, CD57⁺, Granzyme B⁺ T-lymphocytes (**Figure 2**). The T-cell receptor γ was positive for gene rearrangement and showed the presence of two rearranged clones. Therefore, T-LGL leukemia was diagnosed. The patient was started on CsA 250 mg/d, which was increased to 300 mg/d within two months. Due to the possible CsA side effects, the CsA blood level, blood pressure, kidney and liver function were monitored. All of the parameters were within the reference range, except the creatinine levels, which reached a maximum of 136 mmol/l. However, 10 months of CsA therapy resulted in only a partial response according to the criteria of a French group (Hgb >8 g/dL, platelets >50x10⁹/L, and neutrophils >0.5x10⁹/L, no transfusion requirements), with a total WBC of 18,5x10⁹/L, Hgb 84 g/l, platelets 356 x10⁹ and LGL still present in peripheral blood smears. Repeated immunophenotyping and T-cell gene rearrangement confirmed persistent T-LGL leukemia. He was started on low-dose oral methotrexate, with a total dose of 10 mg/d weekly. He was on methotrexate therapy, exhibiting only a partial response, for two and half years (30 months). He was not transfusion dependent, but he was symptomatic due to anemia. Complete remission was not achieved, as demonstrated in the complete blood

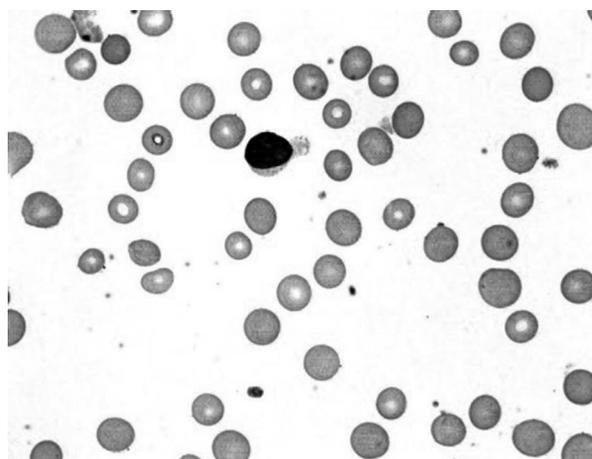


Figure 1. Large granular lymphocyte in peripheral blood
Slika 1. Veliki granulizani limfociti u perifernoj krvi

count values (WBC 13,7x 10⁹/L, Hgb 96 g/L) and the dominant cell population in peripheral blood immunocytochemistry (90% CD3⁺, CD8⁺ lymphocytes). The CsA treatment was reintroduced. The initial and maintenance dose was 300 mg/d. Within only a few months, the patient achieved complete remission. After \approx 3 years, the CsA was tapered down and excluded. The toxic effects of CsA were evident in the elevated creatinine levels (maximum 156 mmol/l). The patient was off CsA therapy for 4 years, and thus far he has been in complete hematological remission, and has repaired kidney function. A molecular response was missing. Although it was substantially decreased, an abnormal T-cell clone was detected by immunophenotyping and the presence of a T-cell receptor γ rearrangement in one clone.

Discussion

T-large granular lymphocyte leukemia is a rare lymphoproliferative disorder that is characterized by the clonal proliferation of CD3⁺ T-cytotoxic cells. It is an indolent disorder. However, its clinical course is quite uncertain. Its mortality may be as high as 20% in four years [5]. Most patients (50–82%) are symptomatic at presentation [3]. Although neutropenia and recurrent bacterial infections are frequent and are considered to be a main cause of morbidity and mortality in patients with T-LGL leukemia, this was not the case with our patient. He had transfusion-dependent anemia, which is reported to occur in only 6% of patients [3, 4]. In addition to neutropenia (severe or moderate with recurrent infections) and associated autoimmune conditions that require therapy (most often rheumatoid arthritis), anemia (symptomatic or transfusion-dependent) is considered to be a therapy indication [3, 4, 6].

It is believed that sustained immune stimulation and a dysregulation of apoptosis underlies T-LGL leukemia pathogenesis, which is why immunosuppressive therapy remains the mainstay of treatment [4]. No standard therapy algorithm has been established, and

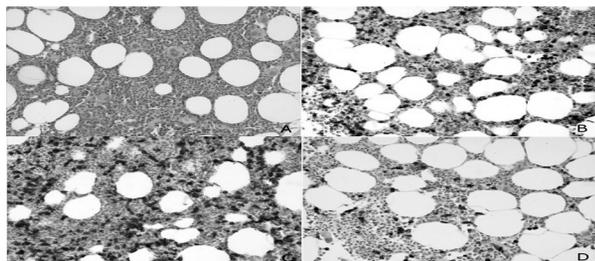


Figure 2. Bone marrow, magnification x 20 (A) Hematoxylin and eosin staining (B) CD3 expression (C) CD8 expression (D) CD 57 expression

Slika 2. (A) Koštana srž, uvećanje x 20 (A) hematoxilin-eozin bojenje (B) CD3 ekspresija (C) CD8 ekspresija (D) CD57 ekspresija

the current recommendations are based on small case studies and a recently published large French cohort study [3]. Lamy and Loughran [4] proposed methotrexate with/without prednisone and cyclophosphamide as a first-line therapy. However, they suggested that CsA could be used as an alternative first-line, particularly in patients with anemia, because in those cases, the overall response rate was 100%. It was first-line therapy in our patient. However, it initially led to only a partial response.

Methotrexate has been used with varying success with overall response rates of 44 to 87%, but generally it has obtained only a partial response [3, 4, 7]. Unfortunately, our patient only had a partial response. Few studies reported the use of purine analogs, polychemotherapy, antithymocyte globulin and other regimens in refractory or relapsed T-LGL leukemia [1, 2].

Because our patient did achieve a partial response during CsA therapy, we reintroduced the therapy; upon its reintroduction, it resulted in a favorable outcome. A complete clinical and hematological response was achieved. However, it did not result in an eradication of the leukemic LGL clone. The current opinion is that CsA should be given indefinitely to maintain a response [4]. However, after a 3-year CsA treatment in our patient, we excluded CsA due to slightly impaired kidney function. Osuji et al. [7] also reported that they were able to discontinue CsA treatment in three patients without any recurrence of cytopenias.

Conclusion

Our case confirms that cyclosporine therapy is effective in treating T-cell large granular lymphocyte leukemia but with a persistent underlying T-cell large granular lymphocyte clone. It also suggests that indefinite treatment may not be needed to maintain response.

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Case report
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EFFICIENCY OF SILDANEFIL MONOTHERAPY IN BENIGN PROSTATIC HYPERPLASIA

NOVA OPCIJA MEDIKAMENTOZNOG TRETMANA BENIGNE HIPERPLAZIJE PROSTATE I SIMPTOMA DONJEG URINARNOG TRAKTA

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Summary

Introduction. High incidences of benign prostatic hyperplasia and lower urinary tract symptoms have a high socioeconomic importance. There are several published studies which have proved the efficiency of phosphodiesterase type 5 inhibitors in treatment of benign prostatic hyperplasia and lower urinary tract symptoms. However, more studies are needed to make this therapy the standard option for treating benign prostatic hyperplasia and lower urinary tract symptoms. This study was aimed at exploring changes in International Prostate Symptom Score, post voiding residuum and maximal urine flow in benign prostatic hyperplasia and lower urinary tract symptoms patients treated by sildenafil for benign prostatic hyperplasia and lower urinary tract symptoms. **Material and Methods.** This study, which was conducted as a prospective, controlled, opened, randomized study, included 30 patients with benign prostatic hyperplasia and lower urinary tract symptoms. Research was conducted at the Department of Urology, Clinical Center of Vojvodina (November 2011 till November 2012). The inclusion criteria were as following: >45 years of age, International Prostate Symptom Score >3, prostatic specific antigen <10, normal urinalysis. The patients were periodically tested for International Prostate Symptom Score, maximal urine flow, and post voiding residuum. **Results.** Statistically significant changes were found in all parameters: mean International Prostate Symptom Score value improved from 12.8 to 8.6 (32.8% change), mean post voiding residuum value decreased from 49.4 ml to 40.2 ml (18.6% change), mean maximal urine flow value increased from 11.8 ml/s to 12.8 ml/s (8.5% change). **Conclusion.** Treatment of benign prostatic hyperplasia and lower urinary tract symptoms with a continuous low dose of sildenafil seems to be a good treatment choice for the patients with mild to moderate benign prostatic hyperplasia and lower urinary tract symptoms, especially in the patients with concomitant erectile dysfunction. The authors are aware that their study is limited by a small number of patients. Since there are not too many studies on this topic, they believe that their study will contribute to the determination of place and role of this treatment approach.

Key words: Prostatic Hyperplasia; Signs and Symptoms; Lower Urinary Tract Symptoms; Urinary Retention; Treatment Outcome; Sildenafil Citrate; Phosphodiesterase 5 Inhibitors

Sažetak

Uvod. Velika incidencija benigne hiperplazije prostate i simptoma donjeg urinarnog trakta imaju značajnu socioekonomsku važnost. Postoji više objavljenih studija koje dokazuju efikasnost *phosphodiesterase type 5* inhibitora u tretmanu benigne hiperplazije prostate/ simptoma donjeg urinarnog trakta. Neophodno je više studija da bi ova terapija postala standardna opcija u lečenju benigne hiperplazije prostate i simptoma donjeg urinarnog trakta. Cilj studije je utvrđivanje promena u Internacionalnom prostata Simptom Skoru, rezidualnom urinu i maksimalnom protoku urina pri *uroflow* merenju kod pacijenata sa benignom hiperplazijom prostate i simptomima donjeg urinarnog trakta tretiranih sildenafilom. **Materijal i metode.** Studija je sprovedena kao prospektivna, kontrolisana, otvorena i randomizirana, uključivala je 30 muškaraca sa benignom hiperplazijom prostate i simptomima donjeg urinarnog trakta. Istraživanje je sprovedeno na Klinici za urologiju, Kliničkog centra Vojvodine (Novembar 2011 - Novembar 2012). Inkluzioni kriterijumi: >45 godina starosti, Internacionalni prostata simptom skor >3, prostata specifičan antigen <10, sediment urina uredan. Svakom pacijentu su periodično određivani: Internacionalni prostata simptom skor, maksimalni protok urina i rezidualni urin. **Rezultati.** Utvrđene su statistički signifikantne promene u svim parametrima: pad srednje vrednosti Internacionalnog prostata simptom skora sa 12,8 na 8,6 (poboljšanje 32,8%), smanjenje srednje vrednosti rezidualnog urina sa 49,2 ml na 40,2 ml (poboljšanje 18,6%), uvećanje srednje vrednosti maksimalnog protoka urina sa 11,8 ml/s na 12,8 ml/s (poboljšanje 8,5%). **Zaključak.** Tretman benigne hiperplazije prostate i simptoma donjeg urinarnog trakta kontinuiranim niskim dnevnim dozama sildenafilu deluje kao korektna terapijska opcija, posebno kod pacijenata sa konkomitantnom erektilnom disfunkcijom. Autori su svesni da je studija limitirana malim brojem pacijenata. S obzirom na mali broj postojećih studija, smatramo da naša studija doprinosi određivanju mesta i uloge ove terapijske opcije u lečenju benigne hiperplazije prostate i simptoma donjeg urinarnog trakta.

