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SADRŽAJ / CONTENTS

Engleski jezik danas je glavni jezik komunikacije u nauci, posebno u oblasti biomedicine. Zbog toga vodeći srpski biomedicinski časopisi, uključujući i Vojnosanitetski pregled, objavljuju radove samo na engleskom jeziku, ili dvojezično – na srpskom i na engleskom, omogućavajući da budu „vidljiviji“ na međunarodnoj sceni. Nedavno objavljeno 2. izdanje Medicinkog rečnika, englesko-srpski, srpsko-engleski, autorke prof. dr Sofije Mićić, sigurno će biti od velike pomoći domaćim autorima u pripremi rukopisa za ove, kao i ostale međunarodne časopise (vidi str. 818–20).

Today, English is the major language of communication in science, particularly in the field of biomedicine. Due to this leading biomedical journals in Serbia, including the Vojnosanitetski Pregled, publish articles in English only or bilingually – in Serbian and in English, making them "more visible" on the international scene.
The recently published second edition of the Medical Dictionary, English-Serbian, Serbian-English, the Author Dr. Sofija Mićić, Associate Professor, will certainly be of great help to local authors in preparing manuscripts for publication in these and other international biomedical journals (See p. 818–20).

E D I T O R I A L / U V O D N I K

Plagiarism detection – how we do that

Otkrivanje plagijarizma – kako mi to činimo

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Key words:
plagiarism; ethics; biomedical research; writing.

Ključne reči:
plagijarizam; etika; istraživanje, biomedicinsko; pisanje.

Introduction

Scientific research is the privilege of exceptional people who are at the top of the intellectual and professional ladder. Unfortunately, there are a great number of experts today who tend to be easily included in scientific and academic community, sometimes through a shortcut that is often just a plagiarism.

Considering plagiarism we should not forget that the most important question is who and for what reasons commits plagiarism – whether it is the one who starts his/her career or the one with already gained reputation in the field of scientific publications. And also – whether it happens intentionally and knowingly or in terms of just a coincidence and pure ignorance.

Ethics and plagiarism

Speaking of plagiarism, we should involve the concept of ethics, because, basically, plagiarism is just a matter of ethics. On the other hand, it seems that ethics is frequently used word, so that it is not unnecessary to remind yourself what it is.

For Kant's followers, through utilitarianism and pragmatism [1], the philosophical concept of ethics has changed. Therefore, the concept of medical ethics is changeable, too. The simplest definition is: "Ethics is a theory or system of moral values [2].

Plagiarism means using someone's ideas and writing without proper citation [3].

Plagiarism also means presenting someone's words or ideas as to the right of ownership of another person [4]. Fortunately, it can be completely legal, with the approval of one who owns the copyright. However, consideration of plagiarism usually refers just to the opposite – to something that is fake or even stealing. Basically, plagiarism may be ignorance or inexperience of the person who is about to start a career in publishing.

Perpetrators of plagiarism

A variety of individuals or institutions deal with plagiarism in scientific publications:

1. Plagiarism searching services, which provide free search or search with appropriate monetary compensation to individuals or institutions.
2. Editors and professional teams in the scientific journals that check the content of submitted manuscripts to plagiarism.
3. The perpetrators of plagiarism, who sometimes deliberately try to duplicate the material in order to manipulate and provide some profit.
4. The authors, from whose article the original material has been taken.
5. Reading public, who often notice someone else's work.
6. Unfortunately, the patients can be found, on this list, too, who may be damaged by harmful publications in biomedical journals.

A questionnaires-based survey conducted among medical students and the university staff, about how much they knew about referencing papers downloaded from the Internet and other sources, showed unsatisfactory results [5]. Medical students knew better the use of quotation marks when copying the text literally (verbatim) (17%) than the university staff (16%), and only about half of both of them had knowledge of referencing within the power point-in programme. Totally 88% of university staff and 63% of medical students showed some knowledge about self-plagiarism, and all have possessed little knowledge of copyright law. However, the majority of the survey respondents (82% of students and 73% of employees at the university) claimed that had never used plagiarized

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work [5]. It is obvious there is the lack of proper education about the plagiarism, not only in developing countries but in developed countries, too [6]. Hereof, it is necessary for a young physician-researcher to be introduced in the world of biomedical publications through thematic lectures, courses, seminars, workshops and other appropriate forms of education in order to become a quality healthcare professional.

Plagiarism detection

On the whole, work on plagiarism detection is a very hard work of skilled individuals and teams striving to preserve truly original ideas and valuable works from misuse by those who, on the one hand, abuse copyright infringement, and, on the other hand, allow themselves career advancement and ultimately – economic profit. Thus, plagiarism detection is an attempt to protect one's possession, and ultimately conviction and punishment of those who reach for other people's possession. But it is not a police investigation. It is, too, everyone's benefit, not only to society as a whole, but to perpetrators of plagiarism, especially when it comes to a young researcher to learn an important lesson for his/ her future work.

Obviously, detecting plagiarism is not a popular work. It is no way to get Nobel Prize for this work.

Plagiarism detection in biomedical journals can be done only by experts – these are usually editors and the members of editorial boards. So, these persons must have necessary professional and scientific knowledge of the matters being investigated, as well as experience. They must be adequately trained. Also, people involved in finding plagiarism in biomedical journals have to be very consistent persons. If they are physicians, we should bear in mind that in the process of detecting plagiarism they must check the manuscripts of their colleagues. On the one hand, they should not violate the author, and, on the other hand, they should not allow previously published articles (also by physicians) to be abused. Therefore, they must be objective, but, often, it is necessary to endure various kinds of pressure that are possible in such situations. That can be a problem.

Once detected, a perpetrator of plagiarism becomes the subject of condemnation and punishment. This refers to authors who are not permitted to publish in a journal for some time, or to enjoy special privileges earned through a plagiarized article (academic degrees, career development, additional earnings, etc.), to those who are exposed to judgment of colleagues, to a sort of court of honor within their professional units, etc. In such cases, different forms of pressure on editorial board are more likely to be exerted.

What is the reaction of perpetrators of plagiarism after some of the measures have been undertaken?

The easiest way is denial and that is just what they do. Perpetrators of plagiarism usually claim to have annoyingly duplicated someone else's work. This is the simplest form of what they consider as justification. Then, it is followed by long phone conversations in which they try to explain the extraordinary circumstances under which plagiarism has been committed. These authors often appear personally, trying to explain and justify something that has already been materialized, that is to say absolutely undeniably. This means that they did not realize the significance of the offense. Perpetrators of plagiarism have to justify themselves in front of entire professional and scientific community and not only in front of individuals – people from the editorial board as it is often the only job they earn a life. They live from the reputation of the journals that are blatantly attacked by perpetrators of plagiarism.

Pressure may also be made indirectly – through other people. All similar situations should be avoided – if possible. But, sometimes, it seems – it is not possible.

Detected plagiarism is unambiguous if it is supported by the facts. For this purpose, various guide books are designed [7], in order to detect plagiarism. Plagiarism can be:

a. Crude, obvious, so-called "blatant", when information from one's article is copied and transmitted without using quotation marks and without giving the original reference work; then similar, less harsh transmission from one's article (from the original notes of one's text, for example). It seems that often done unconsciously, and thus, the perpetrator is often surprised when plagiarism is detected. All this and some other things, are double dipping [4];

b. Plagiarism also may occur due to failure in presenting one's article or not understanding one's text. It also includes paraphrasing, which officially requires to be approved and the cases in which perpetrators of plagiarism "forget" to put quotation marks or references [4].

Much has been written about various subdivisions and ways to implement plagiarism, from the so-called "patchwork plagiarism" (downloading different parts from several texts and creating a new paper), then salari factor [8] (fragmenting one paper in order to make several ones), etc.

Unfortunately, it is often found in the biomedical literature.

Plagiarism detection in the *Vojnosanitetski pregled*

The *Vojnosanitetski pregled* (VSP) is a military medical and pharmaceutical journal of Serbia**.** The VSP is indexed in major international biomedical databases in scientific publishing including Medline and Science Citation Index Expanded (SCIE). According to the value of its impact factor, since 2010 the VSP has been included among 153 the most influential journals worldwide in the field of general and internal medicine. Editorial staff of the Journal is located at the Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia. From January 1, 2012 the editorial staff of the VSP use CrossCheck Service and its iThenticate software in order to detect plagiarism in manuscripts submitted to the Journal.

How plagirism detection in manuscripts submitted to the VSP is conducted

1. After checking the document using a word-processing software, an expert from editorial board controls a total percentage of duplicated (overlapping) text in the manuscript and each of the references the copied material has been taken from. Full access to duplicate text marked by a software is possible, whether in the submitted manuscript, or in facing

the references the text has been copied (duplicated) from. This is the first phase, in which the software has an important role. Then, it is necessary to check it by analyzing the submitted text and comparing it with the original text.

2. In the second phase it is necessary to determine to which parts of the copied text plagiarism is referred to, because detected plagiarism in the part of the text related to the results of a research and the one detected in those parts (such as introduction or discussion, for example) do not have the same significance. Still, sometimes, it is possible the author is not aware that article has been plagiarized. The text is analyzed thoroughly and slowly in order to understand its essence.

3. Furthermore, there is a part of editorial board work that refers to originality the idea of the author's work. It is the most important part. It is the biggest mistake if plagiarism has been done in this part, and, that is to say, it is the professional sin.

4. In the next stage, it is necessary to search through some browser available material of previously published articles of that author. In this way, it is possible to determine whether there are signs of the so-called self-plagiarism – copying their own articles. It is possible to do that searching for similar titles, keywords, data, phrases, work style, or by the same team of authors (but with an altered order), etc.

5. The conclusion and explanation about possible committed plagiarism are sent by e-mail to the first author of the article and to all of the co-authors. Everything considered relevant must be noted in conclusion. If there is no plagiarism detected, it must be noted, too. If plagiarism is detected to a slight degree, the authors are recommend to make corrections in order to change text. Authors are required to paraphrase the text by introducing required corrections, to write references not quoted in the first version and after having taking some parts of the text of other work and the article corrected in this way must be submitted again. Sometimes, editors suggest reviewers to take into account aspects of article that has been observed as the suspected plagiarism. In the case of gross plagiarism authors are informed about the decision that the article has to be retained (not to be published), together with the conclusion of the analysis conducted.

6. Finally – in a flagrant case of plagiarism - implement measures of such cases are undertaken: contact the author (author has to be informed in the first place), and then institutions, university, if necessary, professional branches covering the work of the author who committed plagiarism.

7. At the same time, all material on resolution regarding potential plagiarism in the articles, which has been sent to authors must be kept in editorial board ownership.

The results of checking for plagiarism in the *Vojnosanitetski pregled* in the period January 1 – June 30, 2012

In the period from January 1, to June 30, 2012 a total number of 153 manuscripts submitted for publication to the VSP was reviewed and analyzed on plagiarism at the Institute for Scientific Information with the prior software checking (Table 1). Five (3.3%) manuscripts were rejected as a crude plagiarism, and to the authors of 62 (40.5%) of manuscripts were suggested minor revisions in terms of paraphrasing text – 14 (9.1%) manuscripts, and to incorporate references that not previously listed – 48 (31.4%) manuscripts. Suggestions on suspected plagiarism were sent to reviewers in two (1.3%) cases, whereas the authors of four manuscripts were required their major revisions due to high percentage of overlapping text with previously published articles and their resubmitting after corrections performed. Totally 80 (52.28%) manuscripts did not need any corrections regarding potential plagiarism.

Table 1

The results of plagiarism detection in manuscripts submitted for publication in the *Vojnosanitetski pregled* (VSP) during the previous six-month period (January 1, 2012 – June 30, 2012)

Outcome of plagiarism detection	Manuscripts n (%)
Rejecting	5 (3.3)
Major revision with review repeating	4 (2.6)
To reviewers for additional analysis	2 (1.3)
Suggestions to authors	
to paraphrase text	14 (9.1)
to incorporate corresponding references	48 (31.4)
Without suggestions	80 (52.3)
Total	153 (100.0)

Conclusion

Plagiarism detection in biomedicine is very hard. It must be done by a well-trained team and by using a high quality technology. In the VSP this has recently been started using the software, but thoroughly as before, in order to maintain the long tradition of providing high quality of the journal. The main goal is the benefit and satisfaction of a wide range of our customers.

The extent and types of plagiarism in submitted articles have not been considered as alarming so far, but require additional effort to eradicate it.

Avoiding and preventing accidental plagiarism require a high level of education and plays a crucial role, particularly in the training of young researchers, who are the backbone of future biomedical and scientific expertise, and, thus, for publishing activities, too.

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ORIGINAL ARTICLES

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Assessment of mental health in adults of the northern part of the city of Kosovska Mitrovica

Procena mentalnog zdravlja odraslih stanovnika severne Kosovske Mitrovice

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Abstract

Background/Aim. Mental health disorders lead to disorder of effective functioning of people and deterioration of quality of life. Early detection of individuals at risk of mental health disorders is extremely important from the aspect of mental health disorders prevention. The aim of the research was to determine the frequency of mental health problems among adult residents of northern Kosovska Mitrovica and to examine the association between frequency of mental health problems and socio-demographic and other characteristics of the population obtained by the questionnaire. **Methods.** The cross-sectional study on the representative sample of adult residents of northern Kosovska Mitrovica was performed in October 2009. To obtain information about the characteristics of mental health the Goldberg's General Health Questionnaire (GHQ-28) was used. For performing survey at site the method of rapid epidemiological assessment was chosen. Statistical analysis included the methods of descriptive statistics, multivariate regression analysis and calculation of the Cronbach's alpha coefficient of internal consistency of the questionnaire. **Results.** Mental health problems (total score) were present in almost half of the respondents (49.2%). Psychosomatic problems were present in more than half of the respondents (55.4%), while anxiety and insomnia were present in almost half of the respondents (49.2%). Social dysfunction had more than three fifths of the respondents (63.1%) and depression more than a quarter of the respondents (28.5%). More positive responses in the questionnaire were statistically significantly associated with older age, poor financial situation, abuse and assessing of the current political-security situation as high risk. The value of Cronbach's alpha coefficient was 0.705. **Conclusions.** Almost half of the respondents (49.2%) of North Kosovska Mitrovica had mental health problems. Mental health problems were associated with older age, poor financial situation, abuse and considering the current political-security situation as high-risk factor.

Key words:
mental heath; risk factors; risk assessment; adult; serbia.

Apstrakt

Uvod/Cilj. Poremećaji mentalnog zdravlja dovode do poremećaja efektivnog funkcionisanja ljudi i značajno utiču na pogoršanje kvaliteta života. Rano otkrivanje osoba se rizikom od obolevanja od mentalnih poremećaja izuzetno je značajno sa stanovišta prevencije mentalnih problema. Cilj istraživanja bio je da se utvrdi učestalost problema sa mentalnim zdravljem među odraslim stanovnicima severne Kosovske Mitrovice i ispita povezanost učestalosti problema sa mentalnim zdravljem i socijalno-demografskih i drugih karakteristika stanovnika dobijenih upitnikom. **Metode.** Istraživanje je urađeno kao studija preseka na reprezentativnom uzorku odraslog stanovništva severne Kosovske Mitrovice u oktobru 2009. godine. Za dobijanje informacija o karakteristikama mentalnog zdravlja korišćen je Goldbergov Upitnik za opšte zdravstveno stanje. Za anketiranje na terenu izabran je metod brze epidemiološke procene. Statistička analiza uključila je metode deskriptivne statistike, multivarijantnu regresionu analizu i izračunavanje Kronbahovog alfa koeficijenta interne konzistencije upitnika. **Rezultati.** Probleme sa mentalnim zdravljem (ukupan rezultat) imala je skoro polovina ispitanika (49,2%). Psihosomatske probleme imalo je nešto više od polovine ispitanika (55,4%). Anksioznost i insomniju imala je skoro polovina ispitanika (49,2%). Socijalnu disfunkciju imalo je više od tri petine (63,1%) a depresiju nešto više od četvrtine ispitanika (28,5%). Veći broj pozitivnih odgovora u upitniku statistički je značajno povezan sa starijim životnim dobom, lošijim materijalnim stanjem, zlostavljanjem i procenom trenutne političko-bezbednosne situacije kao visoko rizične. Vrednost Kronbahovog alfa koeficijenta iznosila je 0,705. **Zaključak.** Skoro polovina (49,2%) stanovnika severne Kosovske Mitrovice imala je problema sa mentalnim zdravljem. Problemi sa mentalnim zdravljem povezani su sa starijim životnim dobom, lošim materijalnim stanjem, zlostavljanjem i procenom trenutne politička-bezbednosne situacije kao fakotrom visokog rizika.

Ključne reči:
mentalno zdravlje; faktori rizika; rizik, procena; odrasle osobe; srbija.

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Introduction

According to the definition of the World Health Organization, which is an integral part of the Constitution of this organization [1], mental health is a component of health. The World Health Organization points out that mental health is not merely the absence of mental illness, but it is "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" [2]. Mental health disorders lead to disorders of functioning and significantly affect the quality of life. In addition, mental health disorders are associated with physical health disorders, particularly with chronic diseases from which many people die and suffer, such as cardiovascular disease, diabetes, and etc. [3, 4].

Early detection of people at risk of mental disorders developing is extremely important in prevention of mental disorders [5]. So far, a few questionnaires have been created that can help to detect people at risk of mental disorders developing, but the Goldberg`s General Health Questionnaire is one of the most commonly used for this purpose [6]. This questionnaire has been used in various investigations. This questionnaire has been used to examine mental health of users of primary health care [7], workpeople [8], patients with ischemic heart disease and patients with gastrostoma [9, 10], and to investigate mental health of survivors of the tsunami in Indonesia [11].

Within the last decade of the 20th century, Serbia faced many stressful events, such as disintegration of the former state, the United Nations economic sanctions that lasted three and a half years, conflicts in Kosovo, the bombing by NATO in 1999. All this had an effect on mental health of the population, so that the prevalence of mental disorders increased by 13.5% in the period 1999–2002 [12]. In a study on burden of disease and injury in Serbia in 2002 depression is ranked fourth (third for women, and sixth for men) [13] . After the bombing, in June 1999, the Autonomous Province of Kosovo and Metohia came under UN administration [14], and stressful events continued, especially for non-Albanian population. More than half of Serbs fled the Province, and those who remained were subjected to daily attacks. Many of them were kidnapped or killed [15]. Living in such an unstable political and security area affects mental health, but the data on this component of health are deficient. In September and October 1999 Salama et al. [16] were carried out the study on mental health of the population of Gnjilane and Priština using the Goldberg`s a questionnaire. In 2006 under the Health Survey the residents of northern Kosovska Mitrovica were investigated and some aspects of their mental health[17]. According to this survey, more than half of the respondents had problems with some of the aspects of mental health, urging to conduct a survey with on instrument adapted to assess mental health.

The aim of this research was to determine the prevalence of mental health problems in adult residents of North Kosovska Mitrovica and to study the relationship between mental health problems and the basic characteristics of adult residents of northern Kosovska Mitrovica obtained by the questionnaire (gender, age, marital status, number of family members, education, employment, self-rated financial situation, whether a person is displaced, the existence of mental disorders in the family, social support, abuse, assessment of current and future political and security situation).

We hypothesized that mental health was worse in females, adults, residents with lower education, unemployments, poor, displaced persons, abused and with poor social support. Also, we hypothesized that mental health could be worse in those people who take the political-security situation as high-risk factor.

Methods

This cross-sectional study included the representative sample of adults in northern Kosovska Mitrovica, and was performed in October 2009.

The sample was selected by the list of polling units with the number of votes for each constituency and the list of streets that includes voting record. These data are the part of electoral roll for the parliamentary elections in the Republic of Serbia in 2008. A total number of voters in northern Kosovska Mitrovica was 17,876 residents. The required sample size for assessing the prevalence of mental disorders, with the assumption of their frequency in a population of 20%, with an accuracy of 0.7 (7%) and the confidence level of 95% was 126.

To obtain information about socio-demographic characteristics of respondents we used the questionnaire with questions about gender, age, education, occupation, self-rated financial situation, marital status, the presence of mental disorders in the family, social support, abuse and, considering the characteristics of the territory in which they lived, whether or not displaced and if take the current and future political and security situation as risky.

To obtain information about the characteristics of mental health we used the Goldberg`s General Health Questionnaire (GHQ-28) [7]. This questionnaire allows to estimate the prevalence of mental health problems and psychological distress in the target population [18].

The questionnaire consisted of 28 questions divided into 4 groups with 7 questions related to psychosomatic problems, anxiety and insomnia, social functioning and depression. Of these questions, 7 were formulated in positive terms (eg: Do you feel perfectly well and in good health? – questions A1, C1, C3-C7), and the question 21 was formulated in the negative sense (eg.: Yes Do you feel sick? – other questions). In cases of questions asked in positive way, we used the following response scale: 1 = better than usual, 2 = as usual, 3 = worse than usual, 4 = much worse than usual. For 18 questions asked in negative term the following responses were used: 1 = not at all, 2 = no more than usual, 3 = more than usual, 4 = much more than usual. For the question C2 the following response scale were used: 1 = less than usual, 2 = same as usual, 3 = more than usual, 4 = much more than usual. For the questions D4 and D7 the following response scale were used: 1 = definitely no, 2 = do not think I am, 3 = think I have it, 4 = definitely I am [18]. In this questionnaire respondents assessed their condition in the past few

weeks as compared to normal. The classical way of scoring was as follows: the answers 1 and 2 were scored by 0 (zero), and the answers 3 and 4 scored by 1 (one). This scoring method seemed to be sensitive to temporary conditions and allowed detection of mental health deterioration [18]. The scoring in this way did not reveal long-term chronic problems with mental health [19]. To overcome this deficiency, a new scoring was proposed in 1985, that only the first answer was scored with 0, and the others with 1 [19]. Since the tested territory political and security situation deteriorated for many years, we applied a new, modified scoring system proposed in 1985. The author of the questionnaire in 1998 suggested the best threshold to be arithmetic mean of all points of respondents [20], which was used in this research.

Because of the source of information, for the sample of respondents at site the method of rapid epidemiological assessment was chosen [21]. For each constituency the number of respondents was determined and divided into the streets that made up the constituency. The number of respondents was pre-determined for each street to be interviewed and started from the first building or house on the right side of the start. If it was a building, we first surveyed the people from the first flat and then from every second. One flat was skipped. In case of not cooperating in the survey we skipped apartment, according to the ordinal numbers. In case of a house at the beginning of the street, the survey was performed in the first house and then in every second house. The survey in one street was considered finished when included as many respondents as possible. The surveyed people were older than 18 years. Due to the nature of the issues, the author insisted that the respondents complete the questionnaire independently, and only when they insisted the interviewer read questions and recorded answers, which was significantly less frequent, mainly for the elderly respondents. In this way, we surveyed 130 respondents in 40 households. In five households respondents refused to participate in the survey, which means that the rate of response was 89.0%.

The methods of statistical analysis included descriptive statistics and multivariate regression analysis (using the procedure step by step). To determine the reliability of research instrument we determined the Cronbach alpha coefficient of internal consistency of the questionnaire.

Results

The study included 130 respondents. More than half (56.2%) of them were female. The average age was 45.5 ± 17.3 years. Half of the respondents had secondary level of education, and most of them were married (58.5%). More than half of the respondents (56.9%) were employed. Most of them (42.3%) described their financial condition as middle (Table 1).

Table 1

Demographics and socio-economics characteristics of respondents

Characteristics	n (%)
Gender	
Male	57 (43.8)
Female	73 (56.2)
Age groups	
18–24	18 (13.8)
25–34	22 (16.9)
35–44	24 (18.5)
45–54	26 (20)
55–64	20 (15.4)
65+	20 (15.4)
Education	
With not school	3 (2.3)
Incomplete primary school	3 (2.3)
Complete primary school	10 (7.7)
High school	65 (50)
College	25 (19.2)
Faculty	24 (18.5)
Marital status	
Married	76 (58.5)
Cohabitation	2 (1.5)
Single	35 (26.9)
Divorced	4 (3.1)
Widowed	13 (10)
Employment	
Employed	74 (56.9)
Self-employed	3 (2.3)
Retired	24 (18.5)
Housewife	3 (2.3)
Student	19 (14.6)
Unemployed	7 (5.4)
Unable to work	0 (0)
Financial situation	
Very bad	1 (0.8)
Bad	6 (4.6)
Middle	55 (42.3)
Good	53 (40.8)
Very good	15 (11.5)

Table 2 shows the values of arithmetic means of the results obtained by the Goldberg`s General Health Questionnaire – 28 (GHQ-28), as the threshold for determining whether a respondent is in good or poor mental health as well as the proportion of respondents who scored below or above the mean value. Thus, the psychosomatic problems of all respondents

Table 2

The results obtained by the Goldberg's General Health Questionaire-28 (GHQ-28)

Different aspects of mental health	$\bar{x}$	sd	min	max	$< \bar{x}$	$> \bar{x}$
					n (%)	n (%)
Psychosomatic problems	4.61	2.12	0	7	58 (44.6)	72 (55.4)
Anxiety and insomnia	4.18	2.32	0	7	66 (50.8)	64 (49.2)
Social dysfunction	5.52	1.76	1	7	48 (36.9)	82 (63.1)
Depression	1.22	1.88	0	7	93 (71.5)	37 (28.5)
Total score	15.54	5.91	1	28	66 (50.8)	64 (49.2)

with 5 or more positive answers were classified as positive, and they were more than half of the respondents (55.4%). The same result of arithmetic mean was for anxiety and insomnia, that were present in almost half of the respondents (49.2%). There were 6 positive responses for social dysfunction threshold, present in more than three-fifths (63.1%) of the respodents. The threshold for depression was 2, which was marked by more than a quarter of respondents (28.5%). The threshold for the total score was 16 positive responses, which was given by almost half of the respondents (49.2%).

Table 3 shows the results of multiple linear regression for total score related to mental health. There is a highly statistically significant positive correlation between mental health problems and age, which means that these problems are more frequent in the elderly. Problems with mental health were significantly negatively associated with financial state and abuse, showing that mental health problems are more frequent in patients with poor financial situation and abuse. A statistically significant positive correlation was found between mental health problems and assessment of the current political and security situation showing that those who consider it as high risk are in worse mental health.

Table 4 presents the results of multiple linear regression for psychosomatic problems, anxiety and insomnia, social functioning and depression. Psychosomatic problems were significantly positively associated with age, social support and assessment of future political and security situation and negatively with their financial situation, implying that these problems were more frequent in the elderly, those without social support, who consider future political and security situation as high risk and those who were in worse financial situation. Social functioning was significantly positively correlated with age, implying that older people had more frequent problems with social functioning. Anxiety and insomnia were significantly positively associated with age and assessment of the current political and security situation, showing they were more frequent in the elderly and those who considered current political and security situation as high risk. Depression was statistically significantly positively associated with age and marital status, and negatively with their financial situation, that was more frequent in the elderly, widowed and divorced, those with poor financial condition and in people suffering from abuse.

Table 3

Multiple linear regression model (step-by-step) for mental health in relation to variables that are identified as predictors

Explanatory variables (predictors)	Unstandardized coefficient		Standardized coefficient	*t*	*p*
	b	SE	β		
Age	0.12	0.02	0.338	4.79	0.000
Financial situation	-1.48	0.53	-0.197	-2.79	0.006
Abuse	-2.96	1.22	-0.16	-2.42	0.017
Assessment of the current political-security situation	2.24	0.48	0.333	4.66	0.000
Constant	17.76	4.63		3.84	0.000

Table 4

Multiple linear regression model (step-by-step) for different aspects of mental health in relation to variables identified as predictors

Explanatory variables (predictors)	Unstandardized coefficient		Standardized coefficient	*t*	*p*
	b	SE	β		
Psychosomatic disorders					
Age	0.03	0.009	0.28	3.62	0.000
Financial situation	-0.058	0.208	-0.21	-2.77	0.007
Social support	2.29	1.027	0.16	2.24	0.027
Assessment of the future political-security situation	0.77	0.183	0.32	4.19	0.000
Constant	5.33	1.592		3.35	0.001
Social functioning					
Age	0.04	0.01	0.342	4.12	0.000
Constant	3.94	0.41		9.62	0.000
Anxiety and insomnia					
Age	0.04	0.01	0.26	3.4	0.001
Assessment of the current political-security situation	1.15	0.2	0.436	5.69	0.000
Constant	-0.74	0.65		-1.14	0.256
Depresion					
Age	0.02	0.01	0.208	2.74	0.007
Marital status	0.23	0.1	0.17	2.29	0.024
Financial situation	-0.87	0.18	-0.363	-4.78	0.000
Abuse	-1.5	0.43	-0.256	-3.43	0.001
Constant	7.19	1.55		4.6515	0.000

The value of Cronbah alpha coefficient of internal consistency of the questionnaire was 0.705 (95% confidence interval: 0.612 to 0.780), indicating satisfactory reliability of the questionnaire, as the values higher than 0.7 are interpreted as acceptable [22].

Discussion

This research examined the prevalence of mental health problems of residents in northern Kosovska Mitrovica, and the association of mental health problems with demographic, socio-economic and other characteristics of the population, resulting from the characteristics of the territory. The applied questionnaire – GHQ-28, for mental health assessment in previous research showed to have acceptable reliability and validity for use for adult population in different countries. It has been used as a screening test by the World Health Organization in one of multicenter studies [6]. The applied scoring results proved satisfactory for the detection of chronic problems with mental health [23].

The results showed that the average score of positive answers in the questionnaire was 15.54, taken as the threshold for determining the presence of mental health problems, so that each respondent with 16 or more positive answers was indicated as positive. These respondents were nearly half (49.2%). In a similar research for the rankings, which was done for the region of Montreal in Canada, the limit value was 11.45, a positive was 44.5% respondents [5]. This shows that all respondents in northern Kosovska Mitrovica had poorer mental health as a whole, and in addition, higher proportion of respondents had mental health problems. Salama et al. [16] have come to the conclusion that the average score of positive answers for the Serbs from Kosovo and Metohija is greater than all the population in Europe or in other parts of the world. This result coincides with the results of studies that have shown deterioration in mental health of residents living in areas affected by war and unstable political-security situation [24–26].

The study also found that mental health problems were related to older age, poor financial situation, abuse and assessment of the current political-security situation as high risk. This result coincides with the evidence from literature [2, 27], which states that these characteristics are among the most important determinants of mental health. A connection between mental health problems and an assessment of the current political-security situation as high risk is particularly interesting, indicating that the fear of evidently deteriorated political and security situation affect mental health so to cause psychological distress. This result makes the research itself justified, given that the data about mental health of residents of this territory, especially on its determinants, is deficient. In addition, the Serbian Government in its Strategy for the Development Care for Mental Health points out that it is necessary to support research in all areas of mental health in our community and that epidemiological studies on this subject are extremely rare [28]. Determination of residents with mental health problems, but not to the extend of illness, and to define risk groups is very important in prevention of mental disorders. Preventive strategies are maximally effective if applied before the onset of the disorder and if directed to the groups at higher risk of suffering [29]. By establishing that, nearly half the population of the area have mental health problems highlights the importance of this problem, implying the need to implement preventive strategies.

Possible limitations of this study come from the type of study, which examines the relationship between variables in a defined point in time, so it could lead to call in question a variables causality, since there is no information on their relationship in the long time. The average score of positive answers used as a threshold or borderline between good and poor mental health was higher than in other studies. Increasing the threshold in the interpretation of the results leads to a decrease in sensitivity and increase in specificity of instrument [30], which also could be a limitation of the study. However, data about sensitivity and specificity in this case are not known, since we do not use another instrument, so the results could not be compared. The hypothesis of the research is partly confirmed, a restriction may be the sample size, because the biger sample allows to detect more discrete association as statistically significant. Finally, the data could be generalized only to the area of northern Kosovska Mitrovica, with respect to the method used for sampling.

Conclusion

The obtained results show that almost half (49.2%) of the residents of northern Kosovska Mitrovica have mental health problems. Mental health problems are associated with older age, poor financial condition, abuse and taking the current political-security situation as high risk. Theses results partially confirm the hypothesis of the study, but determining the frequency of mental health problems and risk groups is important for planning and implementing prevention strategies for preservation, enhancement and improvement of mental health.

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Mikrocistin-LR u površinskim vodama reke Ponjavice

Microcystin-LR in surface water of Ponjavica River

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Apstrakt

Uvod/Cilj. Cijanotoksini, odnosno toksini cijanobakterija, spadaju u grupu raznovrsnih jedinjenja kako po hemijskoj strukturi, tako i po dejstvu na ljude i životinje. Najveći značaj u ovoj velikoj grupi jedinjenja imaju mikrocistini. Njihovo prisustvo u vodi može da izazove toksične efekte, posebno na jetru. Mikrocistini su rasprostranjeni širom sveta. Cvetanje toksičnih cijanobakterija i njihovi cijanotoksini karakteristični su i za neke površinske vode u Srbiji. Cilj ovog rada bio je da se uvede HPLC metoda za određivanje mikrocistina-LR, da se izvrši validacija metode i odredi sadržaj mikrocistina-LR u površinskoj vodi reke Ponjavice, veoma eutrofne reke, koja poseduje idealne uslove za razvoj cijanobakterija. **Metode.** Za pripremu uzoraka korišćeni su HLB i C8 ulošci, a za dodatno prečišćavanje upotrebljeni su Sep-Pak silika ulošci. Kvantifikacija mikrocistina-LR vršena je metodom HPLC pomoću detektora na principu fotodiode (HPLC/PDA) korišćenjem kolone RP C18 Zorbax Eclips (4,6 × 150, 5 μm), upotrebom mobilne faze sastava 0,1% rastvor trifluorosirćetne kiseline (TFA) u metanolu: 0,1% vodeni rastvor TFA u odnosu 60 : 40 (v/v), na 238 nm. Retenciono vreme mikrocistina-LR iznosilo je 10 min. Uzorci vode reke Ponjavice za analizu mikrocistina-LR sakupljeni su tokom perioda jun-novembar 2008. godine. **Rezultati.** Validacijom metode utvrđena je osetljivost 0,1 μg/L, prinos 89–92% i merna nesigurnost od ± 5%. Rezultati uzoraka vode reke Ponjavice pokazali su da je vrednost mikrocistina-LR dostigla maksimum tokom avgusta i septembra (1,5 μg/L), i da je iznad maksimalno dozvoljene koncentracije za pijaću vodu (1 μg/L) prema preporuci Svetske zdravstvene organizacije. **Zaključak.** Parametri validacije pokazuju da je predložena metoda osetljiva i selektivna, što je, uz činjenicu da je jednostavna i brza, čini pogodnom za rutinsko određivanje mikrocistina-LR. Predloženom metodom određene su povišene koncentracije ovog toksina cijanobakterija u uzorcima vode reke Ponjavice, koje ukazuju na zagađenost Parka prirode „Ponjavica".

Ključne reči:
voda, zagađivači; toksini, bakterijski; mikrocistini; metodi; hromatografija, tečna, pod vp.

Abstract

Background/Aim. Cyanobacterial toxins befall a group of various compounds according to chemical structure and health effects on people and animals. The most significant in this large group of compounds are microcystins. Their presence in water used for human consumption causes serious health problems, liver beeing the target organ. Microcystins are spread all over the world. Waterblooms of cyanobacterias and their cyanotoxins are also common in the majority of surface waters in Serbia. The aim of this study was to propose HPLC method for determination of mikrocystin-LR, to validate the method and to use it for determination of microcystin-LR in the surface water of the river Ponjavica. The Ponjavica is very eutrophic water and has ideal conditions for the cyanobacterial growth. **Methods.** Sample of water form the Ponjavica river were collected during the summer 2008. Coupled columns (HLB, Sep-Pak), were used for sample preparation and HPLC/PDA method was used for quantification of microcystin-LR. **Results.** Parameters of validation show that the proposed method is simple, fast, sensitive (0.1 mg/L) and selective with the yield of 89%–92%. The measuring uncertainty of ± 5% was obtained. The obtained results for surface water show that microcystin concentration reached the maximum level during August and September (1.5 μg/L). The value is higher than maximum allowable concentration of microcystin in drinking water (1 μg/L) proposed by WHO. **Conclusion.** This study contributes to the issue of pollution of the National Park Ponjavica. Besides, literature data and WHO clearly point out harmfulness of cyanobasterias and their toxins and implicate the necessity of legislation concerning determination and monitoring of these toxins in our country. Method used for quentification of mycrocystin-LR was shown to be sensitive, selective, rapid and simple and could be recommended for routine determination of this toxin.

Key words:
water pollutants; bacterial toxins; microcystins; methods; chromatography, high pressure liquid.

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Uvod

Briga o javnom zdravlju u pogledu cijanobakterija usmerena je na sposobnost mnogih vrsta ovih organizama da proizvode toksine. Ozbiljna oštećenja kao što su hepatoenteritis, simptomatska pneumonija i dermatitis nastaju nakon upotrebe ili kontakta sa vodom koja je zagađena toksinima koje proizvode cijanobakterije [1]. Najveći značaj u ovoj velikoj grupi jedinjenja imaju mikrocistini. Mikrocistini su raznovrsna grupa jedinjenja, a njihovo prisustvo dokazano je širom sveta, u vodi, ali i u algama, školjkama, ribama itd [1]. Kao i mnogi drugi cijanotoksini i mikrocistini su dobili ime prema vrsti u kojoj su prvo identifikovani (*Microcystis aeruginosa*) [2]. Kasnije studije su pokazale da ih proizvode i druge cijanobakterije.

Mikrocistini pripadaju grupi jedinjenja ciklične peptidne strukture molekulske mase koja varira od 800 do 1 100. Do danas je okarakterisano preko 60 različitih strukturnih varijanti ovih jedinjenja. U svojoj strukturi sadrže 7 aminokiselina, sa 2 terminalne aminokiseline X i Z, povezane u cikličnu formu. U slučaju mikrocistina LR, X = L-leucin (L) a Z = L-Arginin (R).

Poznato je da mikrocistini ispoljavaju efekte na mnoge organizme, od mikroalgi do sisara. Mikrocistin-LR je sposoban da paralište pokretljivost zelenih algi, što može da izazove povećano naseljavanje i stvaranje slobodnih zona pogodnih za cijanobakterije [3], a ispoljava i štetne efekte na mnogobrojne organizme u vodi. Ribe, školjke, rakovi i drugi vodeni organizmi koji se koriste u ishrani ljudi mogu biti zagađeni i tako predstavljati potencijalnu opasnost za čoveka. Ljudi mogu biti izloženi mikrocistinima direktno preko pijaće vode [1], vode za rekreaciju [4], vode za hemodijalizu [5] ili preko hrane [6]. Kod sisara, pa i čoveka, mikrocistini su selektivni za ćelije jetre, irervizibilno inhibiraju serin-treonin protein fosfatazu PP1 i PP2 i izazivaju dezintregaciju strukture hepatocita, apoptozu i nekrozu jetre, kao i hemoragiju koja može izazvati hemoragijski šok [7].

Mikrocistini su veoma toksični i za mikrocistin-LR, najčešću izoformu, LD-50 iznosi 50 μg/kg t.m. pri intraperitoneumskom unosu, a pri oralnom 5 000 μg/kg t.m. za miša [1]. Brojni su slučajevi gastrointestinalnih bolesti, kao i oštećenja jetre kod ljudi, koji se mogu povezati sa prisustvom mikrocistina u vodi. Opasnost koju nosi prisustvo ovih supstanci u vodama bila je primećena i zabeležena u spisima koji datiraju od pre 1 000 godina. Tada je u Južnoj Kini zabeležena smrt vojnika koji su pili rečnu vodu, koja je pri tom bila zelene boje. U to vreme tačan uzrok smrtnog ishoda nije bio poznat. Zabeležen je i slučaj koji se desio duž reke Ohio 1931. godine. Nakon kiša, voda koja je sadržala mikrocistine prelila se u glavni tok reke izazivajući seriju bolesti koje nisu mogle da se dovedu u vezu sa nekim infektivnim agensima [8]. Slični problemi se dešavaju i u Harareru (Zimbabve), gde deca koja žive u oblasti grada, a koja koriste posebne rezervoare za vodu, svake godine imaju zdravstvene probleme u vreme raspadanja cveta *Microcystisa* u rezervoarima za vodu. Deca koja su koristila druge izvore vode nisu imala zdravstvenih problema [9]. Još jedan događaj sa velikim brojem smrtnih ishoda izazvan cijanobakterijskim toksinima u pijaćim vodama, zabeležen je u Brazilu kada su poplave donele ogroman cijanobakterijski cvet. Prijavljeno je 88 smrtnih ishoda za 42 dana [10]. Nakon analize, rezultati su pokazali da su toksini cijanobakterija bili odgovorni za trovanja.

Povećane koncentracije mikrocistina opravdano je očekivati u vodenim ekosistemima sa fizičkohemijskim karakteristikama koje ukazuju na ubrzanu eutrofikaciju i u kojima se i vizuelno mogu otkriti kolonije cijanobakterija. Ranija fizičkohemijska i algološka istraživanja reke Ponjavice bila su veoma oskudna. Prvi podaci odnose se na fizičko-hemijske karakteristike vode, sastav algalne flore i saprobnost i ukazuju na proces ubrzane eutrofikacije u periodu od 1984. do 1989. godine, što za posledicu može imati zasipanje ovog vodenog ekosistema i njegovo potpuno nestajanje [11]. Osim toga, uočena je i periodična pojava cvetanja cijanobakterija. Upravo ova saznanja uticala su na izbor ove površinske vode za istraživanje mikrocistina-LR.

Imajući u vidu toksikološki značaj mikrocistina, kao i činjenicu da u našoj zemlji nije uvedena metoda za određivanje mikrocistina, cilj ovoga rada bio je da se predloži metode tečne hromatografije visokih performansi (*high performance liquid chromatography* – HPLC) za određivanje mikrocistina-LR u vodi. Za uvođenje metode u rutinski rad trebalo je: postići efikasnu pripremu uzoraka za analizu, optimizovati uslove određivanja, validovati metodu i odrediti mernu nesigurnost metode. Predložena metoda korišćena je za određivanje sadržaja mikrocistina-LR u uzorcima površinske vode reke Ponjavice. Rezultati ovih ispitivanja trebalo bi da doprinesu sagledavanju zagađenosti nacionalnog parka „Ponjavica“.

Metode

Hemikalije i reagensi

U radu su korišćene hemikalije odgovarajućeg stepena čistoće (HPLC *grade*): metanol (JT Baker, Holandija), koncentrovana trifluorsirćetna kiselina (TFA) (99%, Merck, Nemačka) i standard mikrocistin-LR (ALEXIS Biochemicals, SAD). Svi reagensi su pripremani sa dejonizovanom vodom (HPLC čistoće).

Validacija metode

Prilikom uvođenja nove metode u laboratorijsku praksu potrebno je ispitati njenu pouzdanost. To je naročito važno s obzirom na nekoliko ključnih koraka u kojima može doći do grešaka prilikom analize mikrocistina u uzorcima vode. U tu svrhu su određivani uobičajeni parametri validacije: linearnost, detekcioni i kvantifikacioni limit, tačnost i preciznost metode, kao i ispitivanje pogodnosti sistema [12]. Sve analize su rađene sa sertifikovanim standardom od 500 μg mikrocistina-LR, koji je bio rastvoren u 1 mL metanola.

Linearnost je rađena za opseg od 10 do 200 μg/L. Izračunat je faktor odgovora detektora i apsolutna vrednost izraza $y_{izrač} - y_{izm} / y_{izrač}$ (tabela 1). Tačnost metode je proveravana putem *recovery* testa, a preciznost metode parametrom % RSD.

Tabela 1

Faktor odgovora detektora za mikrocistin-LR

x (μg/L)	Y_{izm}	$Y_{izrač}$	Y_{izrac}-Y_{izm}/Y_{izrac}	(Y_{izrac}-Y_{izm}/Y_{izrac}) < 0,03	F = Y_{izm}/X
10 000	13200	10242.00	-0,29	0,29	1320,0
20 000	25827	23588,00	-0,09	0,09	1291,0
50 000	64595	63150,00	-0,02	0,02	1291,0
100 000	114020	129400,00	0,12	0,12	1140,2
200 000	265908	263000,00	-0,01	0,01	1329,5
Xsred					1274.598
σ					77.01099934
%RSD					6.04

F – faktor odgovora detektora (y_{izm}/x); $y_{izrač}$ – površina pika izračunata iz regresione jednačine za odgovarajući standardni rastvor; y_{izm} – površina pika iz hromatograma odgovarajućeg standardnog rastvora

Nakon kvantifikacije svih izvora nesigurnosti i njihovog izražavanja kao standardne nesigurnosti, izračunata je kombinovana merna nesigurnost određivanja mikrocistina-LR u vodi kao kvadratni koren zbira varijansi svih identifikovanih izvora nesigurnosti.

Dobijeni rezultati su obrađeni u softverskom programu Chemstation.

Uzorci i uzorkovanje

Uzorkovanje je obavljeno pomoću specijalnog teleskopa za prikupljanje uzoraka površinskih voda, na četiri unapred definisane lokacije srednjeg toka reke Ponjavice, od Omoljice do Banatskog Brestovca, tokom proleća, leta i jeseni 2008. godine (period od juna do novembra), kada je uočeno cvetanje cijanobakterija. Uzorci su prikupljeni u staklenim bocama od 1 litar zahvatanjem sa površine vode. Boce su punjene do vrha i zatvarane teflonskim zatvaračima. Uzorci su transportovani do laboratorije u frižiderima na +4ºC.

[Reka Ponjavica se nalazi u južnom delu Vojvodine (Srbija), na obodu pančevačke depresije. Izvire iz Kapetanove bare kod naselja Starčevo, a uliva se u Dunav kod sela Dubovca. Ukupna dužina reke je 20 km, prosečna dubina od 0,2 m, a maksimalna dubina 2,5 m. Ceo tok se može podeliti na tri dela: prvi, izvorišni deo od Starčeva do Omoljice i treći od Banatskog Brestovca do ušća u Dunav, potpuno su izmenjeni i pretvoreni u kanale za odvodnjavanje viška podzemnih voda sa okolnog terena; srednji tok, od Omoljice do Banatskog Brestovca je prirodni, neznatno izmenjeni deo na 78 do 71 metara nadmorske visine, sa očuvanim izvornim ekosistemom karakterističnim za sporotekuće ravničarske reke, ukupne dužine 10 km, a zaštićen je kao Park prirode "Ponjavica". U skladu sa zakonom, tok reke Ponjavice razvrstan je u III kategoriju zaštićenih prirodnih dobara kao značajno prirodno dobro. Površina Parka prirode iznosi 183,46 ha, dok površina zaštitne zone iznosi 60,83 ha.

Snabdevanje vode vodotoka odvija se putem podzemnih izdani koje su registrovane na više mesta duž leve obale. Nivo vode u vodotoku je konstantan, a u sušnom periodu godine priticaj vode iz kanalske mreže praktično ne postoji.

U klimatskom pogledu, područje vodotoka Ponjavice pripada umereno kontinentalnom klimatu, podunavskog tipa, sa toplim letima i hladnim zimama, sa srednjom godišnjom temperaturom 11,3ºC i srednjom godišnjom količinom padavina od 616,4 mm.

Pedološki pokrivač u priobalju Ponjavice je černozem, ritska crnica, livadska crnica, a u krajnjem istočnom delu zaštićenog područja je ilovastoglinoviti aluvijum [11].]

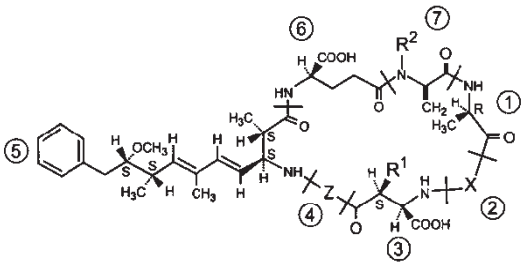
Priprema uzoraka

U prethodnim istraživanjima [13] priprema uzoraka vode za analizu mikrocistina vršena je korišćenjem većeg broja uložaka različite polarnosti (C18, diol, NH_2, CN, silika-gel), kao i različitih sistema rastvarača. U ovom radu korišćeni su HLB ulošci (specijalna vrsta C18 uložaka) i C8 ulošci, za dodatno prečišćavanje upotrebljavani su Sep-Pak silika ulošci (Oassis, Waters, SAD).

Priprema uzoraka za analizu obuhvata filtriranje, prečišćavanje i koncentrovanje. Uzorak se homogenizuje okretanjem boce gore-dole nekoliko puta. Zatim se na 1 000 mL uzorka vode pre filtriranja doda 10 mL 10% TFA. Sve zajedno se promeša i filtrira kroz stakleni membranski filter (GF/C, Whatman). Profiltriran uzorak se sipa u staklenu bocu i doda 10 mL metanola. Ovako pripremljen uzorak se nanosi na HLB-SPE uložak, prethodno kondicioniran propuštanjem metanola (20 mL) i dejonizovane vode (20 mL). Podesi se odgovarajući vakum, tako da protok rastvarača bude 1–2 kapi u sekundi. Voda i metanol se odbace. Nakon toga ulošci se ispiraju sa 10 mL 10% metanola, zatim sa 10 mL 20% metanola i na kraju sa 10 mL 30% metanola. Posle ispiranja, ulošci se eluiraju sa 5 mL 0,1% TFA u metanolu. Dobijeni eluat se uparava u struji azota do suvog, a zatim rastvori u 20 mL metanola. Metanolni rastvor se propusti kroz silkagel uložak (Sep-Pak), koji je prethodno pripremljen sa 20 mL metanola. Nakon nanošenja uzorka uložak se ispira sa 20 mL metanola, a zatim eluira sa 20 mL 10% voda-0,1% TFA u metanolu. Uzorak se upari do suvog a zatim rastvori u 1 mL mobilne faze (0,1% TFA u metanolu : 0,1% TFA u vodi/60 : 40). Ovakav uzorak je spreman za HPLC analizu, a može da se čuva u zamrzivaču na -20º C do trenutka analize.

HPLC/PDA metoda određivanja

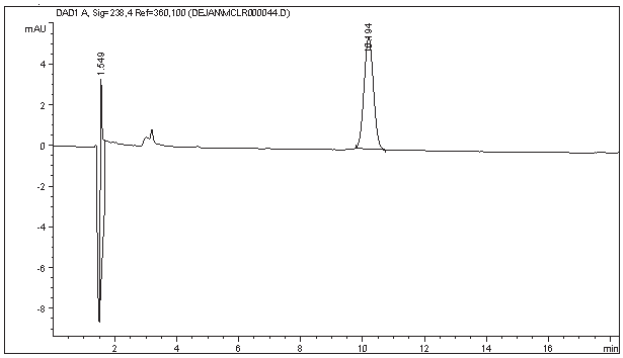
Sadržaj mikrocistina-LR (slika 1) određen je metodom HPLC sa detektorom na principu fotodiode (*photodiode*



Sl. 1 – Opšta struktura mikrocistina (MCYST); X i Z su promenljive L-aminokiseline [kod mikrocistina-LR, × = L-leucin (L), a Z = L-arginia (R)]

array – PDA) (Agilent 1200, SAD). Za analizu korišćena je kolona RP C18 Zorbax Eclips (4,6 × 150, 5μm). Pre početka analize kolona je kondicionirana mobilnom fazom oko 60 minuta pri protoku od 1 mL/min. Zapremina injektovanog uzorka bila je 50 μL. Mikrocistin-LR je korišćen kao sta-

ndard. Eluiranje je vršeno izokratski pri sastavu mobilne faze 0,1% rastvor TFA u metanolu : 0,1% vodeni rastvor TFA u odnosu 60 : 40 (v/v). Detekcija PDA praćena je na 238 nm. Takođe, detektor je pre početka merenja bio uključen 60 minuta. Retenciona vremena i pikovi UV spektara su upoređeni sa standardima, što je iskorišćeno za identifikaciju jedinjenja. Pik mikrocistina-LR registrovan je posle 10 min (slika 2).



Sl. 2 – Hromatogram standarda mikrocistina-LR

Rezultati

Validacijom metode potvrđena je linearnost metode sa koeficijentom korelacije r > 0,995 (r = 0,9972) i odgovarajućom jednačinom y = 1323 × -2988. Za limit detekcije (LoD) određena je vrednost od 3,6 μg/L, a za limit kvantifikacije (LoQ) 6,8 μg/L. Dobijene *recovery* vrednosti, za utvrđivanje tačnosti metode, bile su slične za sva tri ispitivana nivoa koncentracija (za koncentraciju od 50 μg/L srednja vrednost *recovery* je 89,89%; za koncentraciju od 100 μg/L srednja vrednost *recovery* je 90,66% i za koncentraciju od 200 μg/L srednja vrednost *recovery* je 93,99%). Preciznost metode je potvrđena dobijenim parametrom % RSD u vrednosti od 2,461 sa 95% granicom pouzdanosti od 2,057.

Kombinovana merna nesigurnost iznosila je 2 μg/L, a proširena merna nesigurnost U = 2 × 2 = 4 μg/L, tj. 5%.

Analiza vode reke Ponjavice urađena je detaljno tokom juna, jula, avgusta, septembra, oktobra i novembra 2008. godine u Institutu za javno zdravlje Srbije „Dr Milan Jovanović Batut". Fizičko-hemijski parametri kvaliteta vode pokazali su da površinska voda Ponjavice sadrži visoku koncentraciju rastvornih soli što se zaključuje iz podataka o elektroprovodljivosti ovih voda, koja se kreće od 900 do 2 000 μS/cm. Podatak o visokim koncentracijama kalcijumovih i magnezijumovih soli hlorida, sulfata i hidrogenkarbonata bio je u saglasnosti sa ovim vrednostima. Vrednost za pH (preko 8) i alkalitet ukazali su da se radi o blagoalkalnim vodama. Podaci za mutnoću i potrošnju kalijum permanganat ($KMnO_4$) pokazuju da se radi o vodi sa visokim sadržajem organskih materija koje nastaju primarnom proizvodnjom, kao i usled ljudske aktivnosti poput ribolova, navodnjavanja, đubrenja okolnih njiva, bacanja otpada u samu vodu, itd. Visok sadržaj azota je bio takođe evidentan, a činjenica da je gotovo sav azot bio u formi amonijačnog jona, a manji deo u formi nitrita i nitrata ukazao je na to da je reč o redukcionoj vodenoj sredini, gde nije moguć prelazak amonijačnog azota u nitritni i nitratni oblik. Uočena je visoka koncentracija kiseonika tokom letnjih meseci, koja je rezultat visoke koncentracije hlorofila, a koja je detektovana tokom istog perioda. Iako je koncentracija kiseonika bila visoka, pretpostavlja se da visoka temperatura vode (preko 30°C) i organsko opterećenje, ne dozvoljavaju oksidaciju jona amonijuma. Koncentracije rastvornog fosfora bile su niske u periodu kad su vršena merenja, dok su koncentracije organski vezanog fosfora bile izrazito visoke. Uzrok ovakvog stanja su cijanobakterije i drugi fitoplanktoni koji fiksiraju fosfor i koriste ga za svoj razvoj.