Ključne reči: hiperplazija prostate; znaci i simptomi; simptomi donjeg urinarnog trakta; retencija urina; ishod lečenja; sildenafil; PDE5 inhibitori

Abbreviations

BPH	– benign prostatic hyperplasia
LUTS	– lower urinary tract symptoms
PDE	– phosphodiesterase
PDE5	– phosphodiesterase type 5
IPSS	– International Prostate Symptom Score
PVR	– post voiding residuum
Qmax	– maximal urine flow
PSA	– prostatic specific antigen
UA	– urinalysis
ED	– erectile dysfunction
NO	– nitro oxide
cGMP	– cyclic guanosine monophosphate
NOS	– nitric oxide synthase
nNOS	– neuronal nitric oxide synthase
eNOS	– endothelial nitric oxide synthase
iNOS	– immune cell nitric oxide synthase
Ca ⁺⁺	– calcium
DRE	– digital rectal examination
FDA	– Food and Drug Administration
DHT	– dihydrotestosterone

Introduction

Benign prostatic hyperplasia symptoms (BPH) result from: 1) mechanical obstruction - intrusion of enlarged, hyperplastic prostatic tissue into the urine pathway (bladder neck, urethra) and from 2) dynamic obstruction - hyper stimulated adrenergic receptors of smooth muscle and collagen of bladder neck and prostate leads to dynamic obstruction of urine flow. Drugs of choice for mechanical obstruction are 5 α -reductase inhibitors, whereas alpha blockers would be the most appropriate therapy for dynamic component of BPH.

Phosphodiesterase type 5 inhibitors (PDE5) are a group of drugs (sildenafil, tadalafil, vardenafil) that are widely used as a standard treatment for erectile dysfunction (ED) and some of them for pulmonary hypertension as well (sildenafil and tadalafil).

The efficiency of PDE5 inhibitors in benign prostatic hyperplasia and lower urinary tract symptoms (BPH/LUTS) treatment is nowadays being widely studied. Their mechanism of action is by inhibiting autonomous stimulation of smooth muscle and collagen (inhibition of dynamic obstruction). The mechanism of PDE5 inhibitors action involves the nitro oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway. NO is an important non-adrenergic, non-cholinergic neurotransmitter in the human body. It is involved in transmission of neural signals in the urinary tract as well. NO is produced from amino acid L arginine under the influence of nitro oxide synthase (NOS). In human body they are classified by tissue origin as: neuronal NO synthase (nNOS), endothelial NO synthase (eNOS) and NO synthase of immune cells origin (iNOS).

Once NO has been produced, it goes into the cells and stimulates the synthesis of cyclic guanosyn monophosphate (cGMP) by enzyme guanylyl cyclase. cGMP activates protein kinase, ion channels, and cGMP binding phosphodiesterase which leads to the relaxation of smooth muscles by decreasing concentra-

tion of intracellular Ca⁺⁺ and desensibilisation of contractile proteins [1]. The effect of cGMP is discontinued by PDE isoenzyme which catalyzes the hydrolysis of cGMP into the inactive form. PDE5 inhibitors inhibit PDE isoenzyme and increase the concentration and activity of intracellular cGMP and thus, decrease the tonus of smooth muscle of detrusor, prostate and urethra. Eleven different PDE esterases have been discovered so far, among which are PDE esterases 4 and 5 predominant in the transitional zone of human prostate, bladder and urethra [2, 3]. It is possible that NO is involved in micturition also by the inhibition of reflex pathways in the spinal cord [4].

This study was aimed at assessing any changes in voiding parameters: International prostate symptom score (IPSS), post voided residuum (PVR) and maximal urine flow (Qmax), which were assessed at the start of the study before treatment, at the middle of study and at the end of three-month period during which the patients were on sildenafil treatment.

Material and Methods

This research was conducted as a prospective, controlled, opened and randomized study, which included 30 men with BPH/LUTS. It was done at the Clinic for Urology, Clinical Centre of Vojvodina in one year time frame (November 2011 until November 2012). The inclusion criteria were: >45 years of age, IPSS >3, PSA <10, normal urinalysis (UA), digital rectal examination (DRE) with no suspicion of cancer. The exclusion criterion was having a contraindication for using PDE5 inhibitors.

Assessment of Parameters of Voiding

Each study participant underwent physical examination (digitorectal examination, brief neurological examination) during the first visit and completed the IPSS questionnaire form. The IPSS questionnaire has seven questions which are the same as American Urological Association Symptom index (AUA-SI) plus the eighth question known as a bother score, which is designed to estimate disease specific quality of life (QoL). Each question can yield 0-5 points, the minimal and maximal number of points being 0 and 35, respectively. Based on the first seven questions and severity of symptoms all patients were classified into three groups: group I – the patients with mild symptoms (0-7 points), group II – the patients with moderate symptoms (8-19 points) and group III – the patients with severe symptoms (20-35 points). Each participant had to have at least 3 or more points to qualify for the study. Once patients had been qualified for the study, the assessment of Q max and PVR was performed. For the assessment of Qmax, Uroflow study had to be done by means of Solar urodynamic machine – Medical Measurements Systems (the Netherlands). Each participant was asked to urinate at least 150 ml of urine to have valid uroflow study and Q max value determined. The patients were left alone in the examination room (to prevent social inhibition of micturition) and used the

previously activated Uroflow device. The patient urinated in standing position with the comfort height level of urinal (should the urinal be too high, it would be uncomfortable for the patient to urinate and the results of the study would not be valid). Once the patient finished urinating, PVR immediately was determined by means of the Ultrasound – SIEMENS – Sonoline Prima with convex abdominal ultrasound probe of 3.5 MHz. Having passed all examinations and tests, and thus satisfied inclusion criteria, the patient was given a six-week supply of 1x25 mg of sildenafil to have enough up to the next checkup. At the first checkup six weeks after the introduction of treatment, the same procedures (IPSS, PVR and Qmax) were repeated in the same manner and under the same conditions. The patients were provided with another six week supply of sildenafil at a dose of 1x25 mg per a day and then came for the second, i.e. the last checkup and underwent the same diagnostic procedures (IPSS, PVR and Qmax) under the same conditions.

Results

The research results are given in **Tables 1-3**.

Table 1. Mean values for International Prostate Symptom Score, post voiding residual and maximal uroflow for all 30 patients at the beginning of study

Tabela 1. Srednje vrednosti za Internacionalni prostata simptom skor, rezidualni urin i maksimalni protok urina za 30 pacijenata na početku istraživanja

30 patients 30 pacijenata	PVR in ml/rezidualni urin u ml	Qmax/maksimalni protok urina ml/s	IPSS value/Internacionalni prostata simptom skor
Values at the beginning of study Vrednosti na početku istraživanja	49,4	11,8	12,8

Table 2. The mean values for IPSS, PVR and Qmax of all patients at the first checkup (six weeks upon starting sildenafil treatment)

Tabela 2. Prikaz srednje vrednosti Internacionalnog prostata skora, rezidualnog urina i maksimalnog protoka urina pacijenata prilikom prve kontrole (nakon šest nedelja terapije sildenafilom)

30 patients 30 pacijenata	PVR in ml/rezidualni urin u ml	Qmax/maksimalni protok urina ml/s	IPSS value/vrednost Internacionalnog prostata simptom skora
Values after six weeks of sildenafil/Vrednosti nakon 6 nedelja terapije sildenafilom	41.0	12.6	9.0

Table 3. Mean values for International Prostate Symptom Score, post voiding residual and maximal uroflow for all patients at the end of study (12 weeks after the introduction of sildenafil treatment)

Tabela 3. Prikaz srednje vrednosti Internacionalnog prostata skora, rezidualnog urina i maksimalnog protoka urina pacijenata prilikom kontrole na kraju studije (nakon dvanaest nedelja terapije sildenafilom)

30 patients 30 pacijenata	PVR in ml/rezidualni urin u ml	Qmax/maksimalni protok urina ml/s	IPSS value/Vrednost Internacionalnog prostata simptom skora
Values after twelve weeks of sildenafil/Vrednosti nakon 12 nedelja terapije sildenafilom	40.2	12.8	8.6

Discussion

Benign prostatic hyperplasia results in the enlargement of the prostate and may lead to the reduced urinary flow from the urinary bladder. BPH is considered to be a normal part of aging in men and it is hormonally dependent on the testosterone and dihydrotestosterone (DHT) production. It is estimated that 50% of all men at the age 60 have the histological form of BPH. This percentage goes up to 90% at the age of 85 [5].

The administration of PDE5 inhibitors for BPH/LUTS treatment was officially approved by Food and Drug Administration (FDA) in the USA three years ago. However, there are still contradictory data regarding the efficiency level of BPH/LUTS treatment by PDE5.

In our study we have found that the mean value of IPSS improved from 12.8 at the beginning of study to 9.0 (29.6% change) and 8.6 (32.8% change) at the first checkup (six weeks on sildenafil treatment) and at the second/last checkup (after 12 weeks on sildenafil treatment), respectively. In most randomized, placebo controlled studies, which were conducted

lately, the efficiency of all three PDE5 inhibitors was observed through IPSS, Qmax and PVR changes [6–15]. Maximal time frame of studies was 12 weeks. In all of these studies, it was concluded that IPSS significantly improved, from 17% up to 35%.

The uroflow/Qmax mean value changed in our study from 118 ml/s at the beginning of study to 126 ml/s (improvement of 0.8 ml/s - 6,8% change) at the first checkup (six weeks on sildenafil treatment) and 12.8 ml/s (improvement of 1.0 ml/s - 8.4% change) and at the second, i.e. last checkup (after 12 weeks on sildenafil treatment). Our findings were not confirmed in most other studies [6–14]: Qmax was not significantly different comparing to placebo.

Changes within the third parameter were also observed in our study: the mean PVR value was 49.4 ml at the beginning of study and during sildenafil treatment it decreased to 41.0 ml (17% change) and 40.2 ml (18.6% change) at the first checkup (six weeks on sildenafil treatment) and at the second, i.e. last checkup (after 12 weeks on sildenafil treatment), respectively. In almost all other studies there were no significant changes of PVR [6–14]. There are few studies with significant improvement of Qmax. The study done by Guler C et al. [15] showed significant improvement in the mean value of Qmax in the patients treated by sildenafil: 29 out of 38 patients (76%) had improvement of Qmax and it was 38% on average (from 11.4 ml/s to 15.7 ml/s), whereas no significant change in Qmax was observed in the controls. A significant Qmax improvement was found in a study done by Guven E et al. as well (from 15.6±6.8 ml to 19.3±7.2 ml/s) [16].

Besides, there are three studies which compared the efficiency of sildenafil monotherapy vs. sildenafil plus alpha blocker (alfuzosin or tamsulosin) combined therapy. There are three studies that com-

pared efficiency of PDE5 inhibitors (sildenafil or tadalafil) with or without alpha blockers (alfuzosin or tamsulosin) [8, 11, 12]. These studies were conducted on a limited number of patients. Their duration was relatively short-up to six or twelve weeks. Treatment with the combination of these drugs led to a bigger improvement in IPSS, Qmax and PVR than when each drug was given as a mono therapy. However, only the study done by Bechar A et al. [11] revealed significant changes in the parameters. The study sample consisted of 27 patients, who were divided into two groups: those receiving only tamsulosin and those treated with tamsulosin plus tadalafil. The authors found a significant change in IPSS in both groups from 18.4 to 12.7 and 10.2. The improvement was bigger in the patients who were treated with tamsulosin plus tadalafil. The improvement was also observed in Qmax and PVR in both groups of patients (Qmax from 9.6 ml/s to 11.7 ml/s and 12.6 ml/s; PVR from 60 ml to 24.8 ml and 21.3 ml). There was no significant difference in these two parameters between the groups.

Conclusion

Treatment of benign prostatic hyperplasia and lower urinary tract symptoms with continuous low dose of sildenafil seems to be a good treatment choice in the patients with mild to moderate benign prostatic hyperplasia and lower urinary tract symptoms, especially in those patients with concomitant erectile dysfunction. The authors are aware of limited value of this study due to a small number of included patients. However, since there are not too many studies dealing with this issue, we assume that our study may contribute to further determination of the place and role of this treatment approach.

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THE REGULATION ROLE OF CAROTID BODY PERIPHERAL CHEMORECEPTORS IN PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL CONDITIONS

*ULOGA KAROTIDNIH TELAŠCA KAO PERIFERNIH HEMORECEPTORA U REGULACIJI
FIZIOLOŠKIH I PATOFIZIOLOŠKIH STANJA*

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Summary

Introduction. The major oxygen sensors in the human body are peripheral chemoreceptors, also known as interoreceptors- as connected with internal organs, located in the aortic arch and in the body of the common carotid artery. **Chemoreceptor function under physiological conditions.** Stimulation of peripheral chemoreceptors during environmental hypoxia causes a reflex-mediated increased ventilation, followed by the increase of the muscle sympathetic activity, aiming to maintain tissue oxygen homeostasis, as well as glucosae homeostasis. Besides that, peripheral chemoreceptors interact with central chemoreceptors, responsible for carbon dioxide changes, and they are able to modulate each other. **Chemoreceptor function in pathophysiological conditions.** Investigations of respiratory function in many pathological processes, such as hypertension, obstructive sleep apnea, congestive heart failure and many other diseases that are presented with enhanced peripheral chemosensitivity and impaired functional sympatholysis ultimately determine the peripheral chemoreceptor role and significance of peripheral chemoreceptors in the process of those pathological conditions development. Considering this, the presumed influence of peripheral chemoreceptors is important in patients having the above mentioned pathology. **Conclusion.** The importance and the role of peripheral chemoreceptors in the course of the breathing control is still controversial, despite many scientific attempts to solve this problem. The main objective of this review is to give the latest data on the peripheral chemoreceptor role and to highlight the importance of peripheral chemoreceptors for maintaining of oxygen homeostasis in patients with hypoxia caused by either physiological or pathological conditions.

Key words: Carotid Body; Chemoreceptor Cells; Anoxia; Ventilation; Exercise; Hypertension; Oxygen; Homeostasis

Sažetak

Uvod. Periferni hemoreceptori glavni su senzori za kiseonik u ljudskom telu, a takođe su poznati i kao interoreceptori jer su povezani sa unutrašnjim organima koji se nalaze u luku aorte, kao i u telu a. carotis communis. **Uloga perifernih hemoreceptora u regulaciji fizioloških stanja.** Zna se da stimulacija perifernih hemoreceptora u eksperimentalnim uslovima hipoksije, fizičkog napora, pa čak i tokom nekih bolesti izaziva refleksno posredovano pojačanje ventilacije, koje prati povećanje mišićne simpatičke aktivnosti, sa ciljem održavanja tkivne homeostaze kiseonika, kao i homeostaze glukoze. Osim toga, periferni hemoreceptori interreaguju sa centralnim hemoreceptorima koji su odgovorni za promene u nivou ugljen-dioksida i oni se međusobno nadopunjuju. **Uloga perifernih hemoreceptora u regulaciji patoloških stanja.** Istraživanja respiratorne funkcije u mnogim patološkim procesima, kao što su hipertenzija, opstruktivna spiv-apnea, kongestivna srčana insuficijencija i mnoge druge bolesti i stanja, a koja se odlikuju povećanom perifernom hemosenzitivnošću i poremećajem funkcije simpatičkog nervnog sistema, jednoglasno naglašavaju ulogu perifernih hemoreceptora tokom ovih procesa. Imajući prethodno navedeno u vidu, uloga perifernih hemoreceptora je važna kod pacijenata sa navedenim bolestima. **Zaključak.** Značaj perifernih hemoreceptora u kontroli disanja je i dalje nepoznat, uprkos brojnim naučnim pokušajima da se reši ovo pitanje. Glavni cilj ovog rada bio je sažet prikaz najnovijih istraživanja o značaju hemoreceptora, osvetljavajući njihovu ulogu u održavanju homeostaze kiseonika kod bolesnika sa hipoksijom uzrokovanom bilo fiziološkim ili patofiziološkim stanjima.

Ključne reči: karotidna telašca; hemoreceptorske ćelije; hipoksija; vežbanje; hipertenzija; kiseonik; homeostaza

Abbreviations

PC	– peripheral chemoreceptors
CC	– central chemoreceptors
HF	– heart failure
OSA	– obstructive sleep apnea
MSNA	– muscle sympathetic activity
HVR	– hypoxic ventilatory response
RMT	– respiratory muscle training
CB	– carotid body
CO ₂	– carbon dioxide
O ₂	– oxygen

Introduction

Respiration, as measured with pulmonary ventilatory rate (volume per minute), is controlled voluntarily and involuntarily. Voluntary control depends on the brain condition (emotional state, temperature, free will, etc) and is provided by cerebral cortex.

Involuntary control mechanisms of the ventilatory pattern are not yet fully understood, thus involving convergence of signals coming from the respiratory control centers located in medulla oblongata and pons, being integrated in the anterior horn cells of the spinal cord. Involuntary ventilatory rate is determined by pH-sensing central chemoreceptors of the surface of medulla oblongata and by oxygen- and carbon dioxide-sensing peripheral chemoreceptors, with the impulse transferred to the glossopharyngeal nerve (nervus IX) and the vagus nerve (nervus X). The other way of the involuntary ventilation regulation is by mechanoreceptors located in the airways and parenchyma.

Peripheral chemoreceptors (PC), located in the body of the common carotid artery and the aortic arch, are the major oxygen sensors in the human body [1]. They are essential in low-oxygen-characterized situations, prompted to increase in their number and size by low access to oxygen. Although the mechanism is not completely understood yet, it is believed that type II cells, previously thought to have only a supportive role, retain properties of the stem cells, able to differentiate into type I transducer cells [2]. The specific signal of transduction comes through depolarization, caused by inhibition of the potassium channels. The AMP-activated protein kinase (AMPK) opens and closes potassium channels via phosphorylation in oxygen sensing of the type-1 cells [3]. PC work along with central chemoreceptors (CC), which monitor the blood carbon dioxide (CO₂) level in the cerebrospinal fluid around the brain. Altogether, in low-oxygen situations, they send nerve signals to the medullar vasomotor center.

Stimulation of PC causes a reflex-mediated increase in ventilation, followed by the increasing of the muscle sympathetic activity (MSNA), with the non-contracting skeletal muscles, gut and kidneys vasoconstriction, aiming to redirect the peripheral blood into the active muscles [1, 4]. It is a well known fact that environmental hypoxia, exercise or some pathophysiological conditions can lead to the rapid changes in oxygen (O₂) supply or demand. Cardiorespiratory reflex plays the important role in maintaining the tissue O₂ homeostasis [5]. The impor-

tance and the role of PC in the breathing control is still controversial, regarding previous studies of the respiratory function during hypoxia, exercise and some particular diseases. There have been many attempts at solving this question, but the exact role of the PC in the breathing control is still unclear.

Bearing all of the above mentioned in mind, the main objective of this article is to overview recent PC studies, as well as to highlight the importance of PC for the maintenance of the O₂ homeostasis during hypoxia associated both with physiological and pathological conditions.

The electronic database MEDLINE was searched from January 1982 to July 2014, with the following keywords: peripheral chemoreceptors, carotid body, hypoxia, ventilation, exercise, hypertension and chronic heart failure, by choosing articles with different-aged human subjects, between 16 and 74 years of age. This systematic review included healthy, physically inactive people, then people with mild hypertension, congestive heart failure, obstructive sleep apnea and people who underwent therapeutic carotid body resection, as well as professional athletes.

After the preliminary literature search by the selected keywords, there were 2,164 references identified in MEDLINE. The advanced search scan produced 114 potentially relevant studies, which were thoroughly analyzed. Finally, after thorough review and consideration, the total number of papers included in this article was 43.

Function of Chemoreceptor under Physiological Conditions

The Relative Contribution of the PC to the Hypoxic Ventilatory Response

Sympathetic activity is increased during physical activity, leading to redistribution of the blood flow from the inactive muscles and vascular beds into the active muscles [4]. Previous studies have shown enhanced sensitivity of PC during exercise [6, 7], but PC contribution to the muscle blood flow redirection in the terms of hypoxia in humans is still questionable.

Stickland et al. conducted a study on seven healthy participants who were exposed to short and repeated bouts of hyperoxia to demonstrate the role of PC on MSNA at rest and during rhythmic dynamic handgrip exercise [1]. They showed that transient PC inhibition reduced ventilation, but had no effect on either the femoral blood flow or the arterial pressure, neither at rest nor during leg extension exercise. Besides, low-dose dopamine inhibits peripheral chemoreceptors and attenuates the hypoxic ventilatory response (HVR) in humans. However, it is unknown whether it also modulates the hemodynamic reactions to acute hypoxia, cardiac baroreflex sensitivity (BRS) and if there is any effect of dopamine withdrawal [8].

Although there are limited results of the PC involvement during hypoxia, the important role of PC in the skeletal muscles blood flow regulation has been demonstrated during normoxic state of exercise [1]. Furthermore, an advanced study performed by Stickland et al. with similar methodology as the

previous one was conducted on 13 healthy subjects (9 men, 4 women), evaluated at rest and during constant rhythmic handgrip exercise [9]. PC were inhibited using hyperoxic gas inhalation, whereas hypoxic gas inhalation was used for its activation.

Their results pointed at the PC contribution to the regulation of the skeletal muscle blood flow during normoxic exercise. On the other hand, PC stimulation seems to be withdrawn under hypoxia by local vasodilatory factors, confirming once again the limited role of PC in conditions characterized by hypoxia. In addition, afferent signals from the skeletal muscles in contraction are the important source of the brain stem neural input during exercise. These exercise-induced signals are generated by the activation of group III (predominantly mechanically sensitive A- δ fibres) and group IV (predominantly metabolically sensitive C fibres) skeletal muscle afferents which reflexively increase the arterial blood flow pressure (ABP) and the heart rate. Hemodynamic regulation by this reflex loop, termed as the exercise pressor reflex, is primarily mediated by the increased efferent sympathetic nerve activity [9].

Series of studies conducted by Stickland et al. (2008, 2011) have shown the sensitization of PC during exercise. Transient PC inhibition occurring in healthy individuals during physical activity leads to the inhibition of muscle sympathetic nerve activity, leading to blood vessels vasodilatation as a consequence [1, 10].

A similar study done by Housienne et al. with simultaneous metaboreflex and chemoreflex activation was conducted on 13 healthy participants randomized into three groups: group I had PC activation with isocapnic hypoxia, group II had isometric handgrip exercise in normoxia and group III had metaboreflex activation in exercise during hypoxia [11]. The achieved results showed that metabo- and chemoreceptors exert different effects on sympathetic response during hypoxemic exercise. More potent stimulus for MSNA was the exercise alone, as compared to PC alone.