Visoke vrednosti hlorofila i dobijene vrednosti fizičko-hemijskih parametara ispitivanja vode pokazuju da je reka Ponjavica veoma eutrofna voda, što predstavlja idealne uslove za razvoj cijanobakterija.

U tabeli 2 date su koncentracije mikrocistina-LR izmerene u uzorcima vode tokom perioda ispitivanja. Razlike u koncentracijama mikrocistina-LR sa različitih lokaliteta za ispitivane mesece nisu bile izražene, ali je konstatovano povećanje sadržaja mikrocistina-LR za period od juna do septembra kada dostiže maksimum na svim ispitivanim lokacijama, da bi nakon toga usledio pad u koncentraciji mikrocistina. Uočeno je da su tokom juna i novembra koncentracije mikrocistina-LR bile ispod granice detekcije, a tokom avgusta i septembra koncentracija je prelazila maksimalnu dozvoljenu koncentraciju za pijaću vodu (1 μg/L) koju propisuje Svetska zdravstvena organizacija.

Tabela 2

Vrednosti koncentracija mikrocistina-LR u vodi za period jun-novembar 2008. godine

Mesec	Mikrocistin LR (μg/L)			
	Lokacija 1	Lokacija 2	Lokacija 3	Lokacija 4
Jun	< 0,1	< 0,1	< 0,1	< 0,1
Jul	0,5	0,6	0,5	0,5
Avgust	1,1	1,0	1,3	0,9
Septembar	1,1	1,5	1,5	1,2
Oktobar	0,3	0,3	0,2	< 0,1
Novembar	< 0,1	< 0,1	< 0,1	< 0,1

Diskusija

Ograničenost vodenih resursa i sve veća potreba ljudi za kvalitetnom vodom predstavlja veliki globalni problem. Poznato je da su količine podzemnih voda ograničene, tako da stanovništvo svoje potrebe zadovoljava prvenstveno korišćenjem površinskih vodenih resursa. Iz tog razloga briga o kvalitetu površinskih voda, a time i o zdravstvenom stanju

korisnika vode, dobija na sve većem značaju kako u svetu tako i kod nas. Može se reći da su površinske vode, kao deo životne sredine, pod velikim uticajem ljudskih aktivnosti koje negativno utiču na životnu sredinu. Takve aktivnosti su, pored prirodnih procesa, glavni uzročnik povećanja sadržaja nutrijenata fosfora i azota u površinskim vodama, što uz ostale faktore, dovodi do eutrofikacije površinskih voda i njihovog zagađenja. Cijanobakterije zauzimaju važno mesto u takvim vodama, s obzirom na to da proizvode veoma toksične mikrocistine.

Poslednjih godina rasvetljeni su razlozi pojavljivanja brojnih cijanobakterija u površinskim vodama, okarakterisani su novi toksini cijanobakterija, a pored toga mnogobrojna istraživanja su olakšala razumevanje mehanizma toksičnog dejstva cijanobakterija na životinje i ljude. Treba istaći da je kontrola cijanobakterija i toksina koje one proizvede razvijene u svetu, što nije slučaj sa našom zemljom, iako je za određene površinske vode karakterističan problem eutrofikacije.

U ovom radu je modifikovan postupak pripreme uzorka i definisani su uslovi za određivanje mikrocistina-LR metodom HPLC sa PDA detektorom. U odnosu na prethodne postupke pripreme uzoraka [13] u kojima se koriste kolone C18, u postupku pripreme datom u ovom radu dodatno se uvodi i primena Sep-Pak silikonskih kolona. Za kvantifikaciju, kao što propisuje i ISO 2005 [14] korišćena je HPLC/PDA metoda pri čemu su definisani optimalni uslovi merenja. Dobijeni parametri validacije ukazuju na to da je postavljena metoda precizna, tačna i osetljiva, sa mernom nesigurnošću ± 5%. Metoda se, takođe, pokazala jednostavnom i brzom za izvođenje. U poređenju sa nedavnim ispitivanjima [15] postignut je bolji prinos i % RSD, iako je osetljivost bila manja i vrednost limita detekcije viša.

Park prirode Ponjavica izložen je prirodnim procesima i ljudskim aktinostima i, prema već objavljenim podacima, svrstava se u ugroženija područja. Dugogodišnja nebriga dovela je do toga da reka polako „odumire“ i tako ugrožava celokupni živi svet povezan sa ovom rekom [11] te je prema ispitivanjima Zavoda za zaštitu zdravlja Pančevo voda Ponjavice uvrštena u IV kategoriju voda[16]. Ako uzmemo u obzir to da je Ponjavica bila u II kategoriji voda, onda ovaj podatak treba svakako da zabrine nadležne organe i alarmira na hitnu akciju.

Naši rezultati potvrđuju hiperprodukciju koja dalje vodi u veliko organsko opterećenje vode. Ovo sa sobom nosi promenu pH vrednosti vode, povećanje potrošnje kiseonika kao i nastajanje štetnih produkata raspada organskih materija, što se odražava na živi svet u vodi.

Rezultati uzoraka vode reke Ponjavica pokazali su da je vrednost mikrocistina-LR dostigla maksimum tokom avgusta i septembra (oko 1,5 μg/L), što je iznad maksimalno dozvoljene koncentracije koju propisuje Svetska zdravstvena organizacija za vodu za piće (1 μg/L)[1], s obzirom na nedostatak regulative za druge vrste voda. Porast sadržaja mikrocistina-LR u letnjim mesecima može se objasniti povećanom produkcijom *Mikrocystis aeruginosa,* dominantne vrste u letnjem periodu, kada kvalitet vode pogoduje njenoj proliferaciji. Tokom leta primećeno je i prisustvo vodenog cveta u obliku zelene skrame na površini vode, a nakon analize utvrđeno je da cvet čini *Mikrocystis aeruginosa*.

Mora se istaći da je, na osnovu fizičko-hemijskih osobina vode i dominantnog prisustva *Mikrocystis aeruginosa* u vodi, očekivana viša koncentracija mikrocistina-LR kao glavnog produkta ovih algi. Tako, u vodama sa sličnim fizičko-hemijskim i biološkim karakteristikama nađene su više koncentracije mikrocistina. U vodama Meiliang Bay u Kini, koje, takođe, pripadaju grupi hipertrofnih jezera, koncentracije mikrocistina-LR iznosile su oko 10 μg/L [17]. Slični rezultati dobijeni su analizom uzoraka vode iz jezera Aasee u Nemačkoj koje, takođe, pripada grupi hipertrofnih jezera. Analize su rađene tokom septembra 2002. godine, a koncentracije mikrocistina-LR bile su u intervalu od 0,6 do 18,3 μg/L [15]. Vrednosti koncentracije mikrocistina-LR dobijene u ovom radu mogu se objasniti činjenicom da mikrocistin-LR nije stabilan molekul u vodi sa visokim sadržajem huminskih suptanci, pri jakoj sunčevoj svetlosti i temperaturama vode iznad 30ºC [18]. Pretpostavlja se da je to uzrok degradacije mikrocistina-LR i pojave niže koncentracije u našim uzorcima.

Zaključak

U ovom radu je predložena metoda pripreme uzoraka vode i određivanje mikrocistina-LR HPLC/PDA metodom koja se na osnovu dobijenih parametara validacije može prihvatiti kao metoda pogodna za rutinsku analizu mikrocistina-LR. Data metoda je primenjena za određivanje mikrocistina-LR u uzorcima vode reke Ponjavice, kao dela parka prirode „Ponjavica“. Dobijeni rezultati pokazali su da se vrednosti mikrocistina-LR, koje su dostigle maksimum tokom avgusta i septembra (oko 1,5 μg/L), na osnovu podataka iz literature mogu smatrati povišenim, ali ne i alarmantnim. No, neophodno je nastaviti sa monitoringom mikrocistina-LR i preduzeti odgovarajuće mere u cilju očuvanja bogatstva prirode ovog kraja.

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Evaluation of the quality of life in patients with segmental dystonia

Procena kvaliteta života bolesnika sa segmentnom distonijom

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Abstract

Background/Aim. Segmental dystonia is an abnormal movement, characterized by involuntary, sustained and repetitive muscular contractions, causing twisting and abnormal posturing of two or more adjacent body parts. It is not a life-reducing condition, but it deteriorates physical, mental and social functioning. The aim of the study was to define the basic demographic and clinical characteristics of patients with segmental dystonia and to estimate their quality of life. **Methods.** The study included patients treated at the Clinic for Neurology – Clinical Center of Serbia (Department for Involuntary Movements). The patients with idiopathic segmental dystonia fulfilled the following questionnaires: general questionnaire, standard questionnaire for estimation of the quality of life SF 36, a list of questionnaires related to disease, and social participation scales. Statistical analysis involving the methods of descriptive statistics and linear regression analysis was used for predictive values of the characteristics. **Results.** The study included 28 patients with segmental dystonia, the mean age of 53.1 ± 15.8 years. Analysis of SF 36 questionnaire item domains showed that patients with segmental dystonia had the lowest score in the domain of body pain (30.6 ± 28.2) and the highest in the domain of physical function (73.6 ± 19.6). Higher values of the scale of the disease severity (β = -0.526, 95% CI -4.719, -0.996; p = 0.0004) and Hamilton depression scale (β = -0.498, 95% CI -1.295, -0.227; p = 0.0007) were more significant predictors of low quality of life. Higher value of the Leisure activities scale (β = 0.611, 95% CI 0.242, 0.772; p = 0.001) was a significant predictor of better quality of life. **Conclusion.** The most important predictors of low quality of life in patients with segmental dystonia were disease severity, low acceptance of illness, depression and low self-esteem.

Key words:
dystonia; quality of life; questionaires; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Segmentna distonija predstavlja pojavu nevoljne, produžene i repetitivne mišićne kontrakcije, koja dovodi do uvrtanja i zauzimanja abnormalnih položaja dva ili više susednih delova tela. To je bolest koja ne skraćuje životni vek, ali otežava fizičko, mentalno i socijalno funkcionisanje bolesnika. Istraživanje je imalo za cilj da definiše osnovne demografske i kliničke karakteristike bolesnika sa segmentnim distonijama i proceni njihov kvalitet života. **Metode.** Studijsku grupu činili su bolesnici lečeni u Klinici za neurologiju, Kliničkog centra Srbije (Odeljenje za nevoljne pokrete). Bolesnici sa idiopatskom segmentnom distonijom popunjavali su sledeće upitnike: opšti, standardni upitnik za procenu kvaliteta života SF 36, bateriju upitnika specifičnih za bolest i skale socijalne participacije. Statistička analiza uključila je metode deskriptivne statistike, a za ispitivanje prediktivne vrednosti obeležja primenjena je linearna regresiona analiza. **Rezultati.** Studija je obuhvatila 28 bolesnika prosečne starosti 53,1 ± 15,8 godina. Analiza pojedinačnih domena SF 36 upitnika pokazala je da bolesnici sa segmentnim distonijama imaju najniži skor u domenu telesnog bola (30,6 ± 28,2), a najviši u domenu fizičkog funkcionisanja (73,6 ± 19,6). Više vrednosti Skale za procenu težine bolesti (β = -0,526, 95% CI –4,719, -0.996; p = 0.0004) i Hamiltonove skale depresivnosti (β = -0,498, 95% CI –1,295, -0,227; p = 0.0007) bile su značajani prediktori lošeg kvaliteta, dok je viša vrednost Skale aktivnost slobodnog vremena (β = 0,611, 95% CI 0,242, 0,772; p = 0,001) bila značajan prediktor boljeg kvaliteta života. **Zaključak.** Najznačniji prediktori lošeg kvaliteta života bolesnika sa segmentnim distonijama jesu težina i loše prihvatanje bolesti, depresivnost i nizak stepen samopoštovanja.

Ključne reči:
distonija; kvalitet života; upitnici; osetljivost i specifičnost.

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Introduction

Dystonia is characterized by sustained and involuntary muscular contractions, causing twisting, repetitive movements and abnormal posturing of a body [1].

According to distribution of involuntary movements, dystonia is divided to focal, segmental, multifocal, hemi- and generalized. Focal dystonia assumes that a single muscle or a muscular group is involved. Segmental dystonia involves two or more adjacent body parts and may be: cranial – two or more parts of the cranial or cervical musculature are involved; axial – trunk and neck are involved; brachial – either one arm and axial musculature or both arms with or without the neck and trunk are being involved, and crural – either one leg and trunk or both legs with or without the truncal involvement. The onset of segmental dystonia is most often focal, that is, a group of muscles is initially involved, with the progression of disease being observed in 15%–35% of patients, usually affecting the adjacent body part [2–6]. The prevalence of different forms of late-onset focal dystonia ranges from 2 to 57 patients per million inhabitants [7, 8], and it is estimated that the proportion of segmental dystonia accounts for 2%–20% of a total number of late-onset dystonias [7–10].

Dystonia is not life-reducing, nevertheless the affected people having these involuntary movements are faced with the multiple problems related to physical, mental and social health. It is a disease appearing in younger or middle-aged people, *i.e.* in their prime of familiar, professional and life expectations in general. The disease is "visible", cannot be self-controlled, and more or less, stigmatizes the affected people. In a significant number of patients, it is followed by pain and tremor, depending upon the extent of localization of the involuntary movements, it results in functional incapacity of varying degree. Ben-Sholomo et al. [11] analyzing the quality of life in 289 patients with torticollis, found a surprising discrepancy between preserved physical status of patients on one hand, and their poor mental health and emotional state on the other. These results suggest that the quality of life in dystonic patients is not exclusively determined by the presence of involuntary movements, but also by other clinical, social, demographic and psychological factors, as well as their interaction.

The assessment value of the quality of life is based on the fact that therapeutical procedures are not simply intended for elimination or abatement of symptoms, but they also imply the assistance rendered to patients for as much as optimal living with their disease. On the other hand, measurement of the quality of life together with other clinical indicators allows for evaluation of the effectiveness of the applied therapeutical procedures.

The objective of our study was to define basic demographic and clinical characteristics of patients with segmental dystonia, as well as to evaluate the quality of life of these patients considering the effect of different demographic, clinical, psychological, social and other factors.

Methods

The study group consisted of patients treated at the Clinic of Neurology, Clinical Center of Serbia (Department for Involuntary Movements), who were diagnosed with dystonia in the period from 1990 to 2005. Inclusion criteria were as follows: present segmental dystonia with all clinical characteristics of idiopathic dystonias, examined and confirmed by two independent neurologists; normal findings of radiological visualization methods (computerized tomography – CT and or nuclear magnetic resonance – NMR) aiming at ruling out the structural lesion of the central nervous system as the cause of dystonia; normal results of laboratory tests (serum copper and ceruloplasmin, urine copper, acanthocytes in peripheral blood smear, immunoserological tests) with a view to exclude most frequent metabolic, degenerative or immunological causes of dystonia.

The patients who met the required criteria fulfilled the following questionnaires: General Questionnaire, Standard Questionnaire for Estimation of the Quality of Life SF 36, a list of questionnaires related to disease and Social participation scales.

The General Questionnaire was created for collection of basic demographic and clinical data, such as sex, age, qualification, marital status, age at the onset of disease, way and time of disease progression, presence of pain, tremor or other involuntary movements, modes of treatment and their effectiveness, etc. This questionnaire was designed to evaluate the severity of the disease by a patient's self-estimation on the 1–10 scale (higher score-more severe disease).

The Generic Questionnaire for Estimation of the Quality of Life or Short-Form Health Survey (SF-26) is a scale proved to be very sensitive for evaluation of the quality of life, that is, severity of global effect of disease on the affected individual. This questionnaire covers eight health domains, divided into the following subscales: physical activities, physical activities and performance of everyday activities, general health, vitality, social activities, emotional activities and mental health. This study used the questionnaire version which was validated and adapted to Serbian-speaking region. SF-36 scoring of the results was carried out by the Likert method, 0 designating the worse and 100 the best possible health [12].

The disease-specific questionnaires include different scales evaluating the effect of internal factors to the quality of life, *i.e.* variables reflecting the premorbid characteristics of individuals, the way the disease is accepted, defense mechanisms, pattern of behavior as a response to the disease as well as the possibility of reactive depression and anxiety. For testing the abovementioned functions, the following scales were used: Rosenberg self-esteem and self-accusation scale [13], Felton acceptance of illness scale [14], Stigma scale [15], Hamilton depression scale [16], and Hamilton anxiety scale [17].

The social participation scales estimate the effect of cohabitation and different aspects of social support rendered to a patient by his/her cohabitants on the quality of life. To evaluate this aspect of the quality of life, the following scales were applied: Zimet multidimensional scale of perceived social support [18] and Leisure time scale [19].

Statistical analyses included descriptive methods (arithmetical mean, standard deviation and standard error). Linear regression analysis was used for analyzing the predictive values of variables.

Results

The our study included 28 patients with segmental dystonia whose basic demographic characteristics are presented in Table 1.

The eyelids were first affected by dystonic involuntary movements in 10/28 (35.7%) of the patients, the neck in 12/28 (42.9%), the right hand in 5/28 (17.9%) and the left hand in 1/28 (3.5%). After the involvement of the first region, the disease spreaded to another adjacent body parts in 26/28 (92.9%) of the patients during the mean time of 3.28 years (ranging from 10 days to 15 years). In 2/28 (7.1%) of the patients, the disease involved two regions from the very beginning, in one patient the right and the left hand simultaneously, and in another the eyelids and the lower face.

Table 2 illustrates the basic clinical characteristics of the patients with segmental dystonia. Tremor at the site of dystonia was evident in 13/28 (46.4%) and pain at the site of dystonic movement/position was present in 17/28 (60.7%) of the patients. Manifestation of other chronic diseases was reported in 12 (42.9%) of the patients with segmental dystonias. Botulin toxin injections were used for treatment in 15 (53.6%) of the cases, the average number of applications was 3.0 while the mean percent of improvement was 54.0%.

Table 3 illustrates the mean values of specific SF-36 questionnaire domains in patients with segmental dystonia. The patients with segmental dystonia had the lowest score in domain of body pain (30.6 ± 28.2) and the highest in the domain of physical function (73.6 ± 19.6).

Table 4 presents the mean values of different scales used for analysis of the quality of life in the patients with segmental dystonia.

The significance of demographic factors, such as sex, age at the onset of the disease, current age, education, employment and marital status for the quality of life was presented in Table 5, while the impact of clinical factors (duration of disease, tremor, pain, comorbidity and botulin toxin treatment) was illustrated in Table 6. None of these factors had significant effect on the quality of life in this group of the patients.

Predictive value of different scales used for evaluation of the quality of life in the patients with segmental dystonia was given in Table 7. Higher values of the Scale of disease severity (β = -0.526, 95% CI -4.719, -0.996; $p = 0.0004$) and Hamilton depression scale (β = -0.498, 95% CI -1.295, -0.227; $p = 0.0007$) were more significant predictors of the low quality of life. Higher value of the Leisure activities

Table 1

Basic demographic characteristics of the patients with segmental dystonia

Variables	Values
Patients No (males/females)	28 (17/11)
Mean age at the onset of the disease (years)	43.3 ± 17.3*
Mean actual age (years)	53.1 ± 15.8*
Employment (employed/unemployed)	15/13
Marital status (married/single)	23/5

*$\bar{x}$ ± SD

Table 2

Basic clinical characteristics of the patients with segmental dystonia

Variables	Values
Duration of disease (years)	9.9 ± 7.9*
Tremor at the site of dystonia (yes/no)	13/15
Pain at the site of dystonia (yes/no)	17/11
Other chronic diseases (yes/no)	12/16
Botulin toxin treatment (yes/no)	15/13
An average application of botulin toxin injections	3.0 ± 2.2*
Response to botulin toxin injections (improvement in percentage)	54.0 ± 26.4*

*$\bar{x}$ ± SD

Table 3

Mean scores of SF-36 questionnaires in the patients with segmental dystonia

Domains	Values ($\bar{x}$ ± SD)
Physical functioning	73.6 ± 19.5
Physical functioning and performance of duties	32.0 ± 41.9
Body pain	30.6 ± 28.2
General health	64.6 ± 15.7
Vitality	58.4 ± 10.0
Social functioning	50.0 ± 13.6
Emotional functioning	38.1 ± 44.2
Mental health	58.7 ± 9.6

Table 4

Mean values of different scales in the patients with segmental dystonia

Scales	Values ($\bar{x} \pm SD$)
Hamilton depression scale	7.2 ± 6.1
Hamilton anxiety scale	8.7 ± 5.8
Scale of disease severity	5.4 ± 1.7
Leisure activities scale	28.0 ± 11.2
Scale of acceptance of illness	2.9 ± 0.7
Stigma scale	14.4 ± 2.7
Multidimensional scale of personal support	72.3 ± 10.0
Self-esteem scale	15.0 ± 2.3
Self-accusation scale	12.0 ± 2.8

Table 5

Predictive impact of demographic factors on the quality of life in the patients with segmental dystonia

Demographic factors	ß coefficient	95% confidence interval	*p*
Sex	-0.085	-9.189–5.992	0.669
Age at the onset of disease	-0.262	-0.355–0.069	0.178
Actual age	-0.131	-0.355–0.069	0.506
Education	0.200	-2.644–8.071	0.307
Employment	-0.078	-8.884–5.991	0.693
Marital status	0.231	-3.890–15.014	0.237

Table 6

Predictive impact of clinical factors on the quality of life in the patients with segmental dystonia

Clinical factors	ß coefficient	95% confidence interval	*p*
Duration of disease	0.311	-0.086–0.828	0.107
Tremor at the site of dystonia (yes/no)	-0.212	-11.208–3.374	0.280
Pain at the site of dystonia	-0.019	-7.980–7.253	0.923
Other chronic diseases (yes/no)	-0.044	-8.334–6.688	0.823
Botulin toxin treatment (yes/no)	0.235	-2.893–11.608	0.228

Table 7

The values of different scales as predictors of the quality of life in the patients with segmental dystonia

Scales	ß coefficient	95% confidence interval	*p*
Hamilton depression scale	-0.498	-1.295–0.227	0.007*
Hamilton anxiety scale	-0.307	-1.118–0.124	0.112
Scale of disease severity	-0.525	-4.719– -0.996	0.004*
Leisure activities scale	0.611	0.242–0.772	0.001*
Scale of acceptance of illness	-0.359	-7.392–0.171	0.060
Stigma scale	-0.105	-1.693–0.991	0.328
Multidimensional scale of personal support	0.192	-0.192–0.555	0.328
Self-esteem scale	0.369	-0.023–2889	0.053
Self-accusation scale	-0.148	-1.744–0.802	0.454

*** – statistically significant**

scale (β = 0.611, 95% CI 0.772; $p = 0.001$) was a significant predictor of better quality of life in the patients with segmental dystonia. The values of Acceptance of illness scale ($p = 0.0060$) and Self-esteem scale ($p = 0.053$) were close to statistical significance.

Discussion

A total of 28 patients with segmental dystonia were analyzed, having focal disease in over 90% of the cases, which subsequently spread to adjacent regions, giving the image of segmental form. In only 7% of the examined patients, the nature of disease was segmental. At the onset of the disease, our patients were 43.3 (4–75) years old. Although dystonia may appear in any age, in 79%–90% of the time it is manifested between the fourth and sixth decade [9, 20–23]. The course of dystonia is unpredictable. The spread of dystonia is, before all, determined by age and location of the initial disorders; therefore, younger people and the onset of dystonia in legs increase not only the possibility of spreading but also the rate of expansion. Adult-age dystonia tends to progress lesser, and it usually develops several years from the initial manifestations [5]. The highest risk of the disease spreading to other body parts appears during the first

five years [24]. The study performed by Svetel et al [25] reported that the highest risk of dystonia spreading was in patients with the initial blepharospasm followed by patients with hand dystonia, torticollis and spasmodic dysphonia. The same study showed that the blepharospasm was also associated with the highest rate of disease progression. Defazio et al. [6] in their study including 159 patients with the blepharospasm as the initial manifestation, found that the risk of spreading was independently increased by older age at the onset of disease, female sex and head and face injuries followed by loss of consciousness.

The quality of life is a complex category determined by individual and/or mutual action of different factors, such as demographic, social and premorbid, as well as factors related to specific characteristics of the disease itself. There are certain differences in determinants of the quality of life between some types of primary focal dystonias, but the question is how much distribution of these difficulties interferes with the quality of life of patients. Zetterberg et al. [26] in their study in 2008 reported that the quality of life was most strongly associated with the level of physical activity and satisfaction as well as with the efficiency of the applied therapy, but that there was no significant correlation of the quality of life and the form of dystonia. The studies comparing the results of SF-36 questionnaire in dystonic patients with the general population criteria revealed that dystonic patients had significantly poorer quality of life in all domains, especially in those associated with physical and social functioning [27–29]. In our study, none of demographic or clinical factors had significant influence on the quality of life in the patients with segmental dystonia, but depression significantly reduced the quality of life. The research conducted in our country to analyze the quality of life in 153 patients with different forms of focal idiopathic dystonias, showed that pain at the site of dystonic movement/position, depression and anxiety most significantly reduced the quality of life in patients with torticollis [30, 31]. Predictors of poor quality of life in patients with blepharospasm are pain in the affected region, depression, anxiety and unemployment, and in patients with graphospasm – depression and anxiety [30, 31].

Analysis of predictive effect of other scales used in evaluation of the quality of life in patients with segmental dystonia showed that higher values of the Scale of disease severity and Leisure activities scale were a significant predictor of both worse and better quality of life, respectively. The values of the Scale of acceptance of illness and Self-esteem scale were close to statistical significance, and a large-sample study would certainly show higher significance. Therefore, in patients with segmental dystonia, a more severe form of the disease, depression and lower degree of social participation are the most significant predictors of poor quality of life. In distinction of segmental dystonia patients, predictors of poor quality of life in patients with torticollis and blepharospasm are severe form of disease, poor acceptance of illness, higher degree of stigmatization and self-esteem, and better quality of life – a degree of social participation and support [30]. The same study demonstrated that the quality of life in patients with graphospasm was significantly reduced by poor acceptance of illness, higher degree of stigmatization and self-esteem, but significantly improved by higher social participation.

A small number of so far published studies have investigated and compared the quality of life in different forms of dystonias. Comparing the quality of life in patients with focal and non-focal dystonias, Gudex et al. [32] found significantly better quality of life in patients with focal dystonias. Page et al. [28] compared the quality of life in patients with focal, segmental and generalized dystonias by means of SF/36 and Euro-Qol questionnaires. The authors reported that the quality of life in all groups of patients was significantly reduced, especially in the domains of physical and social functioning. Patients with generalized dystonia had significantly worse quality of life in relation to patients with focal disease, in the physical and mental health domains. Predictive factors of evaluation of SF-36 physical activities and the quality of life in patients with focal, segmental and generalized dystonias were as follows: "body concept", functional inability, a feeling of physical defect and unemployment. Depression was a major predictive factor of evaluation of SF-36 mental activities and the quality of life in all patient groups [28]. These results indicated poor "body concept", a feeling of physical defect and depression as the main predictors of poor quality of life in dystonias and confirmed the primary role which postural abnormality caused by excessive muscle contraction played in psychosocial adaption in all forms of dystonia – focal, segmental, hemidystonia and generalized [28]. The effect of physical defect on the quality of life may be reviewed in the light of evidence that physical appearance has a large impact on interpersonal interactions and that the feeling of attractiveness has "halo" effect, considering that all beautiful is comprehended as good [33]. Primary role of the body and physical defect concept in defining the quality of life demonstrates a large psychosocial impact of physical deformity on an individual [34]. The spread of dystonia is a significant predictor of the quality of life, on what account the patients with generalized dystonia complain of worse quality of life in comparison to those with the focal disease [28, 35].