Gujic et al. have come to a similar observation, by examining 15 healthy, physically inactive young males. Three-minute tests were performed in 4 different conditions: during normoxic test, normoxic exercise, hypoxic exercise and hypoxia at rest. The results have confirmed the previously reported data on sympathetic baroreflex sensitivity, mostly determined with metaboreceptor activation, while PC was shown to be mainly responsible for the time between two consecutive R waves in the electrocardiogram (R-R) interval operating point shortening [12].

Previous studies have shown oscillation in PC activity, with the influence on breathing [13]. Moreover, recent studies have demonstrated enhancement of human hypoxic ventilatory response (HVR) during short-duration intermittent hypoxia [14]. HVR is also associated with higher PC response to acute hypoxia [15]. However, it still remains controversial, unresolved and unclear whether there are differences in PC sensitivity between short-duration intermittent hypoxia and long-duration intermittent hypoxia. Foster et al. examined 17 healthy male participants who were randomly ex-

posed either to short- or long-term duration of intermittent hypoxia. Their results showed that increased HVR has no functional significance on PC sensitivity.

There are only a few studies on the role of PC in older adult humans, one of them was conducted by Vovk et al. [16]. They compared 3 groups with 5 members in each of them, representing young men and women, only young males and five older males. They were re-exposed to brief hypoxic pulses after 20 minutes of sustained eucapnic hypoxia. Their results were in compliance with investigational data from Smith et al, showing that HVR characteristics are unswayed by age in healthy and active people [17].

Peripheral Chemoreceptors and Exercise

The main characteristic of a professional athlete is the possibility to achieve series of physiological adaptations, enabling better performance [18]. Exercising muscles are in need of a prompt, but very precise response of the respiratory and cardiovascular system in order to provide fine matching of the blood perfusion to metabolic demands [19–22]. PC reflexes are involved in ventilatory stimulation during exercise [23]. Changes of ventilation are passed through the following 3 phases: a rapid increase in ventilation that occurs at the exercise (I), an exponential increase in ventilation that follows afterwards (II) and a steady state coming at last (III) [24, 25]. During an exaggerated near-maximal and maximal physical activity, the ability of the respiratory system to maintain homeostasis is challenged. Therefore, this kind of physical activity leads to arterial hypoxemia which can be the limiting factor for exercise in that case [26].

Blood flow through intrapulmonary arteriovenous anastomoses (IPAVA) is increased with exposure to acute hypoxia and has been associated with pulmonary artery systolic pressure (PASP). The principal stimulus ultimately responsible for regulating IPAVA recruitment is unknown; however, the literature suggests that pulmonary blood flow, pressure or alveolar hypoxia is a probable mediator. In humans, progressive hypoxia appears to promote a graded increase in the magnitude of microbubble passage despite a small increase in PASP indicating that alveolar hypoxia may be more important than the pulmonary vascular pressure [27].

These responsiveness mediator mechanisms are complex and, though they have been much elucidated in the previous literature, the PC contribution to autonomic exercise response, especially in the population of professional athletes, has not received much attention [28].

There are few studies aimed at this relatively new concept in the exercise physiology. Data from previous studies have emphasized the PC role in the ventilatory stimulation during phase II and III [29–33]. A study done by Stulbarg et al. has shown the decreased ventilatory response to exercise in subjects with carotid body (CB) resection [30].

In addition, those studies have shown that, as compared to the untrained individuals, well-trained endurance athletes have lower peripheral chemosensitivity and lower ventilation per minute in the

course of the exercise [34–38]. Specific mechanism of the reduced peripheral chemosensitivity in physiologically active individuals still remains the key question in the exercise physiology.

McMahon et al. examined the effects of respiratory muscle training (RMT) on peripheral chemosensitivity [31] in 20 trained male cyclists, randomized into the RMT group and the control group. Peripheral chemosensitivity was reduced significantly in RMT group as compared to the controls ($-5, 8 \pm 6, 0\%$ vs. $0, 1 \pm 4, 6\%$, $p < 0, 5$). This reduction in chemosensitivity was not significantly correlated with the exercise ventilation or the cycling endurance. They suggested the possibility that PC role in the ventilation control in the course of exercise was not so important. A study done by Levine et al. has also found no significant change in PC response due to hypoxia at rest [32].

According to the above listed studies, the influence of physical activity on PC is not clear enough, as supported by controversial results. It is still not clearly known whether peripheral chemosensitivity differs at the normal and higher level of physical activity, as presented in professional athletes. Ventilation during exercise is a particular challenge—still not resolved, debating on the excitatory or inhibitory role of the PC (pointing out that they are not the only oxygen sensing cells that can respond in the stress periods) [33].

Function of Chemoreceptor in Pathophysiological Conditions

Previous studies have shown the increased sympathetic activity in many pathological processes, such as hypertension, obstructive sleep apnea, congestive heart failure and many other diseases, which throws new scientific light on the future studies which should be aimed at determining the PC role and significance in those pathological conditions.

The main characteristics of the majority of cardiovascular and other diseases are enhanced peripheral chemosensitivity and impaired functional sympatholysis [35, 36]. Considering this, the presumed influence of the PC on the exercise tolerance level is important in patients with the above mentioned pathology.

According to several studies examining pathology of cardiovascular and other diseases, there is a number of potential explanations for the pathophysiology of the exercise tolerance. Izdebska et al. examined the PC reflex reactivity in young mildly hypertensive men (HTS) [37, 38]. Being the first in this field, they compared mildly hypertensive men and normotensive male controls before the dynamic exercise physical therapy and 3 months after it; their results confirmed the enhanced PC drive in hypertensive patients [39–43], allowing the possibility of important clinical conclusion, as the pressure chemoreceptor reflex contributes to a possible effect of the regular physical activity on arterial hypertension treatment.

A single bout of mild to moderate exercise can lead to a postexercise decrease in blood pressure in hypertensive individuals, called postexercise hypotension. It can last for up to 13 hours in humans, and could be an effective non-pharmacological anti-

hypertensive strategy. Despite the well-documented blood pressure-lowering effect of the exercise, the central neuronal mechanisms have only recently been revealed [44].

Lately, Sinski et al. have found out that reduced sympathetic activity in hypertensive patients by PC deactivation immediately decreases blood pressure in humans [39].

Literature data about the role of the peripheral chemosensitivity in serious cardiovascular disorders and pathophysiological conditions are also available. Previous studies have shown that the patients with chronic heart failure (HF) have an increased sympathetic nerve activity, leading to the highest mortality [45]. Some authors have also speculated on the augmented peripheral chemosensitivity underlying the increased sympathetic nerve activity. Nunes Alves et al. have studied autonomic control and PC role in HF patients lately, showing that systemic hypoxia PC stimulation in HF patients leads to an increase in the sympathetic nerve activity. They have found increased MSNA control by PC, even in mild changes of the oxygen saturation [46].

Seventy years ago it was thought that PC were responsible for asthma, so CB resection was one of therapeutic interventions in asthma. Moreover, scientists conducted physiological studies on human subjects over 20 years of age after CB surgical removal. Kimura's et al. conducted such a study on bronchial asthma patients who underwent therapeutic CB resection [45]. Unilateral CB resected patients showed biphasic ventilatory response pattern, while bilateral CB resected patients did not demonstrate the same ventilatory response. Once again, the important PC influence on ventilation stimulation and HVR control was highlighted.

Studies conducted by Paton et al. and Ribeiro et al. emphasized the idea that inhibition of PC caused by denervation or even surgical removal might represent the advanced method of treatment for those disorders [47, 48].

Although there is a significant attenuation of hypoxic ventilatory response in CB resected subjects as reported by previous studies, there are some precariousness that should be noted. Available data about the non-carotid body chemoreceptors mechanism involved in upregulation are scarce. Almost every cell in our body has chemoreceptors, since they need to control local pO_2 and pCO_2 tonically. As the existing skeletal muscles have chemoreceptors that drive the exercise pressor reflex, massive sympathoexcitation is driven during exercise.

It still remains unresolved whether the above mentioned attenuation comes as a consequence of asthma, or due to non-carotid body chemoreceptor compensatory upregulation, or deficiency.

Regulation of breathing sleeping disorders, such as the obstructive sleep apnea (OSA), has frequently been studied recently. Narkiewicz et al. have studied male OSA patients, emphasizing the striking HVR augmentation [49]. Similar results have also been obtained in Cistulli and Sullivan's studies [50]. Increased peripheral chemosensitivity could be explained by augmented HVR. Contrariwise, a number of studies have shown depressed HVR in those patients [51, 52].

It is possible that increased peripheral chemosensitivity leads to enhancement of ventilatory response in the early stages of this breathing disorder. This initial increase is followed by PC desensitization with insensitivity to hypoxia. Bearing in mind the above mentioned facts, further examination of PC desensitization during intermittent hypoxia should be done.

Conclusion

Chemoreceptors are powerful modulators of the ventilatory and circulatory response in terms of hypoxia, not only in certain physiological conditions, but also in some health disorders. Studies reviewed in this paper evaluated the role of peripheral chemoreceptors in hypoxia-induced ventilation stimulation. In addition, the peripheral chemoreceptors role in stimulation of breathing during exercise is undoubtedly important; however, the reviewed studies including human subjects have only yielded the indirect peripheral chemoreceptors function. As we are unable to get information from live, physically active humans, we must rely on indirect evidence, with the hope that more advanced techniques are going to give us more information.

We should bear in mind additional chemoreceptors, called „paraganglions“, representing tissues similar to peripheral chemoreceptors, placed in the thorax and abdomen. In the population with surgically removed carotid body in order to treat pulmonary di-

seases, which is characterized by chronic absence of peripheral chemoreceptors, hypoxic ventilatory response maintenance is upregulated by non carotid body chemoreceptors. The exact mechanisms for this regulation are poorly investigated, waiting to be examined in the future. Though available evidence suggests increased peripheral chemosensitivity in the early stages of a number of pathophysiological conditions (such as obstructive sleep apnea, chronic heart failure or certain forms of hypertension), the precise mechanism still remains to be explored. There is a potential protective role of peripheral chemoreceptors in the course of the disease progression. The underlying mechanisms for maladaptive responses are unclear. A new avenue for research has been opened by this review, which should clarify further the peripheral chemoreceptors role in subtle tuning between the blood flow and the peripheral chemoreceptors affection. The future for the upcoming studies lies in the new imaging techniques, capable of introducing fine communication relationships between the peripheral chemoreceptor cells and the sensory nerve endings. By revealing peripheral chemoreceptors and hypoxic ventilatory response regulation interaction, the successful completion of those future surveys would certainly produce a deeper vision of the peripheral chemoreceptor-linked pathophysiological process and possible therapeutic approaches.

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NIKOLA TESLA AND MEDICINE: 160TH ANNIVERSARY OF THE BIRTH OF THE GENIUS WHO GAVE LIGHT TO THE WORLD - PART II

*NIKOLA TESLA I MEDICINA – 160 GODINA OD ROĐENJA GENIJA
 KOJI JE SVETU PODARIO SVETLOST – II DEO*

Danijela VUČEVIĆ, Drago ĐORĐEVIĆ and Tatjana RADOSAVLJEVIĆ

Summary

Introduction. Nikola Tesla (1856 - 1943) was a genius inventor and scientist, whose contribution to medicine is remarkable. Part I of this article reviewed special contributions of the world renowned scientist to the establishment of radiology as a new discipline in medicine. This paper deals with the use of Tesla currents in medicine. **Tesla Currents in Medicine.** Tesla's greatest impact on medicine is his invention of a transformer (*Tesla coil*) for producing high frequency and high voltage currents (*Tesla currents*). Tesla currents are used in diathermy, as they, while passing through the body, transform electrical energy into a therapeutic heat. In 1891, Tesla passed currents through his own body and was the first to experience their beneficial effects. He kept correspondence on electrotherapy with J. Dugan and S. H. Monell. In 1896, he used high frequency currents and designed an ozone generator for producing ozone, with powerful antiseptic and antibacterial properties. Tesla is famous for his extensive experiments with mechanical vibrations and resonance, examining their effects on the organism and pioneering their use for medical purposes. Tesla also designed an oscillator to relieve fatigue of the leg muscles. It is less known that Tesla's inventions (Tesla coil and wireless remote control) are widely used in modern medical equipment. Apart from this, wireless technology is nowadays widely applied in numerous diagnostic and therapeutic procedures. **Conclusion.** Nikola Tesla was the last Renaissance figure of the modern era. Tesla bridged three centuries and two millennia by his inventions, and permanently indebted humankind by his epochal discoveries.

Key words: History of Medicine; Famous Persons; Portraits as Topic; Electric Stimulation Therapy; Ozone; Radio Waves; Diathermy; Wireless Technology

Introduction

Nikola Tesla (1856 - 1943) was a genius inventor and scientist whose contribution to the development of medicine is outstanding. Part I of this paper reviewed

Sažetak

Uvod. Nikola Tesla (1856–1943) bio je genijalni pronalazač i naučnik koji je izuzetno doprineo razvoju medicine. U našem prethodnom radu opisan je poseban doprinos ovog naučnika svetskog glasa utemeljenju radiologije kao nove medicinske discipline. U ovom radu dat je osvrt na primenu Teslinih struja u medicini. **Primena Teslinih struja u medicini.** Teslin izum koji je najznačajnije doprineo medicini je transformator (Teslin kalem) za stvaranje visokofrekventnih i visokonaponskih struja (Teslinih struja). Tesline struje se koriste u postupcima medicinske dijatermije, pri čemu se prilikom njihovog prolaska kroz organizam električna energija pretvara u toplotnu, te se na taj način zagrevanjem tkiva u unutrašnjosti organizma postiže terapijski efekat. Poznato je da se Tesla dopisivao sa lekarima elektroterapeutima, Duganom i Monelom. Podstaknut korišćenjem visokofrekventnih struja, Tesla je 1896. godine konstruisao ozonski generator, koji služi za dobijanje ozona, agensa sa snažnim baktericidnim svojstvima. Nikola Tesla je ispitivao i uticaj mehaničkih vibracija i rezonancije na organizam i prvi ih primenio u medicinske svrhe. S tim u vezi, osmislio je oscilator koji je koristio za suzbijanje umora u nožnim mišićima. Malo je poznato da su Teslini pronalasci (transformator i sistem za bežično daljinsko upravljanje) nezaobilazni deo korišćenja medicinske opreme. Pored toga, bežična tehnologija u današnje vreme se takođe u potpunosti primenjuje u sklopu brojnih dijagnostičkih i terapijskih procedura. **Zaključak.** Nikola Tesla je poslednja renesansna ličnost modernog doba. Svojim grandioznim delom spojio je tri veka i dva milenijuma i večno zadužio čovečanstvo.

Ključne reči: istorija medicine; poznate ličnosti; portreti; elektroterapija; ozon; radio talasi; dijatermija; bežična tehnologija

his remarkable contribution to the establishment of radiology as a new discipline in medicine. Part II reviews the application of Tesla currents in medicine.

Abbreviations

AIEE – American Institute of Electrical Engineers

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Tesla Currents in Medicine

A man is born to work, to suffer and to fight; he who doesn't, must perish. Of all the frictional resistance, the one that most retards human movement is ignorance. If you don't know how, observe the phenomena of nature, they will give you clear answers and inspiration. The progress and development of man essentially depends on ingenuity. The most important product of the creative mind is an invention. Its final goal is an overall mastering of the mind over the nature and the exploitation of all its forces for the needs of humankind. An inventor's endeavor is essentially life saving. Whether he harnesses forces, improves devices, or provides new comforts and conveniences, he is adding to the safety of our existence.

Nikola Tesla

Nikola Tesla and Electrotherapy

Historians of medicine consider high-frequency and high voltage currents to be the most important Tesla's contribution to medicine [1]. By the use of these currents, called *Tesla currents*, it is possible to produce heat in tissues of the human body (electrotherapy) [2, 3]. Today, Tesla currents are used in medical diathermy, where electrical energy is converted into heat and thus warms the tissue inside the body [2–6]. These currents are used to treat disorders of the locomotor system, inflammatory processes and chronic diseases, as well as in gynecology and surgery [3]. A similar procedure is called *teslization*, where the human body is subjected to a high frequency electric field of Tesla currents generated by a Tesla coil (“skin effect”) [2–7].

Before Tesla currents were used, direct current electrotherapy had been associated with painful muscle spasms, and even fatalities [8]. At that time, there were ways to generate extremely high-frequency damped oscillations [5]. However, Tesla was the first who succeeded, first using mechanical generators, and then oscillator coils, to produce continuous, undamped high-frequency currents [5, 6].

Tesla explained his decision to start researching high-frequency currents, previously completely unknown: “Some theoretical possibilities offered by currents of very high frequency and observations which I causally made while pursuing experiments with alternating currents, as well as the stimulating influence of the work of Hertz, determined me some time during

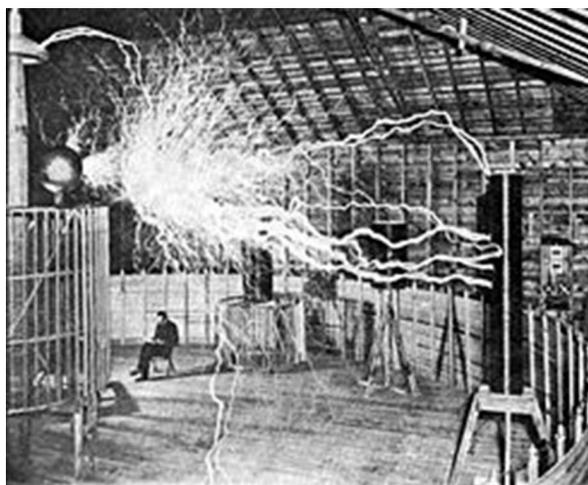


Figure 1. Nikola Tesla - master of lightning – produced by high frequency and high voltage currents in his lab in Colorado, 1899. Source: The Nikola Tesla Museum, document no. MNT, VI/II, 38

Slika 1. Nikola Tesla kao gospodar munja, odnosno visokofrekvencijskih i visokonaponskih struja proizvedenih u njegovoj laboratoriji u Koloradu 1899. godine
Izvor: Muzej Nikole Tesle, dokument br. MNT, VI/II, 38

1889 to enter a systematic investigation of high frequency phenomena. This has proved itself so fruitful, since” [8]. During 1891 and 1892, Tesla designed and made several high-frequency electrical oscillators for medical purposes [8, 9]. As he said, the work was hard, and he struggled “to get from the Scylla to the Charybdis” [8]. Those were mainly high frequency generators (5-10000 cycles per second), operating at tens of thousands volts [3, 9]. Using these devices, Tesla performed amazing experiments [6]. Showers of sparks and lightning erupted around him in his laboratory, making some fascinating scenes [6, 10, 11]. On these occasions, Tesla transformers raised the potential to several million volts at a frequency of several million Hertz [6, 11]. Lightning bolts were flying around his lab a few meters in range [6]. Tesla liked sitting in a chair inside his lab taking notes while the air all around him was filled with such streamers from his giant coil [6, 12] (**Figure 1**).

In his experiments with his oscillating transformer, Tesla connected his coil to a Geissler tube and found it glowing intensely [6]. The luminescence appeared in these tubes without direct connection of conductors with the source of electrical energy [6, 13]. Therefore, in Tesla's hands, light bulbs lit like in hands of a magician, which was a real attraction for observers [1, 6, 12–15] (**Figure 2**).

Tesla conducted a number of experiments on himself using high-frequency and high-voltage currents, and he was the first to report about their beneficial effects on the body [1–3, 5, 6, 8, 9, 16]. In the winter of 1891, Tesla passed high-frequency and high-voltage current through his body without causing any muscle spasms or tissue damage [1]. The scientific world was soon informed of the fascinating properties of Tesla's currents [1, 16]. On February 21, 1891, Tesla pu-



Figure 2. Tesla demonstrating wireless electricity transmission Tesla holding a light bulb illuminating it by hand, without any wire connections. Source: www.tesla-museum.org
Slika 2. Tesla demonstrira bežični prenos električne energije. U njegovoj ruci svetli sijalica bez direktnog povezivanja sa strujnim izvorom. Izvor: www.tesla-museum.org

blished the article “Phenomena of alternating currents of very high frequency” in the journal *Electrical World* [3, 5, 8, 16]. It was also the first paper on high-frequency currents in the world [8]. According to Tesla, his accidental experience with high-frequency currents led to the following conclusions on the physiological effects of these currents on the human body: “The discharge of even a very large coil cannot produce seriously injurious effects, whereas, if the same coil were operated with a current of lower frequency, though the electromotive force would be much smaller, the discharge would be most certainly injurious. This result, however, is due in part to the high frequency. The writer’s experiences tend to show that the higher the frequency the greater the amount of electrical energy which may be passed through the body without serious discomfort” [16]. This was a shocking discovery that disproved Edison’s claims that alternating currents were dangerous and harmful [8, 16]. On the other hand, no one could foresee the amazing effects of high-frequency currents [8]. Tesla’s explanation for this enigma was soon associated with the human body, emphasizing the following: “It seems certain that human tissues act as condensers” [5, 8].

On May 20, 1891, Tesla was invited to give a lecture before the members of *American Institute of Electrical Engineers* (AIEE), now the IEEE, at Columbia University in New York [5, 8, 9]. The lecture: “Experiments with Alternate Currents of Very High Frequency and Their Application to Methods of Artificial Illumination” was held before a large gathering [5]. On this occasion, Tesla amazed the audience, and demonstrated effects of alternating currents on the human body and intense smell of ozone [5, 9]. The lecture ended with the announcement that his future work would be directed towards finding new ways of using natural energy and thus “humanity will move forward with giant steps” [5, 17]. This lecture, published in *Electrical World* and the AIEE proceedings on July 11, 1891, was translated into many languages, and was many times cited both in our and in foreign scientific literature [5, 8].

It is known that Tesla corresponded with physicians and electrotherapists, Dugan William James and Samuel Howard Monell [2–4]. As a young physician, Dr. Monell, later a professor of electrotherapeutics, attended Tesla’s lecture at Columbia University in 1891 [5]. In his book “High-frequency electrical currents in medicine and dentistry”, published in 1910, he wrote about his impressions from the lecture: “On a memorable night in May, 1891, Nikola Tesla, the Slav, young and enthusiastic, with a poet’s mind and the aspirations of genius, stood before the “American Institute of Electrical Engineers” and lighted lamps with currents passing harmlessly through his own body and heated wires to incandescence by the touch of his conducting hand. With smiling countenance and without physical sensation, he placed himself in circuits, that by all the laws of alternating and direct currents should have brought the lecture to a close by the death of the daring lecturer! Yet he went sweeping on, astonishing his audience by demonstration after demonstration of unfamiliar discharges newborn into electrical science which were called “high frequency”. That lecture sent the fame of Tesla round the world” [5, 8, 9].