Conclusion

Regardless of the application of different tests and methodology, the majority of studies suggest that the quality of life in patients with different forms of dystonia is determined, before all, by the presence of depression and anxiety, severeness of disease and its stigmatizing effect. Dystonia spreading to different body parts does not necessarily mean a more severe form of disease, but it certainly leads to higher stigmatization and more difficult treatment of patients, thus to negative influence on the quality of life.

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The importance of timely ophthalmologic examination in preterm infants at risk of retinopathy occurrence

Značaj pravovremenog oftalmološkog pregleda kod nedonoščadi sa prisutnim rizikom od pojave retinopatije

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Abstract

Background/Aim. Retinopathy of prematurity (ROP) is a multifactorial disease in premature infants. The aim of this study was to determine the incidence of ROP in children treated at the Center of Neonatology, Pediatric Clinic, Clinical Center in Kragujevac, Serbia. **Methods.** The study covered all children with birth weight below 2,000 g and/or gestational age below the 37th week, who from June 2006 to December 2009 underwent ophthalmological examination for ROP. The results of fundoscopy were classified in accordance with the International Classification of ROP. The treatment of infants and those with ROP was conducted in accordance with the early treatment of ROP study recommendations. We analyzed gestational age, birth weight and postconceptional age in two groups: healthy infants and those with severe form of ROP. Statistical analysis was performed using the SPSS 16. **Results.** A total of 478 children met the criteria of screening for ROP. Severe stage of ROP, which required laser treatment, had 102 (21.3%) children. Out of the infants with severe ROP 14 (13.7%) of the infants with APD had aggressive posterior disease, while two (0.4%) remained blind. The differences in the mean values of gestational age between the healthy and the children with severe form of the disease were statistically significant ($p < 0.0005$). The mean value of gestational age for the healthy children was 33.33 ± 2.28 weeks and for the seek infants 30.66 ± 2.79 weeks. The mean value of the weight in healthy children was 1.981 ± 407 g, and in sick children 1.535 ± 434 g which was statistically significant ($p < 0.0005$). Multivariate binary logistic regression showed that the occurrence of the disease depends on body weight and gestational age. **Conclusion.** The incidence of severe forms of ROP was 21.3%. Aggressive form of ROP was present in 13.7% of the children. The cut-off value for body weight was 1.740 g, and for gestationl age 32.5 weeks.

Key words:
retinopathy of prematurity; infant, premature; gestational age; birth weight; incidence; serbia.

Apstrakt

Uvod/Cilj. Retinopatija prematuriteta (ROP) je multifaktorijalna bolest prevremeno rođene dece. Cilj ove studije bio je da se utvrdi incidencija retinopatije prematuriteta kod lečenih u Centru za neonatologiju Klinike za pedijatriju, Kliničkog centra u Kragujevcu. **Metode.** Kod sve dece telesne mase na rođenju ispod 2 000 g i/ili gestacione starosti ispod 37 nedelja, u periodu od juna 2006. do decembra 2009. godine, urađen je oftalmološki pregled na retinopatiju prematuriteta. Rezultati oftalmološkog pregleda su klasifikovani prema Internacionalnoj klasifikaciji za retinopatiju prematuriteta. Lečenje dece sa retinopatijom vršeno je laserom prema preporukama studija za rano lečenje. Analizirali smo gestacionu starost, telesnu masu na rođenju i postkoncepcijsku starost dve grupe: zdrava deca i deca sa teškom formom retinopatije. Statistička analiza rađena je korišćenjem programa SPSS 16. **Rezultati.** Ukupno 478 dece je ispunilo kriterijume skrininga za retinopatiju prematuriteta. Tešku formu retinopatije koja je zahtevala lečenje laserom imalo je 102 (21,3%) dece. Od dece sa teškom formom ROP, 14 (13,7) je imalo agresivnu formu, dok je dvoje (0,4%) dece sa agresivnom formom ostalo slepo. Razlika srednjih vrednosti gestacione starosti između zdrave dece i dece sa teškom formom retinopatije bila je statistički značajna ($p < 0,0005$). Srednja vrednost gestacione starosti zdrave dece bila je 33,33 ± 2,28 nedelje, a bolesne 30,66 ± 2,79 nedelje. Srednja vrednost telesne mase zdrave dece bila je 1 981 ± 407 g, a bolesne 1 535 ± 434 g, što je bilo statistički značajno ($p < 0,0005$). Multivarijantna binarna logistička regresija pokazala je da na pojavu bolesti veliki uticaj ima telesna masa i gestaciona starost dece. **Zaključak.** Incidencija teške forme ROP iznosila je 21,3%. Agresivan oblik ROP imalo je 13,7% dece. Granična vrednost za telesnu masu iznosila je 1 740 g, a za gestacionu starost 32,5 nedelja.

Ključne reči:
retinopatija kod prematurusa; nedonošče; gestacijska starost; telesna masa, rođenje; incidenca; srbija.

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Introduction

Retinopathy of prematurity (ROP) is a proliferative disease of immature retina that may cause severe sight damage or blindness [1–3]. Incidence of ROP and blindness in newborns depends on the level of care and methods used in neonatal intensive care units (NICU), and also more recently on economic development of a country [4].

Two epidemics of ROP were recorded in developed countries in the past. The first one was in 1940s and 1950s, where the main causative factor was supplemental use of oxygen [4–5]. Second epidemic occurred in 1970s, due to increased survival rate of extremely prematurely born babies [4–6]. Recently, a "third epidemic" appeared in the developing countries [7]. Possible causes of the "third epidemic" were: increase in rate of preterm birth, increased survival rate of preterm babies due to development of NICUs; wider screening criteria. The babies are being exposed to less controlled risk factors than in developed countries. Like in the first epidemic, the babies affected in the third one were within wider range of birth weights (BW) and gestational ages (GA) [4, 8–11].

Interestingly, both countries with high and low infant mortality rate (IMR) (> 60/1000 live births and < 9/1000 live births, respectively) do not record blindness caused by ROP, or it is very rare. In the countries with IMR between 9 and 60 per 1,000 live births, ROP emerges as an important cause of blindness [4]. In Serbia, the infant mortality rate is 14/1000 live births (national statistics for 2008), but there are no accurate data at the national level that would identify ROP as possible cause of blindness [12]. In order to prevent blindness due to ROP in countries like Serbia, ophthalmological screening of all newborns with risk of premature retinopathy should be conducted. However, screening criteria are different and subject to change in various countries [12], and there exists the need at the national level to carefully review, revise and adapt these various screening guidelines to the context of the ROP situation in Serbia.

During the revision of international classification of ROP in 2005, the aggressive posterior disease (APD) was included in it [13]. The APD is more commonly seen in infants with BW less than 1,200 g, or with gestational age below 24 weeks. However, in the countries like Serbia, it is also present in infants with bigger BW and older than 24 weeks of GA. This disease is very aggressive, progresses rapidly and may cause retinal detachment and blindness. It requires rapid diagnostics and immediate treatment [12–17].

The aim of this study was to estimate the incidence of ROP and to verify the applicability of national guidelines for screening in our country undergoing socio-economic transition.

Methods

The Neonatology Center of Pediatric Clinic in Kragujevac, Serbia, is an interregional center admitting high-risk infants from an area of 10 municipalities in Serbia. All infants admitted from June 2006 to December 2009 to the facility, with BW under 2000 g and/or GA under 37 weeks were submitted to screening [12]. Screening was conducted outside these criterions in cases with high risk of ROP development, such as respiratory distress.

The first ophthalmologic examination was done between the 4th and the 5th postnatal week. Fundoscopy was performed after dilatation of the pupils. We used 2.5% phenylephrine or 0.5% cyclopentolate drops three times per hour before examination, in order to achieve maximal dilatation of the pupils. Binocular indirect ophthalmoscope with condensing 20 D lens and an indenter was used for the examination. The results of fundoscopy were classified in accordance with the International Classification of Retinopathy of Prematurity (ICROP) [13]. This classification includes three parameters: localization of changes at retina, dilatation of pathologically changed blood vessels and stage of pathologically changed vascularisation.

After the first ophthalmological examination all newborns with normal findings were excluded from further follow-up. We continued to monitor newborns with undeveloped retinal blood vessels, but without signs of ROP, every 7 to 14 days. The treatment of newborns with ROP was conducted in accordance with Early Treatment of ROP (ETROP) study recommendations, which stressed necessity of discovering "prethreshold disease" and early treatment [13]. According to this study, ROP that needs treatment is type 1 ROP: zone I, any ROP stage with plus disease; zone I, stage 3 of ROP without plus disease; and zone II, stage 2 or 3 of ROP with plus disease [13]. Type 2 ROP requires follow-up visit: zone 1, stage 1–2 without plus, zone 2, stage 3 without plus.

During ophthalmological examination we searched for significant dilatation and tortuosity of both vessel types in the first zone, in all four quadrants. The APD appears much earlier than classical ROP, already after three weeks of postnatal age. The APD does not follow the classical pattern of stage 1 through stage 5.

We analyzed the post conceptual age (PCA) in all the groups. PCA is defined as actual postnatal age in weeks (days) minus difference of 40 weeks of gestation and gestation at birth. PCA refers to the time of screening, i.e. first ophthalmologic examination. All the children with AP ROP, the first exam marked the time of the first laser therapy.

Statistical analysis was performed using the Statistical Package for Social Sciences software, SPSS 16. The data are reported as means ± SD. The statistical significance of differences between the results was tested using a two-sided independent Student's *t*-test. The results were considered significantly different when $p \leq 0.05$. The independency between categorical variables was tested by the χ^2 test. The optimal data cut-off was determined by the receiver operating characteristic (ROC) curves. Such cut-off was used for computing sensitivity and specificity. Risk of retinopathy was tested by the multiple binary logistic regression.

Results

The study population consisted of 1223 infants admitted to the Neonatology Center. From this primary population, 478 infants had risk factors for retinopathy. The study group consisted of 273 (57.1%) male and 205 (42.9%) female infants.

After the first ophthalmologic examination, 131 (27.4%) infants had normally developed retinal blood vessels The other 347 (72.6%) infants had primarily undeveloped retinal blood vessels. Within this group that was subjected to further ophthalmological monitoring, 170 (35.6%) infants were found with insufficiently developed retinal blood vessels. They were added to the healthy group of 131 infants, and the total number of newborns with normally developed retinal blood vessels was 301 (62.9%). Seventy-five (15.7%) newborns developed stage 1 or 2 of ROP with spontaneous regression. They were added to the healthy infants, while 102 (21.3%) newborns developed severe stage of ROP, and underwent laser therapy (Figure 1).

The average values of GA, BW and PCA of 376 healthy infants and 102 infants with severe stage of ROP are shown in Table 1.

gestational age for the healthy children was 33.33 ± 2.28 weeks and for the seek infants 30.66 ± 2.79 weeks. Gestational age may be a marker (indicator) of the disease (retinopathy). The cut-off value was 32.5 weeks (Table 2). The sensitivity was 69.3% and the specificity 73.1%. The positive predictive value was 40.9 %, while the negative predictive value was 89.9 % (Figure 2).

The differences in the mean values of the weight between healthy and sick children were statistically significant ($p < 0.0005$). The mean value of the weight in the healthy children was 1,981 ± 407 g and in the sick children 1,535 ± 434 g. Birth weight in infants may be a marker of the disease (retinopathy) . The cut-off value was 1,740 g (Table 2). The sensitivity was 72.1%, and the specificity was 72.3%. The positive predictive value was 41%, and negative predictive value was 90.6% (Figure 3).

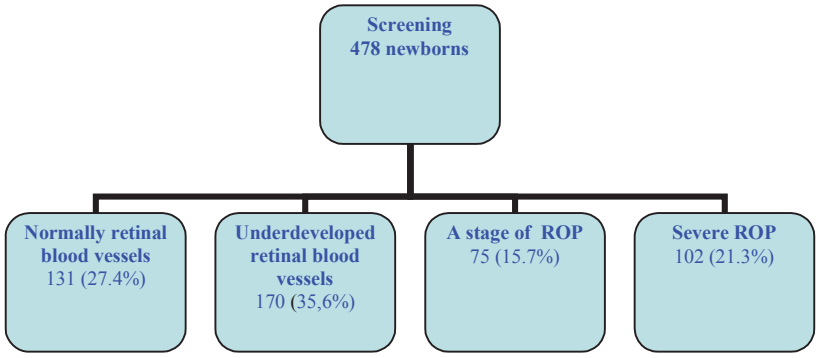

Fig. 1 – Division of premature infants according to the findings in the ophthalmologic examination; ROP – retinopathy of prematurity

Table 1

Primary characteristics of healthy infants (HI) and infants with severe retinopathy of prematurity (ROP)

Parameters	HI (n = 376)	ROP (n = 102)
	x̄ ± SD (min–max)	x̄ ± SD (min–max)
GA [weeks]	33.3 ± 2.3 (26–37)	30.66 ± 2.79 (25–37)
BW [g]	1980.6 ± 406.8 (770–2900)	1535 ± 434 (700–3200)
PCA [days]	245.5 ± 18.2 (210–287)	238.66 ± 19.56 (196–273)

GA – gestational age, BW – birth weight, PCA – post conceptual age

Table 2

Significance of gestational age (GA) and birth weight (BW) in the diagnosis of retinopathy of prematurity (ROP)

Parameters	Test	Infants (n)		Total
		with ROP	without ROP	
GA (weeks)				
< 32.5	positive	70	101	171
> 32.5	negative	32	275	307
Total		102	376	478
BW (g)				
< 1750	positive	74	105	179
> 1750	negative	28	271	299
Total		102	376	478

The differences in the mean values of gestational age between healthy and children with severe form of the disease were statistically significant ($p < 0.010$). The mean value of

Multivariate binary logistic regression showed that the occurrence of the disease depends on body weight ($p < 0.0005$) and gestational age ($p = 0.010$). The odds ratio

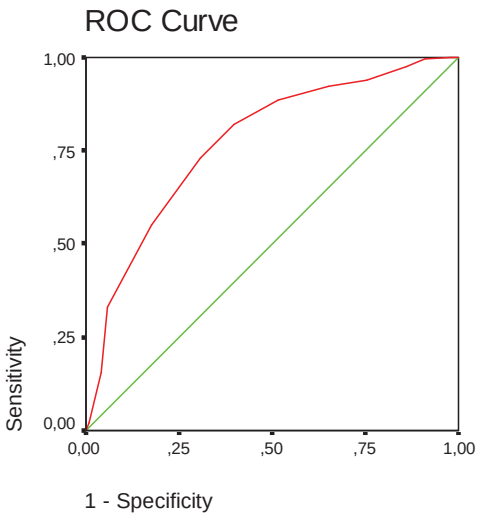

Fig. 2 – ROC curve showing discriminatory value of gestational age (GA) for identifying newborn infants at risk for retinopathy of prematurity (ROP)

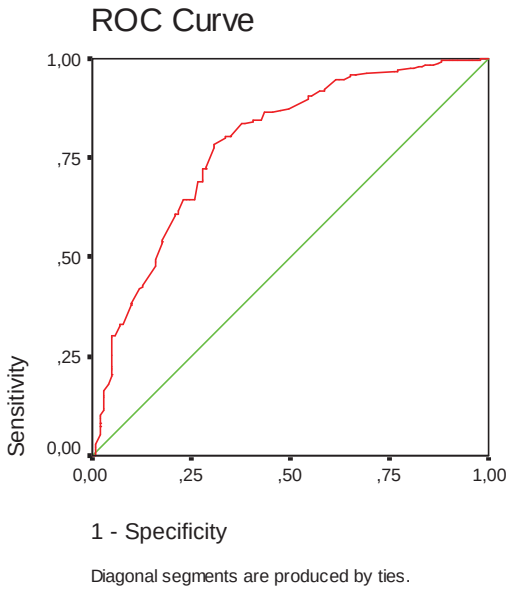

Fig. 3 – ROC showing discriminatory value of birth weight (BW) for identifying newborn infants at risk for retinopathy of prematurity (ROP)

for weight was 0.998 (0.997–0.999). One gram of additional weight reduces the risk of developing the disease by 0.2%. The odds ratio for gestational age was 0.840 (0.736–0.959). One additional week of gestation reduces the risk of developing the disease by 16% (Table 3).

Out of 102 infants with severe stage of ROP 14 (13.7%) developedAPD. Female and male gender was equally present. The average GA of infants with APD was 28.7 (25 to 33) weeks. The average body weight was 1,307.4 g (700 to 1,950) and when APD was diagnosed, PCA was 231.2 days (33 weeks). There were also two (0.4%) blind infants in the screened group, all of them with APD. Both infants had been laser treated immediately after the diagnosis of the disease, but the laser treatment was unsuccessful.

Discussion

ROP is a serious eye disorder that can lead to blindness [5]. Increased survival rate of premature infants requires screening and early treatment in order to control this disease [18]. The aim of screening is to detect all infants with ROP that require treatment. The CRYO-ROP study has defined the "threshold disease" of ROP as a stage when the treatment is necessary [19]. On the other hand, the ETROP study has shown that earlier treatment of highly risky "pre-threshold" stage of ROP leads to even better results [18].

Many countries have national guidelines for screening in relation to BW and GA in accordance with studies on ROP incidence [20–32]. In developing countries (including Serbia) the incidence of ROP is higher, especially among premature infants with higher BW and GA [23–24]. In Serbia, screening is recommended even though the official protocol for screening does not exist. Recommended screening includes infants with GA below 37 weeks and/or BW of 2,000 g or less, as well as newborns at high risk outside this criteria, as discussed in this paper.

The incidence of severe ROP that required laser therapy in our study was 21.45% of all the screened infants. In the group of infants that had laser therapy, the minimal GA was 25 weeks and maximal 37 weeks. BW was in the range from 700 g to 3,200 g. Such a wide range of BW and GA is typical for developing countries, which fall under the "third epidemic" of ROP.

This shows that we should not just follow strictly recommended criteria since the aim of the screening is to discover all newborns at risk for severe ROP. The percentage of severe ROP does not follow closely the percentage of screening, which is high. The American Academy of Pediatrics and the American Academy of Ophthalmology recommend screening in infants with BW of less than 1,500 g or GA of 30 weeks or less, as defined by the attending neonatologist. It also included the selected infants with birth weight between 1,500 g and 2,000 g or GA greater than 30 weeks with an unstable clinical course, as well as those requiring cardiorespiratory support, as determined by their attending pediatrician or neonatologist. UK retinopathy of pre-

Table 3

The influence of birth weight (BW) and gestational age (GA) on the occurrence of retinopathy of prematurity (ROP) (the results of multiple binary logistic regression)

Parameters	Odd ratio	Lower–upper limits	*p*
GA	0.840	0.736–0.959	0.010
BW	0.998	0.997–0.999	0.0005

maturity guideline suggests the following screening criteria: all babies less than 32 weeks GA or less than 1,501 g BW should be screened for ROP and all babies less than 31 weeks GA or less than 1,250 g BW must be screened for ROP [12, 24]. As an example of the need for careful adaptation of screening criteria to the local situation, if we had applied the UK screening criteria directly, we would have missed 31 infants with severe form of ROP, which required laser therapy.

The majority of countries recommend screening in the 4th postnatal week, *ie* between 31 and 34 post conceptional week [19, 23]. Because of early appearance of APD ROP, screening is recommended as early as 30–31 postconceptional week [31]. Screening before 30 weeks and laser therapy would be difficult to administer.

Conclusion

The incidence of severe form ROP in the studied population of our region is very high. Screening criteria applied in this work are much broader than in developed countries. We included all infants with BW under 2,000 g and/or GA under 37 weeks as well as infants outside these criteria in cases with high risk of ROP development. Applying the criteria from developed countries to our case series would have made us to omit a relatively large number of infants with severe form of ROP. In countries in transition, such is Serbia, the necessity for ROP screening is very high, as well as the need to create locally adapted screening criteria.

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Veza između hronične parodontopatije i nivoa serumskih lipida

Association between chronic periodontitis and serum lipid levels

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Apstrakt

Uvod/Cilj. Parodontopatija je lokalni inflamatorni proces koji obuhvata destrukciju parodontalnog tkiva prouzrokovanu bakterijskim insultom. Paradontopatija se karakteriše i sistemskim inflamacijskim odgovorom domaćina, koji delimično može dovesti do povećanog rizika od sistemskih oboljenja, uključujući i poremećeni metabolizam lipida. S druge strane, mnogi ljudi u svetu imaju hiperlipidemiju, koja je poznata kao faktor rizika od ateroskleroze. Cilj ovog rada bio je da se utvrdi veza između parodontalnog oboljenja i nivoa lipida u krvi. **Metode.** U istraživanje je bilo uključeno 50 pacijenata sa parodontopatijom koji nisu imali akutni koronarni ispad u istoriji bolesti. Zdravu, grupu bez parodontopatije (grupa za upoređivanje) činilo je 25 ispitanika. Svi ispitanici su parodontološki pregledani i napravljena im je istoriija bolesti. Mereni su indeks dentalnog plaka, dubina parodontalnog džepa, gingivalni indeks, indeks krvarenja i nivo epitelnog pripoja. Uzorci krvi uzimani su radi određivanja nivoa ukupnog holesterola, triglicerida, „dobrog" i „lošeg" holesterola. **Rezultati.** Utvrđeno je da su kod osoba sa paradontopatijom srednji nivoi holesterola (6,09 ± 1,61 mmol/L), triglicerida (2,19 ± 1,67 mmol/L) i LDL holesterola (4,09 ± 1,40 mmol/L) znatno viši, a nivo HDL holesterola (1,43 ± 0,51 mmol/L) niži u odnosu na osobe bez parodontopatije (4,86 ± 1,37; 1,14 ± 0,71; 3,18 ± 0,64; 1,53 ± 0,32 mmol/L, respektivno). Ova studija je pokazala da postoji značajna veza između parodontalnog oboljenja i nivoa lipida u krvi kod ispitivane populacije. **Zaključak.** Nalazi ove studije pokazuju razliku u koncentraciji ukupnog holesterola, triglicerida, HDL i LDL holesterola u krvnom serumu između osoba sa zdravim parodontom i onih sa parodontopatijom. Rezultati ukazuju na to da parodontopatija može biti faktor rizika i da može doprineti patogenezi ateroskleroze i kardiovaskularnih oboljenja. Međutim, potrebne su dalje studije za potvrdu pretpostavke da parodontalno oboljenje može biti faktor rizika od pojave kardiovaskularnih oboljenja.

Ključne reči:
periodontalne bolesti; rizik, procena; hiperlipidemija; faktori rizika; trigliceridi; lipoproteini, hdl holesterol; lipoproteini, ldl holesterol; periodontalni indeks.

Abstract

Background/Aim. Periodontitis is a local inflammatory process mediating destruction of periodontal tissues triggered by bacterial insult. However, this disease is also characterized by systemic inflammatory host responses that may contrbute, in part, to the recently reported increased risk for systemic diseases, including an altered lipid metabolism. On the other hand, many people in the world are affected by hyperlipidemia, which is a known risk faktor for atherosclerosis. The aim of this study was to determine the relationship between periodontal disease and blood lipid levels. **Methods.** A total of 50 patients with periodontitis included in this study had no documented history of recent acute coronary events. The healthy, non-periodontal subjects (comparison group) comprised 25 subjects. All the patients were periodontology examined and completed a medical history. Dental plaque index, probing depth, gingival index bleeding on probing and clinical attechment levels were recorded. Blood samples were taken on admission for measurements of serum total cholesterol, triglycerides, hight density lipoprotein cholesterol (HDL-cholesterol), and low density lipoprotein cholesterol (LDL-cholesterol). **Results.** The obtained results showed that mean levels of cholesterol (6.09 ± 1.61 mmol/L), triglycerdes (2.19±1.67mmol/l) and LDL cholesterol (4.09 ± 1.40 mmol/L) in individuals with periodontitis were higer, and levels od HDL (1.43 ± 0.51 mmol/L) was lower than those of individuals without periodontitis (4.86 ± 1.37; 1.14 ± 0.71; 3.18 ± 0.64; 1.53 ± 0.32 mmol/L, respectively). **Conclusion.** This study confirms a significant relationship between periodontal disease, regardless its intensity, and blood lipid levels in the studied population. The results imply that periodontitis may be a risk factor and may contribute to the pathogenesis of atherosclerosis and cardiovascular diseases (CVD). However, future prospective randomized studies have to determine whether periodontal disease is a risk factor for the occurence of CVD.

Key words:
periodontal diseases; risk assessment; hyperlipidemias; risk factors; triglycerides; cholesterol, hdl; cholesterol, ldl; periodontal index.

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Uvod

Zbog prisustva velikog broja mikroorganizama, usna duplja može predstavljati izvor hronične infekcije i inflamacije niskog intenziteta, među kojima najvažnije mesto zauzima parodontopatija. Parodontopatija spada u grupu inflamatornih oboljenja u kojima bakterije i njihovi produkti imaju primarnu etiološku ulogu [1]. Kao rezultat parodontalne infekcije i inflamacije, dolazi do gubitka epitelnog integriteta unutar parodontalnog džepa, što dovodi do bakterijemije. Kod pacijenata sa parodontopatijom, čak i dnevne rutinske procedure kao sto su pranje zuba ili žvakanje mogu izazvati tranzitnu bakterijemiju [2]. Zbog moguće bakterijemije, parodontopatija je identifikovana kao potencijalni faktor rizika od većeg broja sistemskih oboljenja [3, 4], posebno za vezu između parodontalnih parametara i rizika od kardiovaskularnih oboljenja (KVO) [5–7].

Kardiovaskularna oboljenja su vodeći uzrok oboljenja i smrtnosti starije populacije u svetu, a ateroskleroza koronarnih arterija se smatra vodećim uzrokom tih oboljenja. Osnova ateroskleroze koronarnih arterija je formiranje aterosklerotskog plaka koje počinje rano u životu. Kardiovaskularna oboljenja su rezultat genetičke predispozicije i izvesnog broja faktora rizika okoline kao što su starost, pol, abnormalni serumski lipidi, pušenje, hipertenzija, povećana telesna masa, fizička neaktivnost i dijabetes melitus. Ovi poznati faktori rizika, nezavisno jedan od drugog ili u kombinaciji, povezani su sa nastankom akutnog koronarnog sindroma uključujući infarkt miokarda [8], ali se smatraju i faktorima rizika od parodontopatije, pa to može biti jedan od prvih mehanizama koji povezuju ova dva oboljenja [9].

Pored klasičnih faktora rizika od koronarnih oboljenja srca, pojavili su se i drugi predvidljivi faktori rizika koji, takođe, mogu imati ulogu u patogenezi koronarnih oboljenja. U te nove faktore uključene su i virusne i bakterijske infekcije praćene inflamacijskim odgovorom domaćina. Druga hipoteza se bazira na činjenici da parodontopatija, odnosno parodontalne bakterije i njihove komponente, mogu ući u krvni tok i izazvati sistemsko oslobađanje proinflamacijskih markera (C-reaktivni protein, fibrinogen i leukociti) i dovesti do promene metabolizma lipida povećavajući njihovo taloženje na zidove krvnih sudova [10].

Tako inflamacija dobija važnu ulogu u patogenezi koronarnih oboljenja srca [11, 12]. Mnogobrojne studije su ispitivale vezu između paradontopatije i KVO čime se doprinelo boljem razumevanju ove veze [13–16]. Matilla i sar. [13] među prvima su koristili ukupni dentalni indeks koji uključuje informacije o karijesu, dubini parodontalnih džepova, perikoronitisu i periapikalnim oboljenjima, i izneli značajnu vezu tih oboljenja sa akutnim infarktom miokarda. DeStefano i sar. [14] iznose da su nivo gubitka kosti i težina parodontopatije povezani sa pojavom KVO. Beck i sar. [15] našli su da je, *odd ratio* (OR) za KVO 1,9, za fatalna srčana oboljenja, a 2,8 za srčani udar. Loesche i sar. [16] iznose da je snižena učestalost oralne higijene povezana sa srčanim udarom, a da poseta lekaru stomatologu ili higijeničaru najmanje jednom godišnje snižava pojavu srčanog udara.

Visoki nivo serumskih lipida je jedan od aktuelnih društvenih problema, pa se hiperlipidemija smatra jednim od najvećih faktora rizika od KVO. Nedavno su izneti podaci da je parodontopatija povezana sa povećanjem koncentracije proaterogenih lipoproteina u serumu [17]. Međutim, ispitivanja Katz-a i sar. [18] nisu našla značajnu vezu između parodontopatije i promena u metabolizmu lipida. S obzirom na različite rezultate ispitivanja i razliku u načinu ishrane ispitivanih populacija, potrebno je dodatno istraživanje da bi se utvrdile realne sistemske promene u koncentraciji lipida izazvane parodontopatijom. Za stomatologe, lekare i njihove pacijente, posebnu važnost ima i pitanje da li se procenjivanje vrednosti oralnog zdravlja i koncentracija serumskih lipida, može koristiti za predviđanje individualnog rizika od KVO, kao dodatak na klasične rizične faktore.

Cilj ovog istraživanja bio je određivanje koncentracije ukupnog holesterola, *low density lipoprotein* (LDL) holesterola, *high density lipoprotein* (HDL) holesterola i triglicerida u serumu i utvrđivanje povezanosti dobijenih vrednosti sa težinom oboljenja parodonta. Takođe, ispitivane su i demografske karakteristike pacijenata sa parodontopatijom koje bi mogle uticati na KVO.

Metode

U studiju je bilo uključeno 75 ispitanika – 50 sa parodontopatijom i 25 ispitanika bez parodontopatije (kontrolna grupa). Pacijenti sa parodontopatijom (27 muškaraca i 23 žene, prosečne starosti 48,76 godina) i bez parodontopatije (18 muškaraca i 7 žena, prosečne starosti 42,80), bili su pacijenti Klinike za stomatologiju Medicinskog fakulteta u Nišu. Niko od ispitanika nije dao anamnestički podatak o postojanju akutne koronarne bolesti ili bilo kog drugog sistemskog oboljenja. Kod svih pacijenata ispitivane grupe postavljena je dijagnoza parodontopatije od strane parodontologa na osnovu kliničkih simptoma (krvarenje gingive, dubina parodontalnih džepova više od 5 mm i nivo epitelnog pripoja više od 4 mm) i rendgenograma na kome je konstatovan gubitak alveolarne kosti. Ispitanici nisu imali terapiju parodontopatije u predhodnih šest meseci. Svi ispitanici su dali saglasnost za uključivanje u ovo istraživanje, a Etički komitet Medicinskog fakulteta u Nišu odobrio je ovo istraživanja (No:01-2800-5).

Posmatrani su standardni klinički parametri: plak indeks po Löe-Sillnes-u (određivan je povlačenjem vrha sonde duž gingivalne ivice, a vrednosti su mu 0–3), gingivalni indeks po Löe-Sillnes-u (vrednosti 0–3), indeks krvarenja po Cowell-u (određivan je sondiranjem parodontalnog džepa i pojavom krvarenja za svaki zub, vrednosti 0–3), dubina parodontalnih džepova (izračunavana je kao rastojanje od ivice gingive do dna parodontalnog džepa) i nivo epitelnog pripoja (izračunavan je kao rastojanje od gleđnocementne granice do dna parodontalnog džepa) [19]. Indeksi su izračunavani za svaki zub, a zatim je određivana srednja vrednost za sve zube. Ispitivanja su vršena pomoću parodontalne sonde (Mičigen O).

Od demografskih podataka, pored godina i pola, bili su uključeni i drugi faktori koji mogu biti rizični za KVO, kao što su socioekonomski status, edukacioni nivo, konzumacija alkohola, indeks telesne težine, dijabetes, pušenje, indeks

telesne mase – *body mass index* (BMI) izračunavan kao odnos telesne mase i telesne visine, kg/m^2). Ispitanici sa dijabetes melitusom i pušači isključeni su iz ovog istraživanja kako bi se izbegao njihov poznati uticaj na parodontopatiju i KVO.

Kod svih ispitanika rutinski je uzimana krv radi kontrole potrebnih biohemijskih parametara: ukupni holesterol, „dobar“ holesterol (HDL holesterol), „loš“ holesterol (LDL holesterol) i trigliceridi. Nivoi frakcije lipida određivani su pomoću standardnih kliničkih hemijskih metoda Centralne biohemijske laboratorije Kliničkog centra Medicinskog fakulteta u Nišu.

U statističkoj obradi podataka korišćen je χ^2 test, Student-ov *t*-test i analiza varijanse (ANOVA) sa *post hoc* Danet-ovim testom za jednake i nejednake varijanse. Za analizu neparamatrijskih vrednosti korišćen je Kruskal-Wallis-ov test. Za merenje prediktivne vrednosti obeležja (demografskih, kliničkih i biohemijskih) na pripadnost grupi (kao nezavisna varijabla) korišćena je regresiona analiza u kojoj je ocenjivan uticaj najpre pojedinačno svakog obeležja kroz univarijantne modele, a zatim uticaj univarijantno značajnih obeležja, kroz multivarijantne modele. Za statističku značajnost određen je nivo od $p < 0,05$.

Rezultati

Polna i starosna struktura, kao i demografske karakteristike pacijenata prikazani su u tabeli 1.

Ispitanici sa parodontopatijom imali su niži stepen obrazovanja, lošiji socijalni status, bili su manje slabije fizičke aktivnosti, više su koristili lekove, konzumirali alkohol i imali su veći BMI, nego osobe bez parodontoptije. Svi demografski parametri razlikovali su se statistički značajno između grupa. Stepen obrazovanja i socijalni status imali su značajnu pozitivnu korelaciju. Fizička aktivnost i BMI takođe su pokazali značajnu korelaciju u obe grupe. U regresionom modelu demografskih parametara najznačajniji prediktivni uticaj na grupu imaju varijable socijalni status, fizička aktivnost i BMI. Pacijenti sa PD imali su veći BMI ($p < 0,001$).

Tabela 2 prikazuje vrednosti biohemijske analize krvi za ukupni holesterol, HDL-holesterol, LDL-holesterol i trigliceride. Za biohemijska ispitivanja korišćene su referentne vrednosti Centralne biohemijske laboratorije Kliničkog centra Medicinskog fakulteta u Nišu.

Vrednosti ukupnog holesterola bile su povećane kod ispitanika sa parodontopatijom (6,09 mmol/L), u odnosu na kontrolnu grupu (4,86 mmol/L) ($p < 0,005$). Takođe, vrednosti LDL-holesterola bile su povećane kod ispitanika sa parodontopatijom u odnosu na zdrave ispitanike (4,09 mmol/L i 3,18 mmol/L; $p < 0,01$). Vrednosti triglicerida bile su u okvirima visokog rizika od nastanka KVO kod grupe ispitanika sa parodontopatijom (2,19 mmol/L) u odnosu na vrednosti kod zdravih ispitanika (1,14 mmol/L) ($p < 0,005$), dok je vrednost HDL-holesterola bila smanjena kod grupe ispitanika sa parodontopatijom (1,43 mmol/L) u odnosu na kontrolnu grupu (1,53 mmol/L) ($p > 0,05$).

Tabela 1

Osnovne karakteristike ispitanika sa parodontopatijom i ispitanika kontrolne grupe

Varijable	Ispitanici		
	Paradontopatija (n = 50)	Kontrolna grupa (n = 25)	Statistički parametri
Pol, broj (%)			
muški	27 (54)	7 (28)	$\chi^2 = 8,715$
ženski	23 (46)	18 (72)	$p < 0,05$
Godine života, $\bar{x} \pm SD$	48,76 ± 15,83	42,80 ± 5,76	ANOVA F = 9,789 $p < 0,001$
Godine obrazovanja, broj (%)			
< 12 godina	32 (64)	8 (32)	$\chi^2 = 7,166$
> 12 godina	18 (36)	17 (68)	$p < 0,05$
Socijalni status, broj (%)			
loš	33 (66)	7 (32)	$\chi^2 = 7,166$
dobar	17 (34)	18 (68)	$p < 0,05$
Fizička aktivnost, broj (%)			Kruskal-Wallis
aktivna	15 (30)	6 (24)	
umerena	35 (70)	19(76)	$\chi^2 = 91,244$
Upotreba lekova, broj (%)			
da	13 (26)	3 (12)	$\chi^2 = 79,087$
ne	37 (74)	22 (88)	$p < 0,001$
Konzumacija alkohola, broj (%)			Kruskal-Wallis
da	29 (58)	14 (56)	$\chi^2 = 9,734$
ne	21 (42)	11 (44)	$p < 0,05$
Indeks telesne mase (kg/m^2), $\bar{x} \pm SD$ (min-max)	26.04 ± 3,38 (19,0–33,5)	22,08 ± 4,10 (17,8–35,9)	ANOVA F=15,784 $p < 0,001$

Tabela 2

Biohemijska analiza krvi kod ispitanika sa paradontopatijom (PD) i kontrolne grupe

Varijable	PD ($\bar{x}$ ± SD)	Kontrolna grupa ($\bar{x}$ ± SD)	ANOVA *post hoc*	*p*
Ukupni holesterol (mmol/L)	6,09 ± 1,61	4,86 ± 1,37	F = 7,042	< 0,005
HDL-holesterol (mmol/L)	1,43 ± 0,51	1,53 ± 0,32	F = 0,550	> 0,05
LDL-holesterol (mmol/L)	4,09 ± 1,40	3,18 ± 0,64	F = 4,999	< 0,01
Trigliceridi (mmol/L)	2,19 ± 1,67	1,14 ± 0,71	F = 7,896	< 0,005

HDL – *high density lipoprotein*; LDL – *low density lipoprotein*

Testirane prosečne vrednosti biohemijskih parametara pokazale su statistički značajnu razliku kod ukupnog holesterola, LDL-holesterola i triglicerida između ispitivane i kontrolne grupe. Promene u vrednostima lipida bile su u granicama koje ukazuju na mogući rizik od KVO kod ispitanika sa parodontopatijom. Veza između LDL-holesterola i ukupnog holesterola bila je veća kod pacijenata sa parodontopatijom nego kod zdravih ispitanika kontrolne grupe. Nivo HDL-holesterola bio je snižen kod pacijenata sa parodontopatijom u odnosu na ispitanike kontrolne grupe ($p < 0,05$).

Koncentracija lipida bila je u statistički značajnoj pozitivnoj korelaciji sa parodontalnim parametrima ($p < 0,001$). Dubina parodontalnih džepova, gingivalno krvarenje i nivo epitelnog pripoja bili su u pozitivnoj korelaciji ($p < 0,001$) sa lipoproteinima (LDL-holesterolom, ukupnim holesterolom, trigliceridima i smanjenom vrednošću HDL-holesterola), za razliku od kontrolne grupe bez parodontopatije gde su vrednosti lipida bile u granicama normale (Tabela 3).

U ovoj studiji prvo je konstatovana moguća veza između parodontopatije i jednog broja poznatih osnovnih faktora rizika od KVO, kao što su stepen obrazovanja, socijalni status, fizička aktivnost, upotreba lekova, konzumiranje alkohola i BMI. Ovi faktori su zajednički za obe grupe oboljenja. Rezultati su u saglasnosti sa rezultatima drugih autora [25, 27]. Zbog slične patologije, koja je evidentna kod oba oboljenja, logično je da se očekuje i neka forma interakcije između njihovih patogenih procesa.

Drugi i veoma važan nalaz ove studije jeste da je parodontopatija direktno praćena promenama metabolizma lipida u odnosu na kontrolnu grupu zdravih ispitanika. Kod ispitanika sa parodontopatijom, vrednosti lipida bile su: za ukupni holesterol 6,09 mmol/L; za trigliceride 2,19 mmol/L; za LDL-holesterol 4,09 mmol/L; a za HDL-holesterol 1,43 mmol/L. U kontrolnoj grupi ove vrednosti bile su 4,86 mmol/L; 1,14 mmol/L; 3,18 mmol/L i 1,53 mmol/L, respektivno.

Tabela 3

Vrednosti parodontalnih parametara kod ispitanika sa paradontopatijom (PD) i kontrolne grupe

Varijable	PD ($\bar{x}$ ± SD)	Kontrolna grupa ($\bar{x}$ ± SD)	ANOVA *post hoc*	*p*
PI	1,64 ± 0,53	0,52 ± 0,42	F = 58,650	< 0,001
IKRV	1,72 ± 0,45	0,40 ± 0,38	F = 86,971	< 0,001
GI	1,76 ± 0,43	0,40 ± 0,38	F = 103,795	< 0,001
DDž (mm)				
Ispitanici sa DDž, n (%)	4,68 ± 1,11	1,90 ± 0,55	F = 94,454	< 0,001
< 5 mm	33 (66)	25 (100)		
≥ 5 mm	17 (34)		$\chi^2 = 17,48$	< 0,001
NEP (mm)	5,72 ± 0,96	1,90 ± 0,55	F = 198,557	< 0,001

PI – plak indeks po Löe-Sillnes-u, IKRV – indeks krvarenja po Cowell-u, GI – gingivalni indeks po Löe-Sillnes-u, DDž – dubina parodontalnih džepova, NEP – nivo epitelnog pripoja

Diskusija

Poslednjih godina pojavile su se studije o vezi dentalnih parametara zdravlja sa rizikom od KVO [5, 7, 20, 21]. Parodontopatija i ateroskleroza, koja je osnova KVO, jesu inflamatorna stanja koja su po prirodi hronična i asimptomatska. Veruje se da parodontopatija može izazvati dugotrajnu sistemsku inflamaciju koja doprinosi razvoju ateroskleroze [22]. Veza između parodontopatije i KVO može biti izazvana zajedničkim faktorima rizika kao što su pušenje, dijabetes, starenje, muški pol, socioekonimski faktori, ali, takođe, postoje dobri dokazi da je i parodontopatija nezavisni faktor rizika od KVO [23, 24]. Takođe, postoje sugestije o vezi parodontalnog stanja i koncentracije lipida [18, 25]. Iznose se i podaci o bliskoj vezi između parodontopatije, prisustva *Porphyromonas gingivalis*-a i povećane koncentracije lipida [26].

Poremećaj frakcije lipida konstatovane kod pacijenata sa parodontopatijom, u odnosu na ispitanike bez parodontiopatije, može biti povezan sa povećanim rizikom od KVO. Poznato je da serumski lipidi igraju važnu ulogu u razvoju ateroskleroze koja dovodi do KVO formiranjem tromba [19, 28]. Neki autori u svojim istraživanjima iznose da ukupni holesterol u krvi, C-reaktivni protein i fibrinogen mogu biti intermedijarni faktori koji povezuju parodontopatiju sa povećanim rizikom od KVO [29, 30]. Sistemska izloženost oralnim bakterijama može dovesti do poremećaja lipidnog metabolizma. Lipopolisaharidi, koji potiču iz parodontalnih patogena, povezuju se u cirkulaciji sa svim klasama lipoproteina [31] i transportuju se u arterijski zid izazivajući aterogenezu [9, 32]. Lipoproteini su važni molekuli za čovečje telo i jedni su od najvažnijih biohemijskih faktora rizika od ateroskleroze [33].

Poremećaj lipida kod parodontopatije, gde postoji inflamirana gingiva, ima proaterogena svojstva i može dovesti do formiranja penušavih ćelija od strane aktiviranih makrofaga [31]. Objašnjenje za vezu između parodontopatije i niske vrednosti HDL-holesterola može biti da hronična inflamacija kod parodontopatije dovodi do oslobađanja lipopolisaharida i proinflamacijskih citokina koji imaju sposobnost da deluju na metabolizam lipida. Pored toga, HDL-holesterol ima antiinflamatorna svojstva, pa njegova snižena koncentracija može indirektno doprineti inflamatornim procesima [9, 34]. Kao u ranijim studijama [18, 25], i u ovom istraživanju nađena je razlika u vrednostima ukupnog holesterola između grupe pacijenata sa i bez parodontopatije. Nalazi koji pokazuju da su ovi parametri veći kod pacijenata sa parodontopatijom ukazuju na to da grupa pacijenata sa parodontopatijom može biti sa povećanim rizikom od KVO. Hiperholesterolemija često se nalazi kod pacijenata sa različitim formama parodontopatije [8, 35]. Tako, parodontopatija može biti nezavisni faktor rizika od KVO, jer promene koje nastaju kod parodontopatije u funkciji ćelija imunog sistema mogu izazvati disregulaciju metabolizma lipida uz pomoć delovanja proinflamacijskih citokina [36].

Ovi podaci obezbeđuju prvi direktni dokaz da parodontopatija, izazvana mikroorganizmima oralnog biofilma, može uticati na akumulaciju lipida *in vivo*. U toku ovog istraživanja, što je u saglasnosti i sa drugim istraživanjima [37, 38], izneto je statistički značajno povećanje rizika od KVO povezanih sa parametrima dentalnog zdravlja. Kako je opisano ranije, parodontopatija stimuliše imune medijatore koji utiču na kardiovaskularni sistem. Zbog toga što je parodontopatija hronična infekcija koja je često asimptomatska, ona može biti izvor poremećenog metabolizma lipida koji je sugeriran kao faktor koji može prethoditi infarktu miokarda i moždanom udaru [39, 40].

Pored toga, nalaz da je poremećaj metabolizma lipida bio prisutan kod parodontopatije sugeriše da ovi pacijenti mogu biti sa povećanom rizikom od KVO, posebno ako ispitanici imaju težu formu parodontopatije. Postoje tvrdnje da osobe sa težom formom parodontopatije imaju manji broj zuba, što može uticati na ishranu pacijenata, pošto te osobe teže žvaću i koriste visokokaloričnu hranu, kao što je masna hrana jer je ona mekša za konzumaciju, a poznato je da je unos masne hrane rizičan za KVO. Ovakva ishrana izaziva povećanje serumskog ukupnog holesterola, LDL-holesterola i triglicerida, dok se vrednost za HDL-holesterol smanjuje. Poznato je da LDL-holesterol povećava odgovore monocita na lipopolisaharide [17], mada postoje i podaci koji ne ukazuju na tu vezu [41]. Razlika u nalazima verovatno može biti zavisna od geografskog položaja prebivališta ispitanika, od kulture i navika ishrane, kao i od stila života različitih populacija.

Na ovaj način se potvrđuju nalazi da je poremećaj koncentracije lipida povezan sa visokom sposobnošću lipida da dovedu do nastanka ateroskleroze kod sistemski zdravih pacijenata sa parodontopatijom. Klinički nalazi ove studije su u korelaciji sa eksperimentalnim radovima na životinjama gde je eksperimentalno izazvana parodontopatija dovela do depozita lipida u krvnim sudovima, dok takav nalaz nije nađen kod zdravih kontrolnih ispitanika bez parodontopatije [42].

Veza između parodontopatije i KVO može biti zavisna od faktora rizika od oba oboljenja koji su česti, ali može biti i direktna veza koja proizilazi iz sistemskog efekta parodontalne bolesti. Parodontopatija, kao potencijalni faktor rizika od sistemskih oboljenja, kao što je KVO, bazira se na pretpostavci da infekcija ima ulogu u patogenezi KVO i da hronična inflamacija kod parodontopatije i odgovor domaćina mogu imati udela u razvoju KVO [24, 43–45]. Prisustvo parodontalnih bakterija takođe može uticati na nastanak KVO [35, 46]. Ovi gram-negativni mikroorganizmi imaju veliku moć probijanja u samo tkivo parodoncijuma, pa je moguća njihova invazija u cirkulaciju gde mogu direktno delovati na oštećenje funkcije endotela ćelija i time doprineti formiranju ateroma, pogotovo što postoje eksperimentalni radovi kojima je dokazano prisustvo *Porphiromonas gingivalis-a* u ateromima krvnih sudova [47]. Pretpostavlja se da su moguće dnevne epizode bakterijemije koje vode poreklo iz širokih parodontalnih lezija (oko 15–20 cm), uzrok za promene u sistemskim faktorima kod parodontopatije [11]. Ovako velika oštećenja površine parodontalnog džepa omogućava prodor, ne samo bakterijskih endotoksina (lipopolisaharida) već i samih bakterija dovodeći do bakterijemije i njihove moguće infiltracije u same ateromatozne ploče oštećenih krvnih sudova [48], o čemu govore i podaci da su parodontalni patogeni identifikovani i u ranim aterosklerotičnim lezijama [22, 24, 49].

Telesna masa je takođe veća kod pacijenata sa parodontopatijom. Kao i u ranijim studijama [50–52] pokazano je da je telesna masa značajno veća kod pacijenata sa parodontopatijom nego kod drugih osoba. Ovi nalazi ukazuju na stil života pacijenata, pošto je konstatovano da pacijenti sa parodontopatijom i promenjenim koncentracijama lipoprotina manje vežbaju, nižeg su socioekonomskog statusa i lošeg materijalnog stanja. Vrednosti lipida u ispitivanoj populaciji mogu zavisiti i od načina ishrane ispitivane populacije pa se na taj način mogu objasniti i razlike. Važno je promeniti i stil života, zbog čega bi pacijenti trebalo da redovno kontrolišu oralno zdravlje kod stomatologa, i stanje parodoncijuma kod parodontologa.

Nalazi ove studije pokazuju da oralni parodontalni parametri mogu igrati važnu ulogu u pojavi rizika od KVO. U ovoj studiji dati su podaci koji potvrđuju statistički značajnu vezu između nekih parodontalnih parametara (gingivalni indeks, indeks krvarenja po Cowell-u, dubina parodontalnih džepova i nivo epitelnog pripoja) i faktora rizika od KVO (povišeni lipidi u serumu).

Prepoznatljivi faktori rizika od KVO, kao što su frakcije lipida, BMI, pušenje, dijabetes melitus i drugi, prisutni su i kod pacijenata sa parodontopatijom koji nikada nisu imali KVO.

Zaključak

Na osnovu rezultata ove studije može se zaključiti da postoji statistički značajna veza između parodontopatije i nivoa ukupnog holesterola, triglicerida, LDL- i HDL holesterola u ispitivanoj populaciji. Na taj način, parodontopatija može biti povezana sa mogućim rizikom od KVO i biti mogući prediktor kardiovaskularnih događaja.

Stomatolozi i lekari trebalo bi da upoznaju svoje pacijente sa vezom između parodontopatije i KVO, a pacijenti da

održavaju dobru oralnu higijenu, kao meru koja obezbeđuje celokupno sistemsko zdravlje.

Kao zaključak može da se iznese i potreba ispitivanja uticaja parodontalnog lečenja na sve predvidljive faktore za nastanak KVO. Pacijentima sa parodontopatijom i abnormalnim serumskim lipidima preporučuju se redovne kontrole i promena stila života kako bi snizili rizik od ateroskleroze i KVO.

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Incarcerated inguinal hernias surgical treatment specifics in elderly patients

Specifičnosti hirurškog lečenja uklještenih ingvinalnih kila kod starijih osoba

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Abstract

Background/Aim. Incarcerated inguinal hernias surgical treatment represents one of the most frequent surgical treatments in elderly patients. The percentage of incarcerated inguinal hernias urgent surgical treatments is growing exponentially with the age in patients over 50. The aim of the study was to investigate some of the factors that may have impact on the incarcerated inguinal hernias surgical treatment outcome in elderly patients. **Methods**. The study included 180 patients classified in two groups: the study group (> 65 years of age) and the control group (≤ 65), managed in the period from January 2005 till March 2009 at the General Surgery Clinic, Clinical Center Niš. **Results**. Most of the patients had right inguinal hernia (52.6%, the study group; 59.1%, the control group). All the study group patients suffered from some of accompanying chronic diseases (100%), opposite to 39 (59%) patients of the control group. Synthetic material was implanted in 124 (68.9%) patients, while the tension technique was performed in 65 (31.1%) patients. The duration of incarceration more than 24 h ($p = 0.015$), previous abdominal surgery ($p = 0.001$), the American Society of Anesthesiologists physical status classification system (ASA classification) ($p = 0.033$) and the presence of chronic diseases ($p = 0.01$) appeared to be statistically significant risk factors for performing intestinal resection in the study group, while in the control group they represented risk factors, but not at the level of statistical significance ($p < 0.05$), except for the duration of incarceration ($p = 0.007$). A higher ASA stage ($p = 0.001$) and the presence of bowel resection ($p < 0.001$) are the most important risk factors for lethal outcome in both groups of patients. **Conclusion.** Incarcerated inguinal hernia in elderly patients is a serious problem. A higher ASA score and the presence of bowel resection are the most important factors related to unfavorable outcome.

Key words:
hernia, abdominal; digestive system surgical procedures; risk factors; aged; comorbidity.

Apstrakt

Uvod/Cilj. Hirurško rešavanje uklještenih ingvinalnih kila predstavlja jednu od najčešćih hirurških intervencija kod starijih osoba. Procenat urgentno hirurški rešenih uklještenih ingvinalnih kila eksponencijalno raste sa godinama starosti kod osoba starijih od 50 godina. Cilj ove studije bio je ispitivanje nekih od faktora koji mogu uticati na ishod hirurškog lečenja uklještenih ingvinalnih kila kod starijih osoba. **Metode**. Studija je obuhvatala 180 bolesnika, razvrstanih u dve grupe: ispitivana (> 65 god) i kontrolna grupa (≤ 65 god), zbrinutih u periodu od januara 2005. do marta 2009. u Klinici za opštu hirurgiju Kliničkog centra Niš. **Rezultati**. Najveći broj bolesnika imao je desnu ingvinalnu kilu (52,6% u ispitivanoj, 59,1% u kontrolnoj grupi). Svi bolesnici ispitivane grupe (100%), imali su neko od pratećih hroničnih oboljenja, nasuprot 39 (59%) bolesnika u kontrolnoj grupi. Sintetski materijal bio je ugrađen kod 124 (68,9%) bolesnika, dok je tenzionom tehnikom bilo zbrinuto 65 (31,1%) bolesnika. Dužina uklještenja preko 24h ($p = 0,015$), prethodne abdominalne operacije ($p = 0,001$), *The American Society of Anesthesiologists* – klasifikacioni sistem fizhičkog stanja (ASA klasifikacija) ($p = 0,033$) i prisustvo hroničnih oboljenja ($p = 0.01$) izdvojili su se kao statistički značajni faktori rizika od izvođenja crevnih resekcija u ispitivanoj grupi, dok su u kontrolnoj grupi predstavljali faktore rizika bez statističke značajnosti ($p < 0.05$), izuzev dužine uklještenja ($p = 0.007$). Viši ASA stadijum ($p = 0.001$) i prisustvo resekcije creva ($p < 0.001$), bili su najznačajniji faktori rizika od letalnog ishoda bolesnika u obe ispitivane grupe. **Zaključak**. Uklještena ingvinalna kila kod starijih bolesnika ozbiljan je problem. Viši ASA skor, kao i postojanje crevne resekcije predstavljali su najvažnije faktore rizika od neželjenog ishoda.