Nine years later, Nikola Tesla was examining the problem of increasing human energy, and in his eponymous paper: “The problem of increasing human energy”, he reflected on the lecture he gave at Columbia University: “I still remember with pleasure how, nine years ago, I passed the discharge of a powerful induction-coil through my body to demonstrate before a scientific society the comparative harmlessness of very rapidly vibrating electric currents, and I can still recall the astonishment of my audience. I would now undertake, with much less apprehension than I had in that experiment, to transmit through my body with such currents the entire electrical energy of the dynamo now working at Niagara – forty or fifty thousand horsepower. I have produced electrical oscillators which were of such intensity that when circulating through my arms and chest they have melted wires which joined my hands, and still I felt no inconvenience. I have energized with such oscillations a loop of heavy

copper wire so powerfully that masses of metal, and even objects of an electrical resistance specifically greater than that of human tissue, brought close to or placed within the loop, were heated to a high temperature and melted, often with the violence of an explosion, and yet into this very place in which this terribly destructive turmoil was going on I have repeatedly thrust my head without feeling anything or experienced any inconvenience” [18].

After this lecture, Tesla received many letters from eminent physicians from the United States of America, inquiring as to the physical effects of such currents of high frequency [8]. That is why Tesla wrote a separate article on the application of high frequency currents in medicine: “Massage with Currents of High Frequency”, which was published in the journal *Electrical Engineer* on December 23, 1891 [2, 3, 5, 8]. He provided specific instructions to doctors how to heat the skin of their patients using his currents [5]. Among other things, in this article Tesla wrote: “I have demonstrated in my lecture that a body perfectly well insulated in air can be heated by simply connecting it with a source of rapidly alternating high potential. The heating will, of course, be superficial, that is on the skin. With such apparatus properly prepared, wouldn’t it be possible for a skilled physician, to find in it a means for effective treatment of various types of diseases?” [8].

After his fascinating experiments at Columbia College in New York, where he passed 50,000 volts through his body, Tesla performed similar experiments in Europe, and captured the attention of the whole scientific world on developments in this area [1, 2, 5]. Thus, on February 3, 4, and 9, 1892, Tesla gave a lecture: “Experiments with Alternate Currents of High Potential and High Frequency” in the famous Royal Society in London before the members of the Institute of Electrical Engineers (IEE) [5, 7]. Then, on February 19, 1892, he delivered a lecture in Paris in the International Association for Electricity, and repeated it in the Association of Electrical Engineers [7]. There he met Jacques-Arsène d’Arsonval, a French physician, who conducted experiments with high-frequency currents, denying the fact that Tesla released observations of physiological effects of these current before him [5]. Both times Tesla’s experiments were considered to be sensational, and hinted at the possibility of therapeutic application of high frequency currents and voltage [1].

On September 13, 1898, Tesla gave a lecture: “High Frequency Oscillators for Electro-therapeutic and Other Purposes”, on the annual meeting of the American Electro-Therapeutic Association in Buffalo, combining all his work in this area [1, 2, 4, 8, 19]. So, Tesla gave a comprehensive overview of his eight oscillators that were already in use [8] and described the effects that high frequency currents caused in his system (heat effect, extreme fatigue, drowsiness, and disorders in breathing and blood circulation) [1]. In addition, Tesla clearly limited his research to living tissues, leaving therapy to doctors: “While it remained for the physician to investigate the specific actions on the orga-

nism and indicate proper methods of treatment, the various ways of applying these currents to the body of a patient suggested themselves readily to the electrician” [19]. In the final part of his lecture, Tesla stated the following: “Finally, though, I had the satisfaction of producing devices which are simple and reliable in their operation, which require practically no attention and which are capable of effecting a transformation of considerable amounts of energy with fair economy. The physician will now be able to obtain an instrument suitable to fulfill many requirements” [8]. Shortly after that, Tesla currents became the basis for diathermy and various other forms of high frequency electrotherapy [6, 8]. Tesla established a good cooperation with the New York doctor Carol, entrusting him one of his high-frequency transformers for therapeutic purposes and they were constantly in contact [5]. In addition, as already mentioned, he kept correspondence with physicians Monell and Dugan [2–4]. They both sent him their books on the treatment using high-frequency currents, but Tesla corrected them on several occasions that the discovery of these currents was wrongly attributed to William James Morton, and the discovery of their therapeutic activity to d’Arsonval [3]. Although Dugan’s “Handbook of Electrotherapeutics”, intended for medical students and doctors, contains a special dedication to Tesla, there is not much information about their relationship [16]. Since the letter in which Tesla thanks Dugan for sending him his book was sent via Tesla’s publisher, it can be concluded that Tesla and Dugan were not very close [3, 16].

In contrast, Tesla archives include a very rich correspondence with Prof. Monell [16]. In a letter dated December 16, 1908, Monell asked Tesla to send him photos and comments about his machines, about which he later wrote in his book on electrotherapeutics [9, 16]. In the same letter, Prof. Monell wrote about his concept for the book according to which his main objective was to stimulate interest of medical students, doctors and dentists in high frequency currents [9]. Their subsequent correspondence was about photographs Monell expected to get from Tesla for his book, as well as Tesla’s explanations for machines in the photos [16].

The Monell’s book, a part of the personal legacy of Nikola Tesla kept in his Museum in Belgrade, contains four photographs, although Tesla sent him more; the first is the well-known figure of Tesla sitting in front of one of his giant Tesla coils, the so-called high-frequency amplifiers, as stated in the legend [9]. The following two photographs present oscillators, a total of four, which have been applied for medical purposes [9, 16]. The fourth presents Tesla coils in resonance from Tesla’s laboratory [9]. Two of these photos have Tesla’s handwritten legends [16].

The first part of the Monell’s book, dedicated to electricity and its effects on the human body, includes a review on Tesla, as the inventor of these valuable therapeutic devices [9, 16]. In the preface of his book,

Monell points out the importance of high frequency currents in medical practice, both in rehabilitation of acute diseases, and in the treatment of chronic diseases, expressing his beliefs that those who read his book will most certainly be willing to use them in their work [16]. Monell also emphasizes that the main effect of high-frequency currents is based on their power to “modify the natural physiological processes in the body” [9, 16]. The improvement of the health status of patients subjected to these currents on daily basis was associated with: “induction of natural sleep, increase of strength, vital energy, joy of life, work capacity, walking capacity; it restored appetite, improved digestion, and provided progressive health improvement” [16].

This general improvement of the health status often manifested after the first session, even before signs of localized effects could be noticed [10, 16]. Apart from statements given by patients, the therapeutic efficacy also included blood and urine tests [16].

At the stage of drafting the book, in a letter dated June 4, 1909, Monell wrote to Tesla about his ideas on the cooperation related to the design, manufacture and marketing of devices based on Tesla’s high-frequency currents [16]. In his letter dated April 19, 1916, Monell proposed foundation of *Monell-Tesla Institute* [3, 16]. The aim this Institute would have been to expand the application of Tesla’s inventions in science and medicine [10, 16]. Tesla’s task was to design devices, and Monell’s to manage their use [16]. Unfortunately, Monell died in 1918, so this plan was never put into action.

In electrotherapy, Tesla used two types of oscillators [9]. The first type was a high frequency coil with two metal plates of considerable surface connected to its terminals [9, 10]. To enable strong currents to be passed through the tissues, the terminals should be large, and covered with cloth saturated with a solution of electrolyte harmless to the skin [9]. Another type of oscillator was connecting one terminal of the high frequency source to the ground and the other to a metal plate, which worked as a transmission antenna and it affected the whole body [9, 10]. Apart from this, the oscillators were huge and occupied a substantial part of doctors’ surgeries [8, 9]. Usually they were steam-powered electric generators producing high-frequency electricity [9].

After 1900, Tesla tried to exploit his inventions commercially in medicine [5]. He founded the *Tesla Electrotherapeutic Company* and designed a miniature transformer for home treatment using high frequency currents, but failed to commercialize his discovery [5]. However, his portable miniature oscillator (cylindrical in shape, about 30 cm long, 3 cm in diameter, 12 or 30 W, with frequency of 400.000 cps, 75 kV), known as “Mini Tesla” or “Pocket Tesla” had a remarkable success [3, 4, 8, 9]. A copy of this oscillator is in the *Nikola Tesla Museum* in Belgrade [8]. According to Margaret Cheney, this device was very popular [8, 20]. The famous French chanteuse Edith Piaf, for example, cured pharyngitis by means of Tesla cu-

rrents, specifically the oscillator “Mini Tesla” [9]. Over time, treatment using Tesla currents had become very effective and very popular [9, 10]. Monell listed various clinics in the United States which investigated effects of these currents and confirmed their beneficial effect on the organism [3, 9]. A similar thing happened in Europe, where d’Arsonval, academician Blondel, and a German doctor from Saarbrücken, Marsel Flug, made a great success with Tesla currents [9].

In his book “Nikola Tesla beneath Cobwebs”, Mario Filipi wrote about using Tesla currents for electro-anesthesia [4, 20]. According to this author, Tesla designed a device with high-frequency currents in a wardrobe of a New York theatre, for actors suffering from stage fright [21].

Nikola Tesla and the Ozone Generator

Tesla’s genius was much more than unveiling the secrets of nature and it was evident in the variety of his interests as well [5]. He published several articles on general biological topics, as well as on proper diet and healthy lifestyle [2, 3]. For example, Tesla emphasized the importance of timely recognition of symptoms of the disease: “Incapacity of observing the first symptoms of an illness, and careless neglect of the same, are important factors of mortality. In noting carefully every new sign of approaching danger, and making conscientiously every possible effort to avert it, we are not only following wise laws of hygiene in the interest of our well-being and the success of our labors, but we are also complying with a higher moral duty. Everyone should consider his body as a priceless gift from one whom he loves above all, as a marvelous work of art, of indescribable beauty and mastery beyond human conception, and so delicate and frail that a word, a breath, a look, nay, a thought, may injure it. Uncleanliness, which breeds disease and death, is not only a self destructive but highly immoral habit. In keeping our bodies free from infection, healthful, and pure, we are expressing our reverence for the high principle with which they are endowed [18]. Like a real mechanical engineer, Tesla analyzed mechanisms for improving the automatism of living beings: “The human energy will be increased by careful attention to health, by substantial food, by moderation, by regularity of habits, by promotion of healthy life generally stated, by respecting ourselves and others as well” [2, 18]. According to him, success in life depends on hard work: “To be successful in this world one must perform the hardest kind of work. You must peg away night and day, and not stop a minute. There is no royal road. This has been the plan I have followed for years” [5]. “My health is good, “Tesla used to point out, “simply because I lived cautiously and moderately, and perhaps the most amazing thing is that I was seriously ill three times in my youth, physically hopelessly destroyed and abandoned by doctors”. At the time when Tesla finished high school, there was an

outbreak of cholera [22]. He contracted cholera and was bedridden for nine months and was near death multiple times [11, 14, 22, 23]. The doctors gave up on him almost completely [11, 14, 22]. Desperate parents watched their only son losing the battle with the illness [11]. Tesla's father, in a moment of despair, promised to send him to the best engineering school instead to seminary if he recovered [11, 12, 14, 22]. This dramatic life experience must be an additional reason for Tesla's commitment to invent something to contribute the fight against diseases, especially those caused by microorganisms. To this end, he experimented with high frequency alternating currents, and revealed their bactericidal properties: "My high frequency currents have bactericidal effects. So it has become a daily routine for the inventor to take off his clothes, stand in front of his coils and a prickly corona would envelop his body and restore his health" [24, 25]. In addition, Tesla noted that high-frequency currents produce ozone in the air, which acts refreshing and in very low concentrations has antibacterial properties [2, 3]. This urged him to use high voltage electrical discharge and design a device for ozone production (ozone generator/ozonizer) and patented it on June 17, 1896 [2, 3, 5]. In 1900, Tesla formed the "Tesla Ozone Company" for production of ozone generators, mostly bought by doctors [2, 3, 16]. One of the products of his company was called "Violet Ray" which was widely used for therapeutic purposes around 1910 and later [16]. In the late 19th and early 20th century, "Siemens" used this idea for water purification [5]. Today, ozonizers are used for air purification and refreshment in rooms with air-conditioning [3].

In May 1898, an *International Exhibition of Health* was held in New York, where Tesla presented his "electrical bath" [5, 10]. On this occasion, Tesla spoke about facts, discovered by famous scientists Louis Pasteur and Robert Koch stating that from 4,000 to 7,000 microbes fly in the air and fall on every square foot of a human body, where they remain [5]. Electric charge with positive or negative entropy creates a repulsive force between two charged bodies, one of which is the great mass of the human body, others are small microorganisms [5, 10]. The result of the electric charge is rejection of microorganisms from the body [5]. Tesla first applied this method himself, and then he described it in detail [5, 10]. The method included rubbing the body with a disinfectant, for example alcohol, the hair in particular, which especially retains microorganisms [5]. Then he used a special battery to electrify his body to reject microorganisms, and eventually the whole process was finished by mild rubbing of the body with alcohol again [5].

Speaking of good and useful electricity, Tesla used to say that one should protect himself from bad electricity, the so-called "evil spirit" [9]. Giving an interview to an amazed journalist of the "Sun" magazine he said: "One of the beneficial effects of water

is that it mechanically washes away the electricity from the skin. If you put some clay on the bottom of the bathtub, it will absorb all the harmful electricity from your body. Grounding is placing one's bare feet on the ground, grass, or sand, especially when it is humid or wet. Rinse your hands and/or feet under running water to remove any static electricity. Spending time by the water, like lakes, rivers, fountains, waterworks or streams, will fill you with natural electricity that will successfully fight the damaging one" [9].

Nikola Tesla and Vibrational Medicine

Nikola Tesla also examined the effects of mechanical vibration on the human body [3]. It is known that he made a "vibrator" for treating painful leg muscle spasms [2–4]. Here is how Tesla later recalled his work in this field of research: "Electrical oscillations of an extremely high rate act in an extraordinary manner upon the human organism. Thus, for instance, I demonstrated that powerful electrical discharges of several hundred thousand volts, which at that time were considered absolutely deadly, could be passed through the body without inconvenience or hurtful consequences. These oscillations produced other specific physiological effects, which, upon my announcement, were eagerly taken up by skilled physicians and further investigated. This new field has proved itself fruitful beyond expectation, and in the few years which have passed since, it has been developed to such an extent that it now forms a legitimate and important department of medical science [18]. On February 6, 1894, Tesla patented his mechanical oscillator called *Means for generating electric currents* [7].

Tesla left a record about how he accidentally came to the discovery of mechanical treatment while using the mechanical oscillator: "I had installed at the laboratory one of my mechanical oscillators with the object of using it in the exact determination of various physical constants. The machine was bolted in vertical position to a platform supported on elastic cushions and, one day, as I was making some observations, I stepped on the platform and the vibrations imparted to it by the machine were transmitted to my body. The sensation experienced was as strange as agreeable, and I asked my assistants to try. They did so and were mystified and pleased like myself. But a few minutes later some of us, who had stayed longer on the platform, felt an unspeakable and pressing necessity which had to be promptly satisfied, and then the stupendous truth dawned upon me". It was a discovery of laxative effects of mechanical oscillators, or technical therapy in a broader sense, about which Tesla said: "When I began to practice with my assistants mechanical therapy we used to finish our meals quickly and rush back to the laboratory. We suffered from dyspepsia and various stomach troubles, biliousness, constipation, flatulence and other disturbances, all natural results of such irregular habit. But only after a week of application, during which I improved the technique and my assistants learned how to take the treatment to their best

advantage, all these forms of sickness disappeared as by enchantment and for nearly four years, while the machine was in use, we were all in excellent health" [12, 26, 27].

Apart from his assistants, Tesla gladly offered his visitors the opportunity to try out the mechanical treatment [12]. One of them was the famous writer and Tesla's friend, Mark Twain [12, 14]. Tesla described it like this: "He came to the laboratory in the worst shape suffering from a variety of distressing and dangerous ailments but in less than two months he regained his old vigor and ability of enjoying life to the fullest extent" [12, 26].

In 1896, Tesla informed the public about the possibilities of mechanical therapy in the *Detroit Free Press* [7]. He had high expectations for his invention and was very optimistic regarding the future of mechanical therapy [5]. Tesla began experimenting more and more with medicinal properties of his oscillators, and good reports were coming from across the country about their extraordinary possibilities of treatment [5, 24]. "These high-frequency "vitality boosters" would generate a "universal healing agent" and enable the body to "throw off all diseases," said Finch Strong [24]. The gathered results included "improvement of mood, sleep, appetite, and bowel functions" [24].

Nikola Tesla and Dr. Georges Lakhovsky achieved amazing results with application of their high-frequency oscillators and vortex antennas on a large number of patients with a variety of health problems (locomotor diseases and injuries, hypothyroidism, sleep disorders, urogenital infections, hemorrhoids, prostate function disorders, osteoporosis, dyspepsia, constipation, cardiovascular disease, hormonal imbalances, etc.) [28]. Some doctors reported that mechanical therapy could treat tuberculosis [24].

At the end of his life, Tesla emphasized the importance of this discovery, calling it, at one moment, his greatest contribution to human well-being [5]. He pointed out that combination of proper diet and mechanical vibrations were a key to maintaining health and prolonging life [5].

Nikola Tesla and Robotics in Medicine

Nikola Tesla was a pioneer in robotics [5]. He used to say: "Every living being is an engine geared to the wheel-work of the universe". Interestingly, especially from our perspective, the Socialist Federal Republic of Yugoslavia (SFRY) was one of the few developing countries with its own medical electronics industry based on Tesla's ideas [8].

In modern medicine, Tesla's ideas have been used for wireless power transfer for medical implants in the human body [10]. Wireless remote control is most often used for nerve functions in people suffering from Parkinson's disease and in patients with essential tremor [8, 10]. These devices are charged by remote transmission of energy [10, 12]. Today, for these purposes, most experiments include microwaves [12]. In the same way, experimental studies are done for implants controlling urination, respiration, vision

and hearing [8, 10]. In addition, wireless implant technology today is also used to control pumps for a gradual drug dosage, as part of the treatment of some chronic diseases and cancer, regulation of insulin levels, managing the work of the diaphragm, heart muscle, artificial hearts, cochlear prostheses, neuroprostheses, etc. [10].

Tesla's idea of wireless transmission of energy provided a significant progress in fostering immobile patients [10]. Using Tesla's invention of wireless control of patients' chairs and beds, patients are less dependent on other people who take care of them, whereas relatives, doctors and other medical staff are more efficient, and the care itself is much easier and simpler [10].

When asked who, in his opinion, were great people, Tesla replied: "Great is a man who overarches others with his gifts of mind and intellectuality, the one that like a bee does with the honey gathers knowledge and reveals new truths, but crowns his efforts with love for humanity, which in return helps him evade the burden of miseries that fear, famine, ignorance, present disease. Not those who humiliate a man, but those who elevate him, who enrich his spiritual heritage, helping his spiritual happiness in process. Those are great". [18]. Living with this belief till the end of his life, this great man kept on working on developing a system of telemechanics and remote control, intuitively heralding the age of humanoid robotics: "Long ago I conceived the idea of constructing an automaton which would mechanically represent me" [10]. He did it in 1896, and designed a teleautomatic and automatic machine, which he patented in November 1898 [7]. Using Tesla's discovery, robotic control systems were introduced into the medical practice [8, 10]. Numerous medical robots, as well as multi-purpose machines that meet modern requirements of flexible automation, eliminate manual work in the course of surgical intervention [10].

Medical practice today uses all kinds of robotic sensors (ambient, tactile, ultrasonic, laser sensors, etc.) as well as all kinds of robotic systems for visualization (cameras, etc.) [10].

One of the ideas Tesla had no time to realize was artificial blood circulation [5]. He started thinking about it due to the illness of his close relative [5]. In a letter written to the inventor George Comstock Baker, on April 11, 1899, he requested an opinion about one of his medical devices. Tesla wrote about his idea: "A few years ago I came up with the idea to put a whole body into a chamber, only the face would be exposed to air. The chamber should have a door through which the person would enter, and it would be hermetically sealed. For the same reason, the window through which the face would be put through should be lined with rubber. If the chamber was made like this, the air inside it could be diluted or compressed. Now, if the air is diluted, I believe that the blood of a person inside the chamber would be drawn to the surface of the skin. If the air is put back into the chamber under compre-

ssion, the blood would rush back and we would get a powerful pump that dilutes the air with each cycle to a certain degree and that can be adjusted to dilute the air as many times as the heart beats per minute. I also thought about a device where the person's pulse would control the pump, so that it would pump the blood in accordance with the heart rate" [5].

Medicine and Tesla's Inventions in the Light of Current Electromagnetic Culture

While interpreting problems of energy and mankind, Nikola Tesla asked himself: "Of all the endless variety of phenomena which nature presents to our senses, there is none that fills our minds with greater wonder than that inconceivably complex movement which, in its entirety, we designate as human life. Its mysterious origin is veiled in the forever impenetrable mist of the past, its character is rendered incomprehensible by its infinite intricacy, and its destination is hidden in the unfathomable depths of the future. Whence does it come? What is it? Whither does it tend? are the great questions which the sages of all times have endeavored to answer" [18]. The central topic of Tesla's research was how to obtain energy from nature [5]. After extensive exploration of natural phenomena, Tesla concluded: "If you want to find the secrets of the universe, think in terms of energy, frequency and vibration. When I think of all the inventions, including those in which I took part, I am fully convinced that our Creator built this planet on the basis of electromagnetics" [29] (**Figure 3**).

All Tesla's inventions in physics and electrical engineering were the result of the kind of intuition that René Descartes described around 1628 in his philosophical work "Rules for the Direction of the Natural Intelligence" (Latin - *Regulae ad Directionem ingenii*) [7, 30]. Attempting to explain intuition as precisely as possible, Descartes defined it as an innate light of reason (Latin - *Ratione luce*, French - *Innée lumière*) [30]. Tesla was closest to Descartes ideal in his fundamental discoveries in the field of electromagnetism and related technologies [7]. In 1904, in "Note on Cabanellas Patent, No. 164995" Tesla wrote about his inventive talent: "From time to time, in rare intervals, Great Spirit of discovery comes to the Earth to announce a secret that should improve humanity. It selects the best prepared and most honorable one, and whispers a secret to his ear. Valuable knowledge comes like a flash of light. When he understands its hidden meaning, he is happy to see a miraculous change: a new world appears in front of his eyes and he barely recognizes any similarity with the old one. This is not a passing illusion, a mere game of his playful imagination or a phantom of the mist that will disappear. The miracles he sees, although far in time, will happen. He knows that, with no shadow of doubt in his mind, and feels it with every part of his body: It is a great idea" [5] (**Figure 4**).