Ključne reči:
hernija, ventralna; hirurgija digestivnog sistema, procedure; faktori rizika; stare osobe; komorbiditet.

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Introduction

Due to abdominal wall weakness and conditions that increase intra-abdominal pressure, external hernia is more frequently seen in elderly patients [1–4]. The estimated incidence of the anterior abdominal wall hernia in patients more than 65 years old is 13 per 1000 [5]. Incarcerated external hernia repairs represent one of the most common emergency procedures performed in elderly patients. Emergency hernia repair rates increase exponentially with the age in patients more than 50 years old [6]. Males predominate among the patients up to 75 years of age, while females prevail in the later age [7, 8]. More recent data indicate that incarcerated inguinal hernias account for about 20% of all small bowel obstructions. Due to the fact that up to 30% of bowel incarcerations require intestinal resection, emergency hernia repair is also associated with significant morbidity and mortality [5]. Up to 75 years of age, 10–15% of men underwent surgical treatment of hernias.

The aim of the study was to examine some of the factors that may affect the outcome of incarcerated inguinal hernias surgical treatment in elderly patients.

Methods

The study included 180 patients divided into two groups: the study group (> 65 years) and the control group (≤ 65 years). All tests were carried out in the period from January 2005 to March 2009 at the Clinic of General Surgery, Clinical Center Niš. During the research, the following parameters were tracked: age, gender, type of incarceration (direct/indirect), the ratio of right to left incarcerated inguinal hernia, related chronic diseases (as it is to do with elderly people with degenerative changes in the body organs and systems), the duration of incarceration (0–24 h, > 24 h), The American Society of Anesthesiology (ASA) classification, intestinal resection, type of surgical procedure (autologous tissue-tension technique or repair with prosthetic material-tension-free technique). In statistical analysis for comparing values sorted by the normality type, parametrical tests (Student's *t*-test, ANOVA – variance analysis with post hock analysis, Bonferroni, Dunnett, Dunnetts T3, Pearson correlation) were used. Analysis of variables not sorted by the type of normality was made by comparing the non-parametrical tests (Mann-Whitney U test, Spearman Correlation, χ^2 test, Fisher exact probability test the null hypothesis). Analysis of survival was made through Cox Regression models, where univariant "Enter" method was used to determine hazard rate (HR). By means of univariant logistic regression, "Enter" method use, the crude odds ratio-cross ratio (OR) has been defined, the risk factors analyzed variables. The statistical significance was determined at the level of $p < 0.05$ and implemented by software package SPSS (version 15).

Results

The study included a total of 180 patients of whom 114 were in the study group and 66 in the control group. The patients in the study group (the average age of 71.28 ± 5.06 years), were significantly older than those in the control group whose average age was 49.68 ± 14.54 years. As expected, there was a statistically significant difference in the age of the study group and control group at the level of significance $p < 0.001$. Out of 114 patients in the study group, 20 (66.7%) had direct and 94 (62.7%) indirect hernia. Of 66 patients in the control group, 10 (33.3%) had direct and 56 (37.3%) indirect hernia. In either of the analyzed groups, no statistically significant differences was observed in the frequency of the occurrence of displayed hernia forms (χ^2: $p > 0.05$). (Table1). The highest number of patients had a right inguinal hernia (52.6% in the study group and 59.1% in the control group). All patients in the study group suffered from some of chronic diseases (100%), which was significantly more than 39 (59%) patients in the control group (Table 1).

Table 1

Characteristics of the patients with incarcerated inguinal hernia

Parameters	Study group	Control group	Total n (%)	*p*
Age (years), $\bar{x} \pm SD$	71.28 ± 5.06	49.68 ± 14.54		< 0.001
Men, n (%)	101 (114)	58 (66)		< 0.001
Women, n (%)	13 (114)	8 (66)		< 0.001
Direct hernia, n (%)	20 (66.7)	10 (33.3)	30 (100)	
Indirect hernia, n (%)	94 (62.7)	56 (37.3)	150 (100)	
Right hernia, n (%)	60 (52.6)	39 (59.1)	99 (55)	
Left hernia, n (%)	37 (32.5)	24 (36.4)	61 (33.9)	
Billateral hernia, n (%)	17 (14.9)	3 (4.5)	20 (11.1)	
Chronic diseases, n (%)	114 (100)	39 (59)	153 (85)	< 0.001

In most cases, the type of surgery in the case of incarcerated inguinal hernia was determined in individual assessment of the surgeons. Of 114 patients in the study group, 45 (39.5%) patients were subjected to tension surgical technique. Among the control group patients, tension technique was applied in 11 (16.7%) patients. Synthetic material was embedded in 69 (60.5%) patients of the study group, and in 55 (83.3%) patients of the control group. It can be asserted, with the error level of $p < 0.001$ that much bigger statistically important number of the control group patients had synthetic material implanted compared to patients in the study group (Table 2).

Table 2

Type of surgical treatment in the patients of the study and control groups

Type of surgical treatment	Study group		Control group		Total		*p*
	n	%	n	%	n	%	
Tension technique	45	39.5	11	16.7	65	31.1	
Synthetic material	69	60.5	55	83.3	124	68.9	0.001
Total	114	100	66	100	180	100	

Owing to univariant binary logistic regression, as a statistically significant risk factor for performing intestinal resection in the study group, there were singled out the duration of incarceration over 24 h (OR = 12 688, 95% CI = 1.64–98.37, p = 0015), previous abdominal surgery (OR = 2119, 95% CI = 0569–5321, p = 0.001), ASA classification (OR = 9344, 95% CI = 1.12–72.82, p = 0.033) and the presence of chronic diseases (OR = 3985, 95% CI = 1236–5695; p = 0.01). Previous analyzed factors in the control group represented the risk factors, but not at the level of statistical significance ($p < 0.05$), except the duration of incarceration (p = 0.007) (Table 3).

Table 4 shows the summary statistics of Cox regression model and log rank test of patients survival length. The patients' age in the study group did not represent a statistically significant risk factor for lethal outcome (p = 0.381). The length in survival in both study and control group seems not to differ by age (p = 0.356). Gender in the study group did not represent a statistically significant risk factor for lethal outcome (p = 0.327). Also, there was no difference between the groups in terms of the length of survival by gender (p = 0.276). By increasing ASA stage for one, a chance for lethal outcome is increased 10.6 times at the level of significance (p = 0.001). The presence of intestinal resection was a

Table 3

Crude Odds Ratio (OR) of the analyzed risk factors for performing intestinal resection

Parameters	Study group	*p*	Control group	*p*
	OR (95% CI)		OR (95% CI)	
Type of incarceration				
direct	1			
indirect	6.145 (0.78–48.39)	0.085	26.721 (13.52–47.63)	0.879
Duration of incarceration				
0–24	1			
>24	12.688 (1.64–98.37)	0.015	27.352 (13.54–40.11)	0.007
Previous abdominal surgery				
no	1			
yes	2.119 (0.569–5.321)	0.001	1.965 (0.211–3.569)	0.325
ASA classification				
1–2	1			
3–4	9.344 (1.12–72.82)	0.033	27.654 (11.35–49.52)	0.876
Chronic diseases				
no	1			
yes	3.985 (1.236–5.695)	0.01	6.396 (2.369–9.574)	0.154

CI – confidence interval

Table 4

Cox regression model for the survival analysis

Factors	Hazard rate	95% CI.	*p*	*p* (Log Rank)
Age (year)				
< 65	1	/	/	
> 65	2.538	0.316–20.416	0.381	0.356
Gender				
male	1	/	/	
female	0.363	0.048–2.760	0.327	0.276
*ASA				
continuous	10.610	2.582–43.590	0.001	
resections				
no	1	/	/	
yes	6.440	2.375–17.461	< 0.001	< 0.001
Duration of incarceration				
$< 24^h$	1	/	/	
$> 24^h$	32.035	0.192–55.535	0.01	0.024

Continuous – parameter ASA was analyzed as a continuous variable

statistically significant risk factor for lethal outcome, increasing the chance 6.4 times ($p < 0.001$) and the patients with resection had a significantly shorter survival time than those without resection ($p < 0.001$). The duration of incarceration over 24 h was a statistically significant risk factor for lethal outcome, increasing the chances by 32 times ($p = 0.01$) and the patients with resection had significantly shorter survival time than the patients without resection ($p = 0.024$).

Discussion

Strangulation hernia is a condition in which the hernia cannot be returned to the abdomen. By putting emphasis on the increased risk of intestinal obstruction, strangulation incarceration gets a great importance [8]. Incarcerated external hernias are the second most important cause of intestinal obstruction [9]. In elderly people about 40% of inguinal hernias are surgically treated, due to incarceration or intestinal occlusion. Although some earlier studies have presented data that only 5% of all inguinal hernias require urgent surgical care [10], others have suggested that this percentage is slightly higher and amounts up to 13% [11]. Since the anterior abdominal wall hernia incarceration, followed by incarceration of intestinal curves, is associated with high percentage of morbidity and mortality [10, 12], urgent surgical intervention is necessary. There is a generally accepted view that hernia should be electively managed in order to avoid later complications [13]. However, many patients are undiagnosed, or consciously reject the proposed surgery, that resulting in occurrence of many emergency surgeries, because of "neglected" cases of hernia. Due to the increased risk of postoperative complications in elderly people, surgeons sometimes reluctantly access the management of elective inguinal hernias [1]. Despite the universal acceptance of the importance of hernias elective management, inguinal hernia is still a common cause of acute abdomen [14]. This is not only attributed to the fact that many patients, especially elderly, experience incarceration while on the waiting list for elective surgery [15], but to the primary factors responsible, such as a large hernia proportion, incarceration (long before a doctor learn about that), the low level of public awareness about the danger of incarceration or just to non-surgical medical staff refusal to speak to the patient about the known risk factors [16]. There were no significant differences in the occurrence frequency of inguinal hernia displayed forms between the groups, as reported by studies done in other healthcare institutions [1, 11]. Comparing the prevalence of hernia types in a number of scientific papers, it seems that indirect hernias dominate over the direct ones in the proportion ranging from 7 : 3 to 10 : 1 in favor of indirect hernias [1]. Of 114 patients in this study group, 20 (66.7%) patients had direct and 94 (62.7%) patients had indirect incarcerated hernia. Of 66 patients of the control group, 10 (33.3%) patients had direct and 56 (37.3%) patients indirect incarcerated hernia. There was not more frequent occurrence of indirect than direct incarcerated inguinal hernia, thus no statistically significant difference existed in the displayed hernia forms occurrence frequency (χ^2: $p > 0.05$) in neither of the groups, concering sex, also.

Another important factor, contributing to the unwanted outcome in the patients with incarcerated inguinal hernia, is related to comorbid chronic diseases [17, 18]. Moreover, this factor gets a statistical significance when talking about mortality [19]. All the patients in the study group had some chronic diseases (100%) which was statistically more significant than 39 (59%) patients in the control group. Symptoms duration in the study group was accompanied by incarceration duration and lasted from one to three days. Duration increased with the age increase, which could be observed in other studies, too [1]. Late hospitalization is generally considered as an important factor for determining the level of intestinal resection and subsequent morbidity and mortality [10, 20–22]. Incarceration and strangulation with or without intestinal obstruction are major complications [23]. Roughly speaking, about 15% of all the patients with incarcerated intestinal curve required resection because of intestinal necrosis caused by strangulation [20, 24]. Manual reposition may be the method of choice without resection in incarcerated inguinal hernia, although there are no strict criteria to clearly differentiate strangulation, except the obvious peritonitis [24]. Statistically significantly a higher number of patients studied in both groups without intestinal resection, had incarceration that lasted less than 24 h (50.3% *vs* 3.4%, $p < 0.001$). Our observations showed that, according to Cox's regression model and logrank test on the patients with and without intestinal resection, the presence of intestinal resection was a statistically significant risk factor for lethal outcome, increasing the chance 6.4 times and the patients with resection had a significantly shorter survival time than those without resection. Open tension-free technique was the most common surgical technique type as in all previous studies [25–27], and in both tested groups of our study. This technique contributed in managing a total of 124 (68.9%) patients. Taking into account general attitude that synthetic material should not be implanted in patients younger than 30 years of age, because of the netting deformation during a young organism development, as well as because of the surgeons' fear to implant synthetic material in intestinal resection cases due to possible complications, we can argue with the level of error ($p < 0.001$), that much higher number of patients in the control group, 55 (83.3%), had a built-in synthetic material, than it was the case in the study group, 69 (60.5%). In previous studies on patients with incarcerated inguinal hernias, it has been observed that a high ASA score is an independent predicting factor for small bowel gangrene [28]. Alvarez et al. [19] not only confirmed the higher rate of complications, but also showed a higher rate of mortality in patients with higher ASA grade. In our study, ASA grade was a risk factor for performing intestinal resection, but not at the level of statistical significance.

Conclusion

Thus, incarcerated inguinal hernia in elderly patients is a serious problem, showing how simple surgical problems may have lethal outcome. It carries a high risk of disease developing in the unwanted direction with the pres-

ence of associated chronic diseases. All the patients in the study group had some of chronic diseases. Statistically significant risk factors for performing intestinal resection in the study group patients were duration of incarceration longer than 24 h, previous abdominal surgery, higher ASA classification, whereas in the control group, the only statistically significant risk factor was duration of incarceration for more than 24 h.

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Appearance of femoropopliteal segment aneurysms in patients with abdominal aortic aneurysm

Pojava aneurizmi femoropoplitealnog segmenta kod bolesnika sa aneurizmom abdominalne aorte

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Abstract

Background/Aim. To promote better treatment outcome, as well as economic benefit it is very important to find out patients with simultaneous occurrence of both aortic and arterial aneurysms. The aim of this prospective study was to determine the frequency and factors affecting femoropopliteal (F-P) segment aneurysms appearance in patients with abdominal aortic aneurysms (AAA). **Methods.** This study included 70 patients who had underwent elective or urgent surgery of AAA from January 1, 2006 to December 31, 2007. After ultrasonographic examination of F-P segment, all the patients were divided into two groups – those with adjunctive F-P segment aneurysm (n = 20) and the group of 50 patients witho no adjunctive F-P segment aneurysm. In both groups demographic characteristics (gender, age), risk factors (diabetes mellitus, elevated serum levels of cholesterol and triglycerides, arterial hypertension, smoking, obesity) and cardiovascular comorbidity (cerebrovascular desease, ischemic heart desease) were investigated. **Results.** Twenty (28.57%) patients who had been operated on because of AAA, had adjunctive aneurysmal desease of F-P segment. Diabetes was no statistically significantly more present among the patients who, beside AAA, had adjunctive aneurismal desease of F-P segment ($\chi^2 = 0.04$; DF = 1; $p > 0.05$). Also, in both groups there was no statistically significant difference in gender structure ($\chi^2 = 2.05$; DF = 2; $p > 0.05$), age ($\chi^2 = 5.46$; DF = 1; $p > 0.05$), total cholesterol level ($\chi^2 = 0.89$; DF = 1; $p > 0.05$) and triglyceride ($\chi^2 = 0.89$; DF = 1; $p > 0.05$) levels, the presence of arterial hypertension ($\chi^2 = 1.38$; DF = 2; $p > 0.05$), smoking ($\chi^2 = 1.74$; DF = 1; $p > 0.05$), obesity ($\chi^2 = 1.76$; DF = 1; $p > 0.05$) and presence of cerebrovascular desease ($\chi^2 = 2.34$; DF = 1; $p > 0.05$). Conversly, ischemic heart desease was statistically significantly more present among the patients who, beside AAA, had adjunctive aneurismal desease of F-P segment ($\chi^2 = 5.45$; DF = 1; $p < 0.05$). **Conclusion.** Twenty patients, beside AAA, had adjunctive F-P segment aneurysm. The results of this study suggest the necessity of preforming ultrasonographic examination of F-P segment in all patients with proven AAA.

Key words:
aneurysm; femoral artery; popliteal artery; risk factors; diagnosis; ultrasonography; aortic aneurysm, adominal.

Apstrakt

Uvod/Cilj. Zbog boljeg ishoda lečenja kao i ekonomske koristi, veoma je važno otkriti bolesnike sa istovremenom pojavom aneurizme aorte i arterije još u ranom stadijumu. Cilj ove prospektivne studije bio je da se utvrde učestalost i fakori koji utiču na pojavu aneurizme femoro-poplitealnog (F-P) segmenta kod bolesnika sa aneurizmom abdominalne aorte (AAA). **Metode.** Studijom je bilo obuhvaćeno 70 bolesnika kojima je u periodu od 1. januara 2006. do 31. decembra 2007. godine, AAA lečena operativno, elektivno ili urgentno. Nakon ultrasonografskog pregleda femoropoplitealnog (F-P) segmenta formirana je grupa od 20 bolesnika koji su imali, odnosno 50 bolesnika koji nisu imali pridruženu aneurizmu F-P segmenta. Kod bolesnika obe grupe analizirane su demografske karekteristike (pol, životno doba), faktori rizika (šećerna bolest, povišen serumski nivo holesterola i triglicerida, arterijska hipertenzija, pušenje, gojaznost) i kardiovaskularni komorbiditet (cerebrovaskularna i ishemijska bolest srca). **Rezultati.** Dvadeset (28,57%) bolesnika operisanih zbog AAA imalo je pridruženu aneurizmatsku bolest F-P segmenta. Šećerna bolest nije bila statistički značajno češće prisutna kod bolesnika koji su pored AAA imali i pridruženu aneurizmatsku bolest F-P segmenta ($\chi^2 = 0,04$; DF = 1; $p > 0,05$). Takođe, kod obe grupe bolesnika nije bilo statistički značajne razlike u polnoj strukturi bolesnika ($\chi^2 = 2,05$; DF = 2; $p > 0,05$), životnom dobu ($\chi^2 = 5,46$; DF = 1; $p > 0,05$), nivou holesterola ($\chi^2 = 0,89$; DF = 1; $p > 0,05$), nivou triglicerida ($\chi^2 = 0,89$; DF = 1; $p > 0,05$), prisustvu arterijske hipertenzije ($\chi^2 = 1,383$; DF =

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2; $p > 0,05$), navici pušenja ($\chi^2 = 1,74$; DF = 1; $p > 0,05$), gojaznosti ($\chi^2 = 1,76$; DF = 1; $p > 0,05$), prisustvu cerebrovaskularne bolesti ($\chi^2 = 2,34$; DF = 2; $p > 0,05$). Nasuprot tome, ishemijska bolest srca bila je statistički značajno češće prisutna kod bolesnika koji su pored AAA imali i pridruženu aneurizmatsku bolest F-P segmenta ($\chi^2 = 5,45$; DF=1; $p < 0,05$). **Zaključak.** Pored AAA, dvadeset bolesnika imalo je i pridruženu aneurizmu F-P segmenta. Rezultati ove studije sugerišu neophodnost izvođenja ultrasonografskog pregleda F-P segmenta kod svih bolesnika sa dokazanom AAA ukoliko imaju prisutne faktore rizika.

Ključne reči:
aneurizma; a. femoralis; a. poplitea; faktori rizika; dijagnoza; ultrasonografija; aorta, abdominalna, aneurizma.

Introduction

Many different forms of aortic and arterial aneurysms get a huge expansion [1–3]. With efforts to have better both medical and economic effects of aneurismatic disease treatment, for many years there have been corresponding screening programmes carried out across the world. Screening is reasonable to perform if the disease lasts for a long time, if during screening the disease can be detected in early stage, if detecting the disease in its early stage the outcome of treatment would improve, if a screening programme is low priced, if it is painless, safe and comfortable for the patient, and if the treatment cost is reduced in that way [4, 5].

The benefit is bigger if screening includes target groups [6]. The aim of this study was to determine the frequency and factors contributing to femoropopliteal (F-P) segment aneurysms in the patients with abdominal aortic aneurysm (AAA), as well as to define a group of patients for whom the screeneng programme is indicated.

Methods

This prospective study included 70 patients who had underwent elective or urgent surgery of abdominal aortic aneurysm at the Surgery Clinic, Clinical Center Banja Luka, from January 1, 2006 to December 31, 2007. In electively treated patients, F-P segment was examined by ultrasonography before the operation, and in urgently treated patients after it. For ultrasonographic examination an ultrasonographic device (Siemens Acuson Antares with 10 MHz and 7.5 MHz probes) was used. On that basis, the group of 20 patients with and the group of 50 patients with no adjunctive F-P segment aneurysm were formed. In both groups demographic characteristics (gender, age), risk factors (diabetes mellitus, elevated serum levels of cholesterol and triglycerides, arterial hypertension, smoking habit, obesity) and cardiovascular comorbidity (cerebrovascular disease, ischemic heart disease) were analyzed, with the aim to establish their possible association with aneurismal disease of F-P segment. The presence of cerebrovascular disease included cerebrovascular insult, transitory ischemic attack or performed carotid endarterectomy in the medical documentation. The presence of coronary artery disease included past myocardial infarction, angina pectoris or coronary artery by-pass grafting performed. The collected data were analyzed by different models of descriptive and analytic statistics (statistical significance of the difference between the groups was tested by χ^2-test ($p < 0.05$ was considered as statistically signifficant), using computer support and programs for statistical analysis (SPSS 10-Science, Chicago, Illinois).

Results

Twenty (28.57%) patients who had been operated on because of AAA had adjunctive aneurysm disease of F-P segment. Out of them, 11 patients had popliteal artery aneurysm, and 9 patients had aneurysm of femoral artery. Demographic characteristics of patients, risk factors and adventitious diseases were shown in Table 1.

Table 1

Demographic characteristics of patients, risk factors, comorbidities and statistical influence of some parameters on appearence of multiple aneurysms

Characteristics	Isolated AAA (n = 50) n (%)	AAA + F-P segment An (n = 20) n (%)	χ^2	DF	*p*
Sex, n (%)					
male	38 (76)	14 (70)	2.05	2	> 0.05
female	12 (24)	6 (30)			
Average age (years)	68.38	71.60	5. 46	1	> 0.05
Risk factors, n (%)					
diabetes mellitus	21(42)	9 (45)	0.04	1	> 0.05
increased cholesterol	14 (28)	8 (40)	0.89	1	> 0.05
increased triglycerids	14 (28)	8 (40)	0.89	1	> 0.05
arterial hypertension	49 (98)	19 (95)	1.38	2	> 0.05
smoking habit	33 (66)	11 (55)	1.74	1	> 0.05
obesity	10 (20)	7 (35)	1.76	1	> 0.05
Comorbidity, n (%)					
cerebrovascular desease	11 (22)	8 (40)	2.34	2	> 0.05
ischemic heart desease	41 (82)	11 (55)	2.44	1	< 0.05

AAA – abdominal aortic aneurysm; AAA+F-P An – abdominal aortic aneurysm with an adjunctive femoro-popliteal segment aneurysm

Males were dominant in both groups, but there was no statistically significant difference in gender structure (χ^2 = 2.05; DF = 2; $p > 0.05$).

Even though the average age of patients in the group with adjunctive F-P segment aneurysm too, was bigger than in the group with isolated AAA (71.60 *vs* 68.38 years), that was not statistically significant (χ^2 = 5.46; DF = 1; $p > 0.05$).

Twenty one (42%) patients from the group with isolated AAA, and 9 (45%) patients from the group with adjunctive F-P segment aneurysm had diabetes mellitus, but there was no statistically significant difference between the groups (χ^2 = 0.04; DF = 1; $p > 0.05$).

The serum level of cholesterol was increased in 14 (28%) patients who suffered from isolated AAA and in 8 (40%) patients who had an adjunctive F-P segment aneurysm. This difference was not statistically significant (χ^2 = 0.89; DF = 1; $p > 0.05$).

Serum level of triglyceride was increased in 14 patients who suffered from isolated AAA and in 8 patients with adjunctive F-P segment aneurysm. There was no statistically significant difference between groups (χ^2 = 0.89; DF = 1; $p > 0.05$).

Arterial hypertension had no patient from the group suffering from isolated AAA and only one patient from the group with adjunctive F-P segment aneurysm. There was no statistically significant difference between the groups (χ^2 = 1.38; DF = 2; $p > 0.05$).

There were 33 (66%) smokers in the group with isolated AAA, and in the group with adjunctive F-P segment aneurysm there were 11 (55%). This difference was not statistically significant (χ^2 = 0.74; DF = 1; $p > 0.05$).

Although obesity was more frequently present in the group of patients who, apart from AAA, had also adjunctive F-P segment aneurysm than in the group suffering from isolated AAA (35% *vs* 20%), this difference was not statistically significant (χ^2 = 1.76; DF = 1; $p > 0.05$).

In the group with isolated AAA and in the group with adjunctive F-P segment aneurysm, 22% and 40% of the patients had cerebovascular disease, respectively. However, statistical analysis showed no statistically significant difference (χ^2 = 2.34; DF = 1; $p > 0.05$).

In the group of patients suffering from isolated AAA, there was even 82% of patients with ischemic heart desease (IHD), while in the group suffering from adjunctive F-P segment aneurysm IHD had about 55% of patients. This difference was statistically significant (χ^2 = 5.45; DF = 1; $p < 0.05$).

Discussion

According to some data, there are over 80% of all peripheral aneurysms artery localised in F-P segment [7, 8]. Evolution of these aneurysms is done in a quite usual way, *i.e.* like all other aneurysms, and they can rupture, thrombose, give distal embolism and may perform compression on the surrounding structures [9]. Bearing in mind the importance of clinical results of these changes, since 1961 Hunter et al. [10] classified all the complications of popliteal artery aneurysms into large (major) and small (minor).

Large complications are: thrombosis, distal embolism and rupture and small ones are complications of compression on the surrounding structures and angulation under knee arterias.

Thrombosis and distal embolism are the most common complications of F-P segment aneurysms. Due to its larger dimensions and decreased flow, aneurysms of this region considerably more thrombose, compared to AAA [11]. The last consequence of thrombosis and/or distal embolism of these aneurysms, is the irreversible ischemia and limb loss [12, 13]. Rupture is essentially unusual complication among F-P segment aneurysm [14].

In arteriosclerotic form it occurs in about 5% of patients, as we found in the previous study analyzing 2,000 cases published from 1948 until 1989 [12, 13].

The biggest incidence of up to 16% of ruptured popliteal artery aneurysms, claimed Gifford et al. [15] in 1953. This is reasonable because it was a period when diagnosis of popliteal artery aneurysms was not that simple, adequate as well as timely. Recording on the experience may gained in the analysis until then the largest series of 100 popliteal artery aneurysms treated at the Mayo Clinic since 1913 until 1951, the most illustrated and at the same time very concise, they defined medical importance of the disease, saying that "the poplietal artery aneurysm is sinister harbinger of sudden catastrophe" [15].

The conclusion is much reasonable due to the significant number of patients who have been asymptomatic until recently, comes with advanced, irreversible ischemia of the feet and lower leg, when it is only possible and indicated to do amputation. By analysis of data published since 1948 until 2000, the already mentioned studies, we found that the average incidence of primary amputation at the popliteal artery aneurysm is 18.5% [12, 13].

Another important problem is more frequent adjunctions of F-P segment aneurysms in patients with AAA [16, 17]. According to current data, AAA is present in 85% of patients with femoral artery aneurysms and in 62% of patients suffering from popliteal artery aneurysm [11, 18]. On the other hand, 14% of patients with AAA have an F-P segment aneurysm [19]. In our study, adjunctive F-P segment aneurysm was considerably more frequent. Specifically, it was found in 20 (28.5%) patients. These patients were on average older. They had no more often diabetes, hyperlipidemia, obesity, smoking habit and cerebrovascular disease. Conversely, patients with isolated AAA had more often coronary artery disease. Sex structure and hypertension were equally represented in both groups.

Our study, similar to some previous ones [20], suggests the necessity of performing ultrasonographic examination of F-P segment in all patients with proven AAA.

Conclusion

Our study shows that 20 patients, beside AAA, had an adjunctive F-P segment aneurysm. It is more difficult, but

there is an equally essential question which category of people need screening of aneurysmatic aortic and peripheral artery desease. If in patients with AAA the existence of F-P segment aneurysm is not established at the first ultrasonographic examination, that does not mean that it will not appear later. It is, therefore, highly advisable to run skreening ultrasonographical examinations even after that, especially if the patient has any of risk factors.

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Increased inflammatory response in patients with the first myocardial infarction and nonsignificant stenosis of infarct-related artery

Pojačan inflamatorni odgovor kod bolesnika sa prvim infarktom miokarda i nesignifikantnom stenozom infarktne arterije

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Abstract

Introduction/Aim. Atherosclerosis presents a serial of highly specific cellular and molecular responses, and could be described as inflammatory diseases. Accordingly, for development of acute myocardial infarction (AMI), structure and vulnerability of atherosclerotic plaque are more important than the extent of stenosis of infarct-related artery. Consequently, inflammation and atherosclerosis and its complications are in good correlation. C-reactive protein (CRP) as nonspecific inflammatory marker, has prognostic significance in coronary artery diseases. The aim of this study was to establish the correlation between inflammatory response expressed as levels of CRP and fibrinogen in serum and extent of coronary artery stenosis. **Methods.** Study included 35 patients with acute myocardial infarction, as the first manifestation of coronary artery disease, which were treated with thrombolytic therapy according to the guidelines. All the patient had a reperfusion. The patients with acute or chronic inflammatory diseases, an increased value of sedimentation, fibrinogen, CK ≥190 U/L, early and late complications of AMI were excluded. CRP was measured on admission, after 24, 48 and 72 hrs, and 21 days latter, while fibriogen only on admission. **Results.** All the patients underwent coronary angiography, and were divided into two groups: the group 1 (23 patients), with significant stenosis of infarct-related artery (stenosis ≥ 75%), and the group 2 (13 patients) without significant stenosis (< 75%). Mean value of CRP serum level on admission in the group 1 was 4.4 mg/L, and in the group 2 7.2 mg/L ($p < 0.001$). The mean value of fibrinogen on admission in the group 1 was 2.7 g/L, and in the group 2 3.0 g/L ($p < 0.001$). The mean CRP value after 48 hrs in the group 1 was 21.7 mg/L, and in the group 2 42.4 mg/L. ($p < 0.001$). After three weeks, the mean CRP value was 4 mg/L in the group 1 and 5.5 mg/L in the group 2 ($p < 0.001$). There was no significant difference between the groups 1 and 2 related to gender, age, localization of AMI, CK, EF value, and risk factors for coronary artery disease. **Conclusion.** The patients with nonsignificant stenosis of infarct-related artery had increased inflammtory responses according to the CRP value, as a result of inflammatory process in atherosclerotic plaque and/or enhanced individual reactivity.

Key words:
atherosclerosis; myocardial infarction; inflammation; coronary stenosis; acute disease; c-reactive protein; fibrinogen.

Apstrakt

Uvod/Cilj. Ateroskleroza predstavlja seriju visokospecifičnih celularnih i molekularnih odgovora, koji se najbolje mogu opisati kao inflamatorno oboljenje. U tom kontekstu, za nastanak akutnog infarkta miokarda (AIM) sastav i vulnerabilnost ateroskelrotske ploče mogu biti značajniji od stepena stenoze infarktne arterije (IA), odnosno biološko, inflamatorno stanje, može biti pokazatelj kojom će se brzinom i smerom razvijati ateroskleroza i njene komplikacije. Cilj rada bio je da se ustanovi da li postoji korelacija između inflamatornog odgovora, prikazanog c-reaktivnim proteinom (CRP) i fibrinogenom i stepena stenoze infarktne arterije (IA) kod bolesnika sa AIM, kao prvom manifestacijom koronarne bolesti. **Metode.** Istraživanjem je bilo obuhvaćeno 35 bolesnika sa AIM, kao prvom manifestacijom koronarne bolesti, koji su lečeni trombolitičkom terapijom po važećim preporukama. Bili su uključeni samo bolesnici sa koronarogafki dokazanom reperfuzijom koronorne arterije. Istraživanjem nisu bili obuhvaćeni bolesnici sa akutnim i hroničnim inflamatornim oboljenima, zatim bolesnici koji su na prijemu imali povišenu sedimentaciju (SE), fibrinogen, kreatinin-kinazu (CK) ≥ 190 U/L, kao ni oni sa ranim i kasnim komplikacijama AIM. C-reaktivni protein određivan je odmah po prijemu, potom 24,

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48, 72 sata nakon prijema, te 21. dana od hospitalizacije. Fibrinogen je određivan samo na prijemu. **Rezultati.** Na osnovu koronarografskog nalaza bolesnici su bili podeljeni u dve grupe: grupa 1 (23 bolesnika) bez značajne stenoze IA (stenoza ≥ 75%), i grupa 2 (13 bolesnika) sa značajnom stenozom IA (stenoza < 75%). Srednja vrednost CRP na prijemu u grupi 1 iznosila je 4,4 mg/L, a u grupi 2 7,2 mg/L ($p < 0,001$). Srednja vrednost CRP nakon 48 sati u grupi 1 bila je 21,7 mg/L, a u grupi 2 42,4 mg/L ($p < 0,001$). Srednja vrednost fibrinogena na prijemu u grupi 1 bila je 2,7 g/L, a u grupi 2 3,0 g/L, ($p < 0,001$). Nakon tri nedelje vrednost CRP u grupi 1 bila je 4 mg/L, a u grupi 2 je 5,5 mg/L ($p < 0,001$). Grupe se statistički nisu razlikovale po polu, godinama, lokaciji AIM, vrednostima CK, EF i faktorima rizika od koronarne bolesti. **Zaključak.** Kod bolesnika sa nesignifikantnom stenozom infarktne arterije postoji pojačan inflamatorni odgovor akutne faze. Ovo pokazuje da postoje različiti patogenetski mehanizami u nastanku iste kliničke slike i/ili različite individualne reaktivnosti na inflamatorni stimulus.

Ključne reči:
ateroskleroza; infarkt miokarda; inflamacija; koronarna arterija, stenoza; akutna bolest; c-reaktivni protein; fibrinogen.

Introduction

Atherosclerosis and coronary artery disease (CAD) as inflammatory diseases, set the new light on the pathogenesis of unstable angina pectoris (UA) and acute myocardial infarction (AMI) or acute coronary syndrome (ACS) [1–3]. The most common causes of coronary thrombosis are endothelial erosion and rupture of atherosclerotic plaque [4]. Rupture of plaque with a thin fibrous cap and large lipid core is more common in places with less narrowing of the lumen [2–4], while endothelial erosion mainly develops on plaque with a thick fibrous cap, and these plaques usually make big narrowing of coronary arteries [2, 4]. In both cases (rupture, erosion) the increased concentration of activated macrophages and T lymphocytes provide a greater endothelial loss (erosion), damage or rupture of the fibrous plaque cap, ie. active inflammatory process favors plaque instability [2–4]. Angiographic studies [5] and data obtained by atherectomy of the coronary arteries in patients with ACS [6, 7] and by autopsy of patients who died of sudden cardiac death, suggest that in pathogenesis of ACS an active inflammatory process in atherosclerotic plaques is more important than percent of coronary stenosis [8, 9]. In fact, inflammatory process determines plaque morphology and its stability [1].

Inflammation, systemic or local, induces production of multipotential proinflammatory, primary cytokines, interleukin (IL) 1β, TNF-α. The primary cytokines stimulate the production of "messenger" cytokine IL-6, which induces the expression of genes responsible for production of acute phase inflammation protein C-reactive protein (CRP) [10]. Serum CRP concentration increases six hours after acute stimuli, the maximum value is recorded in the period 24–48 hours; its half-life in circulation is 19 h [11]. High CRP serum concentration is associated with adverse prognosis of ACS [12, 13], and numerous prospective epidemiological studies have shown that elevated serum concentrations of CRP within the normal range (in the control group) is a predictor of future myocardial infarction or stroke [14]. In studies that examined the acute phase response and kinetics of proinflammatory cytokines in patients after AMI, it was noticed that the intensity of acute phase response is in direct correlation with the size of infarction and the short- and long-term prognosis. However, in some of these studies, particularly those with thrombolytic therapy, there was no correlation between infarct size and intensity of acute phase response [15–17]. This fact is extremely important, because it indicates that approximately the same active stimulus (plaque rupture and / or myocite necrosis) in different patients induces various acute phase inflammatory response. This has been confirmed by a research in which inflammatory response in patients with AMI which was preceded by UA was compared to that in patients with AMI as the first manifestation of coronary heart disease [18]. Enhanced inflammatory response in patients with preinfarction UA is consistent with earlier observations that in time of hospital admission an activation of monocytes was observed in patients with unstable angina but not in patients with AMI and stable angina pectoris [18]. Also, some studies suggest that CRP serum level reflects inflammatory activity of plaque rupture and its morphology [15–19]. In that context, the aim of our study was to determine the inflammatory state immediately preceding AMI as well as the correlation between serum concentrations of CRP and fibrinogen and infarct artery stenosis.

Methods

The study included 35 patients with AMI as the first manifestation of ischemic heart disease, indicated for thrombolytic therapy at an accelerated protocol for rt-PA, having in mind contraindications for this therapy [20]. The survey did not include patients with CK values ≥ 190 U/L at admission, with clinically defined heart failure and echocardiographic estimated ejection fraction (EF) of less than 45%, those with early complications of AIM (postinfarction angina, reinfarction, pericarditis), left bundle branch block and atrial fibrillation, and patients with diabetes mellitus. Also, the study did not include patients with acute infectious syndrome and other inflammatory diseases that are associated with increased acute phase response proteins, nor patients with neoplasms which were established by clinical and laboratory findings. We have not included patients with an elevated sedimentation rate (for women above 20, and for men more than 10), fibrinogen higher than 3.5 g/L, and leukocytosis (greater than 10x109 /L). All analysis were performed before the therapy, *ie.* at the admission. All the patients were treated with thrombolytic therapy with r-tPA in an accelerated protocol (15 mg in bolus, then 50 mg in an infusion for 30 minutes, and 35 mg for a period of sixty minutes). All the patients were receiving continuous infusion of heparin in the first 24 hours as well as intravenous infusion of nitroglycerin at a dose 0.8 mg/hour,

during the first 48 hours, and then isosorbidmononitrate. All the patients were receiving oral aspirin from the beginning of the treatment, and ACE-inhibitors from the second day of hospitalization. Twenty-eight patients were receiving beta-blockers, and three patients calcium antagonists.

Based on the coronarographic findings, the patients were divided into two groups: the group 1 with significant stenosis of the infarct artery (≥ 75%); and the group 2 with nonsignificant stenosis of the infarct artery (< 75%) [21, 22].

Serum CRP concentrations were determined by agglutination with monoclonal antibodies to CRP, and read out by nephelometric method. They were determined at admission (CRP0) and 24, 48 and 72 hours after admission, and on twenty-first day. CRP concentrations were determined by Behring Nephelometer 100 Analyzer (normal values 0–5 mg/L). Sedimentation rate was determined immediately upon admission of each patient, on a Monitor-S AUTO e.s.r. Analyzer. Serum fibrinogen concentration was determined immediately after admission in all patients, on a Behring Nephelometer Analyzer II (normal values 1.8 to 3.5 g/L). Leukocytes were determined from complete blood count on a Bayer-Technicon H * 3RTX device.

The concentration of CK was determined on admission, then every 6 hours in the first 24 hours, and twice daily on the second day and once daily till normalization of enzyme values (Hitachi 911 Automatic Analyzer; normal values 0-190 U/L). All analyses were performed at the Institute of Biochemistry, Military Medical Academy.

Left ventricular ejection fraction was determined by the method of Simpson. Coronary angiography examinations were performed at the Institute of Radiology, Military Medical Academy, and interpreted by the two independent experts.

For all parametric observations mean values and standard deviations were calculated. Statistically significant differences between individual parameters were calculated by the Student's *t*-test. For nonparametric observations the frequency was determined and the differences were calculated by χ^2 test. A degree of correlation between each parameter was specified by linear correlation coefficient or by contingency coefficient. The significance of differences was accepted at 0.05.

Results

The study included 35 patients, 26 men and 9 women (ratio male : female, 3 : 1). The average age in the entire group was 55 years. The youngest patient was 31 and the oldest one 72.

On the basis of angiographically assessed stenosis of the infarct artery, patients were divided into two groups: the group 1 with significant stenosis (n = 22 patients); the average stenosis in the group was 86%, the lowest 75% and max 90%, the group 2 with nonsignificant stenosis (n = 13 patients); the average stenosis in the group was 47%, max. 70% and three patients did not have stenosis of infrarct-related artery. The percent of men and women in both groups was similar (77% and 69%, respectively).

The time from symptom onset till the administration of thrombolytic therapy was almost identical in both groups (107 and 108 minutes). The studied groups did not differ significantly in basic characteristics (gender, hypercholesterolemia, hypertension, family history of heart attack, localization of the infarction, the number of stenotic coronary arteries). Data on risk factors were obtained from the medical history and laboratory tests (Table 1). There was no statistically significant difference between the groups in age, EF,

Table 1

Clinical characteristics of patients with coronary artery stenosis

Parameters	Group1 (n = 22)	Group 2 (n = 13)	*p*
Age (yr), $\overline{X} \pm SD$	57 ± 8.5	51 ± 10	0.68
Female sex, n/total n	5/17	4/9	0.60
Risk factors, n (%)			
hipercholesterolemia	11 (50%)	4 (31%)	0.27
hypertension	7 (32%)	3 (23%)	0.58
curent cigarette use	14 (64%)	8 (62%)	0.9
family histori of coronary artery disease	12 (55%)	4 (31%)	0.17
AIM location, n (%)			0.15
anterior	10 (45%)	6 (46%)	
inferior	12 (55%)	5 (39%)	
lateral	0	2 (15%)	
The maximum values of CK (U/L); $\overline{X} \pm SD$	1879 ± 1064	1661 ± 772	0.52
Ejection fraction (%), $\overline{X} \pm SD$	52 ± 5	52 ± 4	0.94
Incidence of the disease, n (%)			0.79
single vessel	11 (50)	8 (62)	
two vessel	6 (27)	3 (23)	
three vessel	5 (23)	2 (15)	
collaterals	0	0	
The degree of stenosis of the infarct related artery (%), $\overline{X} \pm SD$	86 ± 6	47 ± 27	< 0.001
min. stenosis	75%	0	
max. stenosis	90%	70%	
The time interval from the beginning symptoms before the therapy (min), $\overline{X} \pm SD$	107 ± 32	108 ± 36	0.95

The group 1 – patient with coronary artery stenosis ≥ 75%.
The group 2 – patient with coronary artery stenosis < 75%.

maximal levels of CK serum activity (table 1), as well as the sedimentation rate, leukocyte count, the values of CK on admission (Table 2). There was no correlation between the degree of stenosis and EF, extent of disease, localization of AMI, the time interval, SE, white blood cell count. There was a statistically highly significant difference between the two groups in the percentage of residual stenosis ($p < 0.001$).

At admission, elevated serum acute phase proteins, *ie.* CRP and fibrinogen, were registered in 17 (48.6%) patients, 13 patients in the group 2, and only four (18%) patients in the group 1. In the group with significant stenosis of infarct artery (the group 1), the average value of CRP at admission (CRP0) was 4.4 mg/L, a minimum value 3 mg/L and a maximum value 6.6 mg/L. Of 22 patients, 18 (82%) had values of CRP0 within normal range, only four patients (18%) had values CRP0 more than normal (more than 5.0 mg/L) (Table 2). In the group 2 the average value CRP0 was 7.2 mg/L, a minimum value 5.7 mg/L, a maximum value 10.7 mg/L. All 13 patients had values CRP0 more than normal (Table 2).

Both groups showed an increase of CRP concentration with maximum value 48 hours after initiation of the therapy. In the group 1 the maximum value of CRP was 21.7 mg/L. In the group 2 the maximum CRP value was 42.4 mg/L.

Table 2

Fibrinogen. white blood count (WBC), erytrocyte sedimentation rate (ESR) and serum creatine kinase (CK) in patients with coronary artery stenosis on admission [x̄(min-max)]

Patients	Fibrinogen (g/L)	WBC ($x10^9$)	ESR	CK (U/L)
Group 1	2.7 (2.1–3.1)	6.2 (4.9–7.8)	7 (2–16)	120 (86–168)
Group 2	3.0 (2.8–3.2)	5.8 (4.8–7.1)	6 (2–15)	105 (69–142)
p	0.001	0.73	0.92	0.79

The group 1 – patient with coronary artery stenosis ≥ 75%
The group 2 – patient with coronary artery stenosis < 75%

Increased levels of CRP after three weeks were recorded in eight (23%) patients, and in the group 1, only in one patient (4.5%), and in the group 2 in seven (54%) patients (Figures 1 and 2). There was a statistically significant difference between the two groups in the CRP0 ($p < 0.001$), CRP values after 24 hours ($p < 0 .001$), 48 hours ($p < 0.001$) and 72 hours ($p < 0.002$), and three weeks after AMI ($p < 0.001$) (Table 3, Figures 1 and 2).

Tabela 3

C-reactive protein (CRP) values in patients with coronary artery stenosis [mg/L, x̄(min-max)]

Patients	CRP_0	24 h	48 h	72 h	CRP_1
Group 1	4.4 (3.0–6.6)	19.8 (6.7–49.1)	21.7 (5.9–48.1)	18.9 (5.0–40.6)	4.0 (2.9–6.0)
Group 2	7.2 (5.7–10.7)	40.7 (19.1–71.3)	42.4 (13.1–79.8)	35.7 (10.7–74.6)	5.5 (4.1–7.3)
p	< 0.001	< 0.001	< 0.001	< 0.002	< 0.001

The group 1 – patient with coronary artery stenosis ≥ 75%;The group 2 – patient with coronary artery stenosis < 75%; CRP_0 – value on admission; CRP_1 – value after three weeks

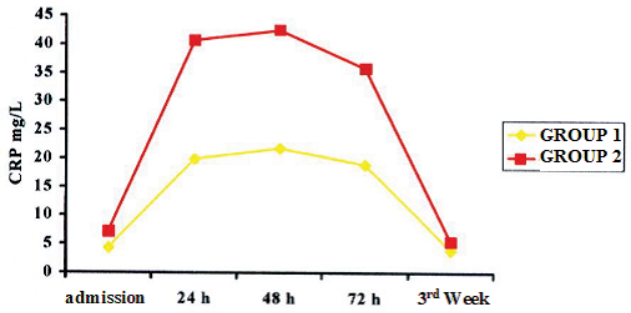

Fig. 1 – Inflammatory response expressed by C-reactive protein (CRP) value in patients with coronary artery stenosis

The group 1 – patient with coronary artery stenosis ≥ 75%
The group 2 – patient with coronary artery stenosis < 75%

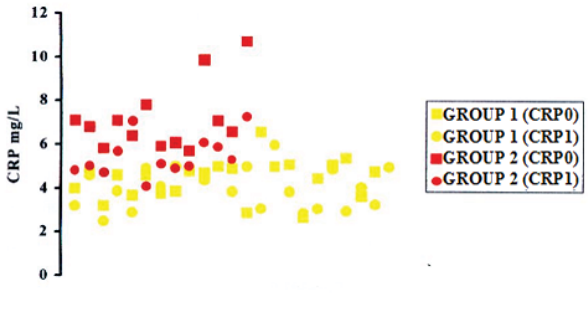

Fig. 2 – Comparison of C-reactive protein (CRP) values on admission and after three weeks

CRP_0 – value on admission, CRP_1 – value after three weeks

Also, there was a very significant difference between the two groups in the values of fibrinogen at admission ($p < 0.001$) (Table 2). There was a statistically significant negative correlation between stenosis of the infarct artery and CRP_0 value, CRP value after 24, 48, 72 hours and after three weeks ($p < 0.001$, $p < 0.001$, $p < 0.01$, $p < 0.004$, $p < 0.003$, respectively). Using the formula which links the maximum value of CRP and CK after AMI, for each patient the degree of inflammatory response (IO) was calculated [18]: IO = (max. CRP value/max. CK value) x 100 According to this formale

IO in the group 1 was 1.4 (± 0.6), and in the group 2 was 2.9 (± 0.7), ($p < 0.001$).

Discussion

The results show that about half of the patients (48.6%) with AMI as the first manifestation of CAD have a significantly enhanced response of acute phase proteins, *ie.* CRP and fibrinogen. Acute phase response was significantly increased in all the patients with nonsignificant stenosis of the infarct artery (NSIA), in the group 2, and only in four (18%) patients in the group 1. The patients with NSIA (the group 2), totally 13 (37%), patients had much higher levels of CRP immediately after admission and also significantly higher levels of CRP after myocardial necrosis, and after three weeks (Table 3, Figure 1). Consistently, elevated levels of CRP in all patients with NSIA (the group 2), and only 4 (8%) patients in the group 1, are in accordance with other researches that found that for the occurrence of ACS more important is biological (inflammatory) state of atherosclerotic plaque than the degree of coronary artery stenosis [3, 23]. The results are also consistent with earlier observations that AMI usually occurs with previously moderate stenosis of coronary artery [24, 25], and after thrombolytic therapy, not a high number of infarct arteries are with high percent stenosis [5, 6].

The study group (all 35 patients) was very homogeneous in terms of general characteristics (the first attack, the time interval until the beginning of the treatment, achieved reperfusion, ...). Also, between the groups, there were no statistically significant differences in gender, EF and other risk factors for CAD (Table 1).

In all the patients of the group with NSIA (the group 2), and in only 4 patients of the group 1, elevated levels CRP_0 and higher levels of fibrinogen (within the normal range) were found (Table 2).

Considering the facts that in all the patients from the onset of symptoms till administration of thrombolytic therapy passed less than two hours, and that acute stimuli lead to elevated levels of CRP after six hours (maximum values after 24–48 hours; half-life in circulation about 19 hours) [11], elevated levels of CRP_0 were not a result of myocardial necrosis (the levels of CK in all patients on admission were within normal range). Elevated levels of CRP on admission cannot be attributed to the severity and to the extent of atherosclerosis [26]. In fact, the degree of atherosclerosis and acute phase response in patients with stable angina pectoris (SAP) and/or peripheral vascular disease, despite more extensive atherosclerosis and existence of thrombotic process, did not show a significant degree of correlation [26, 27]. CRP_0 higher values cannot be consequences of episodic activation of hemostatic system, because systemic markers of thrombin activation do not lead to elevation of acute phase protein [26, 28] neither can be attributed to ischemia-reperfusion lesion, because the circulating neutrophils are not activated, and levels of CRP are not elevated in patients with a variant angina [29, 30].

It cannot be excluded that a proportion of patients (but not the majority!) had silent ischaemia preceding AMI. However, in the group 2 in all the patients, and in the group 1 in 18% of the patients there was an increase of CRP0, which limits this assumption. In addition, elevated CRP levels in the group 2 were maintained even after three weeks (5.5 mg/L compared to 4.0 mg/L in the group 1). CRP_0 higher values cannot be justified by acute infectious and/or other diseases, because eritrocyte sedimentation rate (ESR), fibrinogen and white blood cells (BC) were within normal values (Table 3). In addition to normal ESR, Le, BC, and, especially, fibrinogen support the hypothesis that myocardial infarction was not preceded by unrecognized ischemia [1, 13]. For elevated CRP0 value is, most likely, responsible activation of inflammatory processes within the atherosclerotic plaque, which is consistent with the role of inflammation in the destabilization of the plaque [3, 4]. This process is not localized, but by the proinflammatory and messinger cytokines leads to the system response *ie.* to the production of acute phase protein [1, 18]. Therefore, cytokine production occurs in the atherosclerotic plaque as a reflection of qualitative and quantitative (inflammatory) properties of the plaque, especially in active plaques that directly precipitate the ACS [3, 17].

The inflammatory response may be an indicator of angiographically insignificant plaques which normally are more prevalent than the "bigger" plaques [31]. Also, and as our research shows, "smaller" plaques are often the cause of AMI as the first manifestation of CAD [32], and more often lead to sudden occlusion of the vessel, among other factor, because they are in a lesser extent associated with the protective effects of collateral circulation. Coronary angiography cannot precisely visualize atherosclerotic plaques that narrow the lumen of less than 40%, however, such plaques have a "large" inflammatory potential [1, 17]. On the other hand, CRP may be a measure of individual reactions to the same stimulus, wich is, in this case, the pathological substrate that leads to "the origin and development" of atherosclerotic plaque in coronary arteries. Actually, there is an interindividual difference in response to risk factors for CAD, as well as to antigens and autoantigenes that can lead to the development of atherosclerotic process [1, 10, 18].

Myocite necrosis is a potent proinflammatory stimulus [33, 34]. Experimental studies have shown that even brief periods of ischemia (15 minutes), after which follows reperfusion, cause a cascade of proinflammatory reactions that include: production of reactive oxygen metabolites (ROM) [35], leukocyte-mediated myocardial cell lesion [36] and cytokine IL-1 and Il-6, which are the main determinants for the production of acute phase proteins [1]. Studies that examined the acute phase response and kinetics of proinflammatory cytokines in patients after AMI, have documented that the acute phase response is in direct correlation with the short and long term prognosis [12, 13, 37]. However, in some of these studies, particularly those with early thrombolytic therapy, there was no correlation between infarct size and acute phase response [15 16]. Our data show a typical increase in acute phase proteins after myocardial necrosis, with maximum values 48 hours after the thrombolytic therapy, which is in accordance with the mentioned studies (Table 3). Acute phase response was markedly higher in patients with NSIA (the group 2 with a mean CRP 42.4 mg/L compared to 21.7 mg/L in the group

1, $p < 0.001$). Also, if we adjust the maximum levels of CK and CRP, according to previously mentioned formula, IO in the group 1 was 1.4 (± 0.6), while the group 2 was 2.9 (± 0.7), $p < 0.001$, *ie.* there was twice the response in the group with nonsignificant infarct artery stenosis. Since the two groups did not differ significantly in the estimated size of infarction, infarct localization, and because all patients achieve recanalization of the infarct artery, it is logically to assume that the nature and intensity of the stimuli provoked by necrosis were similar in both groups. Explanation for the elevated serum CRP in the group 2 could be in the studies that reveal genetic determinated variability in production of cytokines from human monocytes after endotoxin stimulation *in vitr* [38], as well as in the variation of the inflammatory response to oxidized low-density lipoproteins of certain strains of mice [39]. Alternatively, monocytes and granulocytes of patients with NSIA could be induced to produce more cytokines and ROM on similar stimuli. These results are consistent with similar studies that compared inflammatory response in the patients with unstable angina and AMI (as the first manifestations of CAD [18], and with the observations that a proportion of patients have an elevated reactivity (measured with CRP) after uncomplicated angiography or PCI [40, 41]. The theory of increased individual reactivity to the stimulus (autoantgen, viruses, bacteria, inflammatory molecules) could explain the fact that one group of patients experience the first myocardial infarction without significant stenosis of the infarct artery.