Figure 3. Tesla's famous electric motor (induction motor) constructed in 1887. It is the best machine for converting electrical energy into mechanical energy ever. A rotating magnetic field invented by Tesla in 1888, is a key principle in the operation of this "wheel of modern age". It is almost noiseless device with high efficiency (95 %). Source: www.wikipedia.org

Slika 3. Teslin čuveni elektromotor (indukcioni motor) konstruisan 1887. godine. To je do sada najbolja mašina koja pretvara električnu energiju u mehaničku. Radi na principu obrtnog elektromagnetnog polja, koji je Tesla otkrio 1882. godine. Popularno je nazvan „točak modernog doba“. Gotovo je bešuman. Ima stepen korisnog dejstva 95 posto. Izvor: www.wikipedia.org

The four fundamental forces in the nature are gravity, electromagnetism, weak, and strong nuclear forces [7]. Electromagnetic force is of crucial importance for the Second Industrial Revolution, and Nikola Tesla, the main character of our story, was often credited with starting it [7]. The background of the modern process of globalization and global networking is the information/communication technology, philosophically known as "electromagnetic culture" [7]. Tesla's work is within the foundations of modern electromagnetic culture [7]. Its main feature is high-speed flow of information that corresponds with Descartes ideal [7].

According to Tesla himself, he discovered a new type of electromagnetic waves more than a century ago, and called them non-Hertzian waves in order to differentiate them from conventional, so-called Hertzian electromagnetic waves [31]. Non-Hertzian waves, called Tesla waves, have properties that cannot yet be measured, as they are still beyond observations and measurements [31]. However, science only recognizes electromagnetic waves, experimentally proven in 1888 by Hertz [31]. In his Canadian

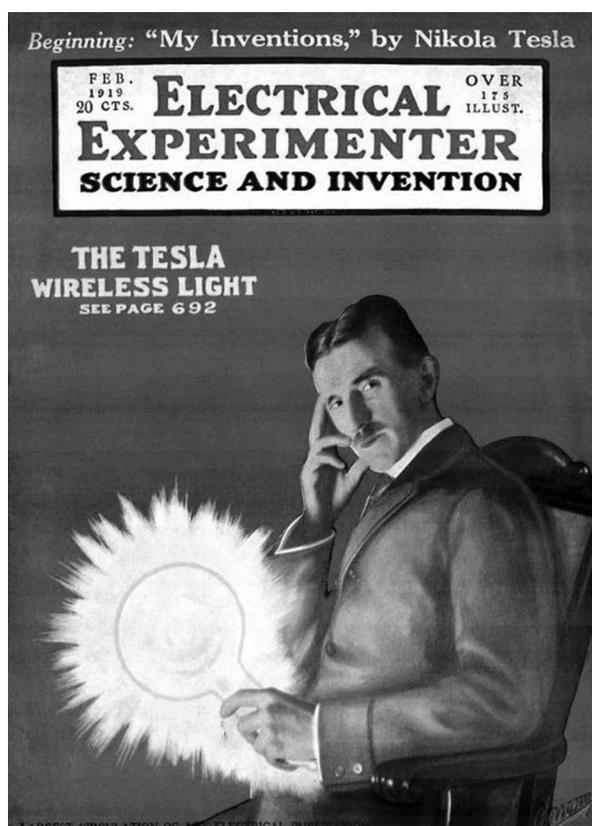


Figure 4. Tesla on the cover of the American journal “Electrical Experimenter”, in 1919, which published a series of Tesla’s articles that constitute a unique autobiography “My inventions” Source: <http://electricalexperimenter.com/n10electricalexperi06gern.pdf>

Slika 4. Tesla na naslovnoj strani američkog časopisa *Electrical Experimenter* 1919. godine. U ovom časopisu Nikola Tesla je u nastavcima objavio svoju autobiografiju „Moji izumi“. Izvor: <http://electricalexperimenter.com/n10electricalexperi06gern.pdf>

patent 142,352 “Art of transmitting electrical energy through the natural mediums”, Tesla wrote the following: “It is necessary to employ oscillations in which the rate of radiation of energy into space in the form of Hertzian or electromagnetic waves is very small. To give an idea, I would say that the frequency should be smaller than twenty thousand per second, though shorter waves might be practicable. The lowest frequency would appear to be six per second, in which case there will be but one node, at or near the ground-mate. and, paradoxical as it may seem, the effect will increase with the distance and will be greatest in a region diametrically opposite the transmitter” [25]. In addition, Tesla predicted an extremely fast progress of science in the future: “The day science begins to study non-physical phenomena, it will make more progress in one decade than in all the previous centuries of its existence” [32].

In 1900, Nikola Tesla announced the connection between the human body and electromagnetism [33]. This realization has led to the creation of magnetic resonance imaging devices of invaluable importance, because they can detect diseases at an early stage and thus extend the human life [33]. Tesla’s numerous inventions in the field of electromagnetism in the late 19th and early 20th century have also opened the door to the development and implementation of other modern technologies in medicine [5, 7, 10, 31, 34]. Tesla’s views that the entire Cosmos acts on the principle of vibration and resonance are the basis of the modern theory of strings [34] and the backbone of microwave resonance therapy [28, 33, 35, 36]. That is one of the reasons why Tesla has been considered the founder of quantum medicine, bearing in mind that he was the first to use high-frequency waves to improve health. His holistic approach to scientific research has constantly attracted great interest of the scientific community. Thus, inspired by Tesla’s inventions, an American physician, Dr. Raymond Rife, found that cells exposed to some form of energy of appropriate frequency, absorb the energy through the resonant elements of their structure. If the absorbed energy exceeds a certain limit, the cells are destroyed. This was also a motive to design and implement the “frequency generator”, which became very popular in a short time [37].

Tesla realized that human body is a complex electromagnetic network [8]. He thought that if we affected the biological flow within our body, we could increase our energy potentials or take care of some “short circuits” [8]. The same principle goes for acupuncture [8]. However, although acupuncture and other kinds of energy treatment were known to ancient civilizations, and changed forms and types of application through centuries, energy healing becomes a subject of scientific research in the 20th century, through electroacupuncture, quantum physics and cyber technology [29]. Thus, it has been established that disharmony in the human energy field precedes pathological changes at the cellular and organ levels [29].

Before beginning the treatment, it is necessary to start changing one’s consciousness, which in practice means changing habits at the conscious level [29]. Nikola Tesla was a forerunner in researching the phenomenon of consciousness [38–41]. He argued that memory in the classical sense does not exist and that the information is “causing” a strong visual, thought and language associations [40–42]. He also pointed out that the ability of the brain to “translate” the senses in the real world, observations of numerous frequencies from the environment (light, sound, heat and physical vibrations), would be more logical if the brain was a hologram [40]. Not many researchers know that Tesla had never written down a single formula in electrical engineering [43]. All his discoveries were made after meditation and altered state of consciousness [43]. Tesla was actually focused on specified addresses on the level of collective consciousness [43, 44]. He

received extrasensory information directly from the consciousness [43–47]. The information is then transferred from the level of consciousness, or acupuncture system, to the nervous system crossing the barrier of neural synapses of some eighty milli electron volts [43]. Most people have insufficient energy at the acupuncture system [43]. It is interesting to point out that his motivation for inventions was so enormous that he enhanced information on the invention in regard to all the other information he received in the aforementioned manner, at the level of sensory consciousness [43]. In addition, Tesla hoped to be able to photograph a thought by detecting neural feedback to the retina and emission of light [1].

The aim of the increasingly popular electrotherapy is to detect disharmony in the human bioenergy field and to restore the natural balance and harmony [29]. This means maintaining the human body and maximizing its potential, increase one's energy, mental clarity, support immunity to stress and infections, emotional balance and good physical condition [29]. Today scientists are “rediscovering“

the power of words, thoughts and mind, confirming that words and thoughts can program the human body [40–42].

Conclusion

Nikola Tesla was the last Renaissance figure of the modern era. His outstanding inventions bridged three centuries and two millennia, and the mankind owes a huge debt of gratitude to Tesla. His extraordinary enthusiasm and refined sense of beauty and measure showed that all the noble ideas of the mind can be realized only if the scientific and professional truth seekers have the knowledge, endless patience, dignified and curious spirit, professional responsibility and unlimited intellectual honesty. *“The world will long have to wait for a mind equal to Tesla's, a mind of such creative possibilities and such wealth of imagination. What is created is great, and, as time passes, it becomes even greater“*. Tesla's life, enthusiasm, humanism and principles will remain a lasting legacy for future generations around the world.

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Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriče arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (<http://www.nlm.nih.gov/tsd/serials/lji.html>). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al.*

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

* Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. *J Thromb Haemost* 2003;1:1435-42.

* Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002;40(5):679-86.

* Bez autora

21st century heart solution may have a sting in the tail. *BMJ*. 2002;325(7357):184.

* Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxis. *Pharmacol Res Commun* 1988;20 Suppl 5:75-8.

* Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. *J Clin Psychopharmacol* 1988;8(4 Suppl):31S-37S.

* Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by *Toxoplasma gondi* [abstract]. *Clin Res* 1987;35:475A.

Knjige i druge monografije

* Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. *Medical microbiology*. 4th ed. St. Louis: Mosby; 2002.

* Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. *Histocompatibility testing 1972*. Copenhagen: Munksgaard, 1973:12-8.

* Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: Saunders; 1974. p. 457-72.

* Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. *Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland*. Berlin: Springer; 2002. p. 182-91.

* Disertacija

Borkowski MM. *Infant sleep and feeding: a telephone survey of Hispanic Americans* [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

* Članak iz časopisa u elektronskom formatu

Aboud S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle>

* Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

* Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legendi slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, ||, ¶, **, † †, ‡ ‡.

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektivna mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1st, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

<http://aseestant.ceon.rs/index.php/medpreg/user/register>.

Manuscript submission should be made on the web address:

<http://aseestant.ceon.rs/index.php/medpreg/>

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to **Medical Review** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, their reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the Obased solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (<http://www.nlm.nih.gov/tsd/serials/lji.html>). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

** A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. *J Thromb Haemost* 2003;1:1435-42.

** An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002;40(5):679-86.

** No author given*

21st century heart solution may have a sting in the tail. *BMJ*. 2002;325(7357):184.

** A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxis. *Pharmacol Res Commun* 1988;20 Suppl 5:75-8.

** An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. *J Clin Psychopharmacol* 1988;8(4 Suppl):31S-37S.

** A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by *Toxoplasma gondii* [abstract]. *Clin Res* 1987;35:475A.

Books and other monographs

** One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. *Medical microbiology*. 4th ed. St. Louis: Mosby; 2002.

** Editor(s) as author(s)*

Danset J, Colombani J, eds. *Histocompatibility testing 1972*. Copenhagen: Munksgaard, 1973:12-8.

** A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: Saunders; 1974. p. 457-72.

** A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. *Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming*; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

** A dissertation and theses*

Borkowski MM. *Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]*. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

** A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle>

** Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

** A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, ||, ¶, **, † †, ‡ ‡.

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.