The exact, *in vivo*, morphology of an inflamed plaque, which causes ACS, cannot be determined by any currently available method. Intracoronary ultrasound detects unstable plaque in patients with UA, which are angiographically inapperent, but this invasive method is coupled with a significant risk. Extravascular ultrasound, ultrafast computed tomography and magnetic resonance imaging have proved to be useful but have their limitations.

Contemporary concepts, based on molecular cardiology, favor the concept of vulnerable or inflamed plaque, as a crucial pathological substrate in the development of ACS, putting aside the degree of stenosis of coronary arteries. In our study, by following CRP kinetics in the first days of AMI, and compared with the degree of infarct artery stenosis, we detected a group of patients with elevated CRP and nonsignificant infarct artery stenosis.

The results of the study suggest two things: a) insignificant stenosis in a relatively large number precipitates developement of AIM, b) insignificant stenosis of infarct-related artery is associated with enhanced inflammatory response. The object of our interest in this paper was not the prognosis of these patients in the context of coronarographic findings and CRP. We had a special interest for the kinetics and strength of the acute-phase response in selected patients. Arising from the research results, and based on the experience of others authors, we believe that inflammation plays an important role in the prognosis of CAD, but more as individual than a group character. In fact, markers of the inflammatory milieu, and the inflammation itself, local and/or systemic, are determinants that show "rate of development of atherosclerosis and its complications ¨, favoring the occurrence of ACS in younger patients and making plaque "more atheromatous and less fibrous".

However, from a clinical point of view, both morphologic forms (nonsignificant and significant stenosis of coronary arteries) lead to myocardial infarction, and in this context periprocedural serum concentration of CRP lost significance. Namely, heart attack develops in patients with elevated, as well as in those with normal CRP values. In this context, the value of CRP may have significance if it is compared with the clinical outcome of patients after definitive care (medical therapy, percutaneous coronary revascularization or surgical implantations). In fact, preprocedural value of CRP may help in deciding on the modalities of treatment [42].

Conclusion

Patients with nonsignificant stenosis of infarct-related artery had increased inflammtory responses according to the CRP value, as result of inflammatory process in atherosclerotic plaque and /or enhanced individual reactivity.

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CURRENT TOPICS

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Organization of healthcare about patients with cerebrovascular disease in the Czech Republic

Organizovanje zdravstvene zaštite bolesnika sa cerebrovaskularnom bolesti u Češkoj

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Key words:
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Ključne reči:
cerebrovaskularni poremećaji; mozak, infarkt; zdravstvena zaštita; zdravstveni programi, nacionalni; upitnici; češka republika.

Introduction

The growing burden of chronic disease of civilization during the 20th century and at the beginning of the 21st century in the context of demographic change, health promotion and treatment, is becoming a dominant agenda of the process of health policy making according to World Health Organization (WHO). Cerebrovascular disease (CVD) is not only the world's second leading cause of death, but also an important factor causing the reduction of self-sufficiency of chronically ill in both developing and developed countries [1]. The first half of the 90s, thanks to the work of the Harvard School of Public Health and its application by the WHO, brought about a new comprehensive framework for the evaluation of morbidity, mortality and also self-sufficiency of chronically ill called "Burden of disease" (or "disease burden") [2].

The new combination of years of life lost due to premature death and years of life lived in less than full health.

CVD represents an illness which leads to an average of 9.3 years lost due to premature death or disability in developed countries [2]. In comparison with other diseases, CVD has one of the major socioeconomic and health impacts on society. The concept of the Disease Burden (DALYs) without doubt becomes the basis of the new approach to the formulation of health policy priorities, both in the field of medicine and health promotion [1].

The question is how, in the current practice of the Czech health policy discussions, we manage to orientate the action of risk groups, patients and doctors to the control of risk factors on one hand, and to the treatment of acute stroke and particularly the care about chronically ill patients after acute phase (if the model of care about chronically ill is efficient) on the other one.

International trends in morbidity and mortality from cerebrovascular disease

Research on the incidence, prevalence and mortality of stroke is based on a various data sources (hospital´s patients database, data from the acute care, demographic data on specific mortality, epidemiological studies) [3–11]. Opportunities for the comparison of these data are complicated by methodological differences, diversely defined age groups, but also by the uncertainty about the reliability of the diagnosis with the definition of stroke by the WHO [12]. The need for the reliability and consistency of methodologies, including age-standardized data, arise especially when we want to observe the long-term developmental changes [7]. Current epidemiological values of age-standardized incidence of stroke for people younger than 55 years, range from 4.2 to 11.7 per thousand per year (Figure 1). Actual values show significant differences depending on the observed territorial units. The average age of patients with stroke is about 70 years for men and about 75 years for women. More than half of the cases of stroke occur at the age below 75 years [7].

While in younger age groups we can observe the decline of emergence of CVD, in older age groups there is a stabilization or increase in the incidence. Differences (variation in the incidence, prevalence and mortality) are also ob-

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served in accordance to the ethnicity of specific groups, where we can see also the similarities in the policies of prevention, but also in their economic conditions. As the determinants of these differences, we can consider the quality of the acute care and the prevention of risk factors [6].

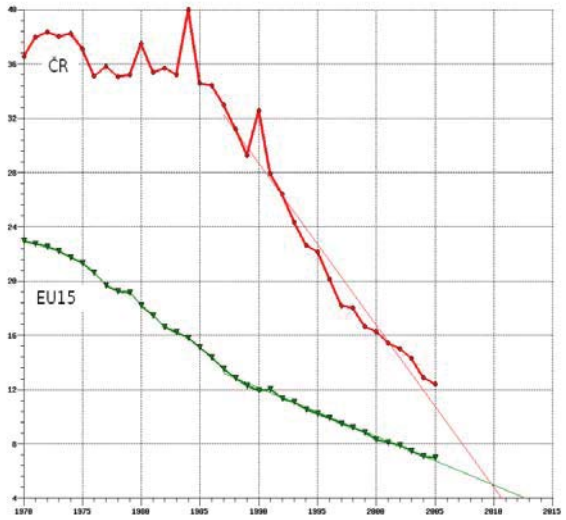

Fig. 1 – Standardized specific cerebrovascular disease (CVD) mortality in all age-groups – comparison of the Czech Republic (CR) and EU15 (before accession) [12]

The publications of the Center for Disease Control in the USA are a global perspective on the development of the overall burden of disease of CVD, including the review of the situation on the level of effectiveness of risk factors control [13]. The data (large correlation maps appended with graphs) are available on the WHO site [12]. The values of the years of life lost due to premature death or due to disability (measured by the index DALYs) range in the North America and Western Europe below 5. The values for the Central and Eastern Europe along with the values for the countries of North Africa vary from 5 to 9. The worst situation is in Russia and in some Central Asian states like Kazakhstan (values greater than 15). The values from 10 to 14 are found in Africa and South America, China and India [14]. A global approach to the differences in morbidity and their determinants have become an important stimulus for research and formulation of strategies focused on the solution of these problems. In the context of demographic change in developed countries and under the existing conditions of combined risk factors, we can expect the increase in the number of diseases in the group of CVD.

The EUSI Report (2003) [15] states that the main causes of disability (of DALYs), for men aged 49–69 are tuberculosis (TBC) at the first place with a value of 9.3, then coronary heart disease (CHD) with 7.6 and CVD with 6.7. At the age over 60 years, CVD is the first cause (13.8), at the second place is CHD with 11.7 and at the third place is chronic obstructive pulmonary disease (CHOPD) with 9.6.

For women, stroke is the main cause of DALYs in both age groups: age 49–69 years: 1. CVD (8.7), 2. TBC (5.6), 3. CHD (4.7); age over 60 years: 1. CVD (16.5), 2. CHD (11.6), 3. CHOBPN (8.1).

Taking into account the available data, partial studies and review articles, it is clear that the importance of the epidemiology of stroke was more underestimated in the past in comparison with controlled clinical experiments. Disparities in the methodological approaches lead to the need for greater attention to this issue within the neurological community. An example of this approach is the publication of Feigin and Bennett in 2007 [7].

Mortality and morbidity from cerebrovascular disease in the Czech Republic

In the Czech Republic (CR) the accurate epidemiological data on stroke are missing. The value of mortality on stroke in the population aged under 65 years doubled in comparison with the countries of Western and Northern Europe, with a maximum values for men in the category of 45–65 years (National Cerebrovascular Program). In the upcoming decades the increase in the incidence of stroke is expected, due to the increase of the percentage of elderly population (in Europe it is expected that the elderly would represent about 30% of the population). But the charts of the development of specific stroke mortality in the CR in comparison with EU15 shows that the trend of future development is promising. The CR has the opportunity to reach the level of developed European countries in 2015 (Figure 2) [4, 16, 17].

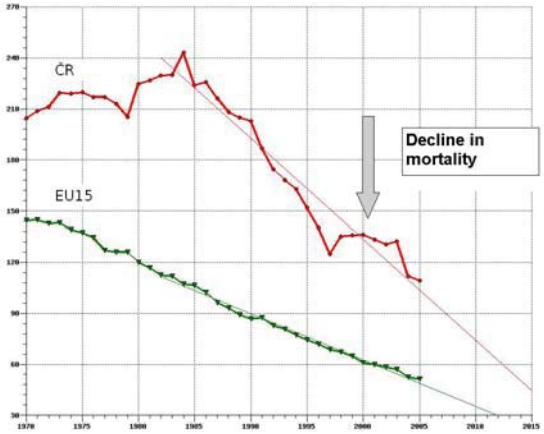

Fig. 2 – Standardized specific cerebrovascular disease (CVD) mortality in the age-group 0–64 years – comparison of the Czech Republic (CR) and EU15 (before accession) [12]

The development of standardized mortality of cerebrovascular and coronary heart disease in the CR during the 90s was favorable in both the age group from 0 to 64 years, and in all age groups with the exception of the standardized mortality rate for cerebrovascular disease in all age groups in 2000–2005, when there was a significant decrease in the sus-

pension of the decline of mortality and thereby a "delay" in the process of achieving the EU15 level. A vulnerable group includes in this case patients older than 64 years. The question is what factors participate in this problematic difference in mortality in the CR in comparison with developed EU countries [16].

Strategy for prevention and treatment of stroke

Strategy for prevention and treatment of CVD is discussed internationally within several scientific disciplines, which are primarily focused on different subjects. Medical disciplines such as neurology and cardiology and the corresponding professional society in the US, Europe or in CR formulated in the last 20 years a number of recommendations (guidelines) to which are subsequently incorporated new research findings. In the US the synthesis of recommended procedures for treatment and prevention of stroke is available freely on the Internet [18]. Since the early 90's some parts of these recommendations have been published in Stroke journal. It is a joint production of professional cardiological society (American Heart Association – AHA) and professional society for stroke (American Stroke Association – ASA). The volume of financial resources in this area clearly exceeds the resources spent in Europe and that is what also determines the difference in the production of new findings. In the US, the tradition of research on health services is more open than for example in the CR and the results are commonly used for further upgrade of health care provision.

The European strategy of CVD treatment has been the subject of quite intensive professional discourse since the early 90´s, which has been repeatedly summarized [19]. Relatively detailed informations about this development are regularly published in the journal Cerebrovascular Diseases. Helsingborg declarations [20] arose on the basis of consensus, roofed by the WHO. The Declaration of 2006 is divided into five main areas (organization of care for patients with stroke, acute care management, prevention, rehabilitation after stroke, evaluation of achievements and quality). Helsingborg declaration of 2006 sets out the objectives for Europe till 2015. These goals apply to all patients after CVD. However this declaration does not contain direct links to the publications in professional journals and books so the targets rather show the direction of useful action. The representatives of patients were also involved in the process of creation of the declaration. Taking into account the need of multidisciplinary approach, the "roof making strategy" of the WHO creates an important opportunity for mutual meetings of both the representatives of the medical disciplines and of public health and health promotion. From the formulations in the Helsingborg Declaration it is clear that there exists an opportunity for cooperation of multiple disciplines, the cooperation that may lead to a significant reduction in burden of CVD.

In Europe, more detailed information how to deal with stroke are the subject of Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack. This document was formulated by the European Stroke Initiative. We can compare this activity to the American AHA and ASA. The European recommendations for the treatment of stroke are formulated on 80 pages and accompanied by a list of about 400 scientific references. In this respect it is comparable to the production in the US, but it is clear that in the US the relevant documents are not only larger and more numerous, but also supported by more detailed arguments. It is interesting that in the document of the European Stroke Strategies (ESO) 2009 there is the intention of harmonization of the treatment and prevention of CVD recommendations of the WHO, ESO and national institutions is declared.

Compared with the two above-mentioned approaches, the situation in the CR is more modest. On the site of the Cerebrovascular Section of the Neurological Society of JEP (Czech Medical Society of Jan Evangelista Purkyně) the National Cerebrovascular Program is available, which is not, however, defined in terms of time. We can only expect that it was created in 2003, because it refers to the Helsingborg Declaration of 1995 and there are no references to the European Stroke Initiative in 2008. This document does not contain links to literature and its attachments are not accessible for the public user. There is no indication if the presented data are age-standardized or not so the validity of the eventual international comparison is doubtful.

Professional discourse concludes that in this area there are relatively adequate knowledge resources, including the availability of required data. The problem and challenge is still a difference in the level of quality, organization and accessibility of health services, or activities in health promotion (according to the MONIKA research [21], the CR does not manage to control the risk factors, which could be seen as a deficit and a challenge).

A key task of the future strategy for Europe is to resolve how we could reduce the health gaps between countries. Patients with stroke should be treated in specialized centers with stroke units (Stroke Unit Trialists Collaboration, 1997). Minimum requirements of such centers include continuous availability of CT (X-ray computed tomography), the presence of neurologists and other physicians able to treat these patients, the presence of professional staff and adherence to guidelines for providing care and treatment. Centers and units for such patients are not the only prerequisite for the treatment of patients with stroke. The optimal functioning of the whole system is possible only on the basis of available, well-established and functioning network, which would sent patients to subsequent specialized centers and rehabilitative facilities. The collaboration with general practitioners in the fields of primary and secondary prevention is an apparent condition. If the care should be optimal, it is absolutely essential that all the patients with stroke are immediately transported to hospital which can provide adequate care. The patients benefit most from the care on stroke units. Patients in critical condition must be placed onto the resuscitation unit (European Ad Hoc Consensus Group, 1997). The recommendations of the Stroke Council of the American Heart Association and the European Ad Hoc Group Consensus imply that in the acute phase of stroke, it is necessary to sort patients according to their clinical condition.

Situation in the Czech Republic, the existing problems in organization in stroke care

Organization of care for patients with cerebrovascular diseasis regulated Bulletin No. 2/2010 of the Ministry of Health of the Czech Republic. The Bulletin provides material, technical and staffing complex of cerebrovascular stroke centers and centers that make network of devices that are able to provide acute and follow-up care to patients with cerebral vascular events. The reason for the existence of a network of healthcare facilities – complex cerebrovascular centers (KCC) and stroke centers (IC) is that from January 1, 2011 it is a necessity that all patients with acute stroke are transported to the nearest medical facility (IC KCC), which meets the personal and material conditions for the provision of acute and subsequent treatment. The network is designed on the principle of availability of acute recanalized therapy (systemic thrombolysis or endovascular therapy) within the IC or the KCC indicated for each patient with stroke. According to the experts, only the strict centralization of acute care with a concentration of trained personnel and material conditions will achieve an increase in percentage of patients treated with systemic intravenous thrombolysis in the acute stage of cerebral infarction. In 2007, in the Czech Republic, only 4,3% of all patients with ischemic stroke were treated [22].

For the survey of care organization, we chose the case method in which we created and used questionnaires for the patients. At the beginning of the questionnaire the informed consent was included of the interviewed citizen. The first part of the questionnaire consists of basic information about the person, education, work activities, social and economic determinants of health. The second part contains personal and family risk factors involved in stroke disease. The third part relates to lifestyle and diet before the onset of the disease. The fourth part contains questions about the course of the disease, immediate treatment, postacute treatment, rehabilitation and other outpatient treatment. The fifth part of the questionnaire contains the questions of related to the patient's health condition at present, including mental health, satisfaction with life, assessing the degree of addiction, lifestyle and diet. At the end there is an open question, which constitutes the patient to express his feelings, comments, etc., which could not be divulged in the questionnaire questions. Comments, suggestions and feelings to communicate both by the patients and relatives, who were with a patient at home care and home health care nurse who regularly visits the patient and long-term home.

The patients are selected from a database Rehabilitation Institute, praise, Prague, which is focused on patients after stroke. The patients are moved to Rehabilitation Centre (RS) for acute beds after the first attack of stroke, or from home to after-care and rehabilitation (rehab) which is already at a later stage. In this way we can gain valuable information about the following services: information about the chain postacute care-home care, secondary prevention (general practitioner, specialist). During patient's stay in the RS we can detect contrast and continuity of care-postacute-acute care, including widespread and specialized rehabilitation for patients after stroke.

Conclusion

The treatment of acute stroke in the Czech Republic may be on a bed of internal or neurological department. This selection is determined by general medical conditions. The network of stroke centers should be easily accessible to every patient. Timely transfer of patients to the intensive rehabilitation is limited by the capacity and their helth condition. Intensive rehabilitation homes are often not able to také care of more severely disabled patients (insufficient number of nursing staff and failure to adapt the rehabilitation program for elderly or severely disabled patients). Acute and individual medicine in the Czech Republic is currently at the same level as in EU countries. Preventive and risk factors of control are not satisfactory. There are several reasons. Organization and coordination of services: primary care – acute medicine – secondary care, do not usually work. The population is not sufficiently informed about the importance of prevention and control of risk factors. All these factors increase the incidence of stroke. Sufficient long-term care and rehabilitation, as well as well-coordinated secondary prevention are often after hospitalization for acute bed. Prevention and control of the determinants of health requires greater cooperation and stronger social relations to economic and social factors of the disease. These parameters indicate that social cooperation in public and social policy is necessary for effective results.

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CURRENT TOPIC

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Heart rate – predictor of cardiovascular risk

Srčana frekvencija – prediktor rizika od kardiovaskularnih bolesti

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Key words:
cardiovascular diseases; risk factors; prognosis; heart rate; mortality.

Ključne reči:
kardiovaskularne bolesti; faktori rizika; prognoza; srce, frekvencija; mortalitet.

Introduction

A trend of hypertension occurrence in patients with rapid resting heart rate (RHR) was observed more than six decades ago [1]. Since then, the role of rapid RHR in cardiovascular and total mortality has been proved in the general population and in the population of patients with cardiovascular diseases [2–9]. However, it remains controversial whether RHR could be accepted merely as one of the well-known risk factors of development of cardiovascular diseases (arterial hypertension, hyperlipidemia, smoking, obesity).

Epidemiological data associating RHR and the outcome in the general population and the population of cardiovascular patients

Many clinical or epidemiological studies have shown that RHR is an independent risk factor of total and cardiovascular mortality [2–5]. Dyer et al. [2] revealed statistically significant relationships between RHR and both cardiovascular mortality and total mortality in men followed for 15 years in the Chicago People Gas Company study and for 17 and 5 years, in the Chicago Western Electric Company (n = 1,899) and Chicago Heart Association Detection Project (n = 5,784) respectively. RHR was also an independent risk predictor of sudden death, even when other cardiovascular risk factors, such as age, blood pressure, total blood cholesterol, smoking and body weight, were taken into account in a multivariate analysis. A significant relationship was also found in the Framingham study between a high RHR and increased rates of cardiovascular mortality, coronary heart disease and sudden death both in men and women followed for 30 years [3].

Jouven et al. [4] tested the hypothesis that abnormal heart rate profile was associated with the risk of sudden death during stress and recovery phase. The study included 5,713 asymptomatic working men aged 42 to 53 who were followed for 23 years. They found that the risk of sudden death in acute myocardial infarction was increased in patients with RHR higher than 75 beats per minute (bpm) (RR 3.92; 95% CI: 1.91–8.00).

The evidence that rapid RHR is an important predictor of cardiovascular and total mortality in middle-aged people was followed by studies which detected its adverse effect in the group of elderly. Namely, Palatini et al. [5] showed, in a sample of 763 men and 1,165 women older than 65 years of age, during a 12-year follow-up, that the increased RHR was a convincing predictor of cardiovascular mortality in elderly men.

The above mentioned researches showed that RHR and profile of heart rate in stress were the predictors of cardiovascular mortality in men. Some studies excluded women, others obtained inconsistent data, so the relationship between RHR and cardiovascular and cerebrovascular events in women has long been unknown. The dilemma about the relationship between RHR and cardiovascular and total mortality in women was based on two contradictory facts. On one side, there is the fact that the average life expectancy in women is slightly longer and the other fact is that RHR in women, even after adjustment to age, is from 2 to 7 bpm higher than in men. Tverdal et al. [6] in a large cohort study, which included 180,353 men and 199,490 women aged 40 to 45 with no history of cardiovascular disease and diabetes, confirmed the previous findings and resolved the dilemma about the impact of gender on the relationship between RHR and cardiovascular morbidity and mortality. However, they found that the correlation between cardiovascular mortality and RHR was still weaker in women.

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A more recent study of Hsia et al. [7] has shown that RHR was a predictor of coronary events in women independently of physical activity and conventional risk factors. They emphasized that the correlation between rapid RHR and coronary events was stronger in women aged between 50 and 64. At the same time they showed that RHR was not a predictor of stroke in women.

Increased RHR is not only a significant predictor of total and cardiovascular mortality in healthy population, but also in patients with suspected or proven coronary artery disease.

Diaz et al. [8] analyzed the influence of heart rate on cardiovascular morbidity and mortality during 15 years in 24,913 patients with suspected or proven coronary artery disease, who were included in the Coronary Artery Surgery Study registry. They found that rehospitalizations due to cardiovascular diseases were more frequent in patients with RHR higher than 77 bpm independently on other risk factors in comparison with patients with a lower heart rate. The RHR was associated with body weight and progression of coronary artery atherosclerosis and it was an independent predictor of plaque rupture.

Hjalmarson et al. [9] followed 1,807 patients from the second day after myocardial infarction on to the end of the first year in order to determine the impact of RHR on total postinfarction mortality. Intra- and extra-hospital mortality correlated with RHR. The total mortality of patients whose heart frequency on admission was between 50 and 60 bpm was 15%, but 41% for those whose frequency was greater than 90 bpm and even 48% in patients with frequency over 110 bpm. They found that cumulative mortality of the patients with heart failure ranged from 60% to 68% depending on the admission heart rate.

The goal of INVEST study was to determine the relationship between RHR and adverse outcomes in patients with coronary artery disease treated for hypertension [10]. In contrast to previous studies which revealed a linear relationship between RHR and total cardiovascular mortality, this study found a J-shaped relationship. More precisely, the study noted an increase of risk in patients with relatively low RHR. This relationship was shown in the studies that included high-risk patients with isolated systolic hypertension, unstable angina and men with acute myocardial infarction without ST elevation [11–13].

Framingham Heart study confirmed that RHR was an independent predictor of total and cardiovascular mortality in patients with arterial hypertension [14]. The new analysis of the results of the study VALUE identified that most of the risk occurred in patients with arterial hypertension and with heart rates of 79 bpm or more. There was an increase of the primary end point in the highest quintile of heart rate ($\geq$ 79 bpm) compared with the lower four quintiles. The annual incidence of new primary-end-point events in the highest quintile (compared with the lower four) was 30% higher in the first year of the study, 55% higher in the second, 55% higher in the third year, 52% more in the fourth, and 46% greater in the fifth year of the study. A similar trend was seen throughout the trial of the heart failure and sudden death components of the end point [15].

Palatini et al. [11] showed that the rapid RHR was a predictor of mortality in elderly patients with isolated systolic hypertension. This research undoubtedly proved that the clinical method of measurement of heart rate, which was applied in almost all these studies, was equally precise as heart frequency obtained by ambulatory 24-hour holter monitoring of ECG. In fact they found a similar predictive power of the heart rate obtained by these two modalities.

Pathophysiologic mechanisms that connect rapid heart rate, atherosclerosis and cardiovascular diseases

In order to explain the role of rapid RHR in the development of endothelial dysfunction and atherosclerosis, it is important to know to which hemodynamic forces arterial wall is exposed. These forces include flow-generated shear stress which is tangential and produced by the friction of blood flow on the endothelial surface and blood-pressure-induced tensile stress that is circumferential and represents the blood-pressure derived force imposed on the circumference of the arterial wall. Accelerated heart rate increase the magnitude and frequency of tensile stress on arterial walls, which prolongs exposure to oscillatory shear stress [16]. Increased tensile stress directly induces endothelial injury and increases permeability for low density lipoprotein (LDL) and inflammatory mediators.

Rapid RHR intensifies pulsatile movement of the heart and periodically changes geometry of the coronary artery, affecting the local hemodynamics. These processes lead to additional structural and functional changes of coronary artery endothelial cells, which leads to atherosclerosis [17].

In addition to small diameter arteries, rapid RHR also affects large elastic arteries. Moderate tachycardia (over 100 bpm) increases blood pressure and tensile stress and can promote endothelial injury and wall stiffness [18]. It has been proved that one of the consequences of RHR increase in mice, provoked by electric pacing, was progressive reduction in arterial compliance and distensibility [19].

Accelerated RHR reflects, but also contributes to cardiovascular pathology [16]. Increase in RHR affects the contraction-perfusion matching that determines the myocardial supply and function. In a healthy heart, increased metabolism due to increased contractile function, results in increased myocardial blood flow and increased oxygen consumption. In the presence of coronary artery disease perfusion-contractile discrepancy is reflected in the areas with inadequate blood supply. When coronary flow cannot suffice, contractile and diastolic functions in the affected areas are reduced. Increase in RHR results in not only the increase in oxygen consumption but also in the reduction of diastolic perfusion time and damage of collateral perfusion supply. This imbalance may promote ischemia, ventricular arrhythmias, and ventricular dysfunction, *i.e.* acute coronary artery event, heart failure and sudden death.

Under the circumstances of the previously present changes of shear and pulsatile stress endothelium additionally releases growth hormones (transforming growth factor

beta and insulin-like growth factor 1?) and vasoconstrictive peptide (endothelin), which is associated with the increased platelet aggregation and relative deficiency of NO synthesis [17].

Prolonged rapid RHR causes increase of noradrenaline synthesis in the heart and the circulating level of noradrenaline is on the increase. This increase in sympathetic activity may have a direct cytotoxic effect, increase apoptosis and contribute to ventricular remodeling [19].

In patients with stable angina pectoris or previous myocardial infarction, the reduced supply of O_2 can be also caused by vasoconstriction, which is detected in the experimental conditions of accelerated heart rate [19].

In patients with stable angina the occurrence of ischemia is affected by RHR and stress duration. Patients with RHR higher than 80 bpm have two times higher prevalence of ischemic episodes than those with RHR lower than 70 bpm. Experimental studies showed that RHR is not only important for the occurrence of ischemia but it also may be a trigger for the occurrence of rhythm disturbances [19].

The relationship between RHR and the left ventricular dysfunction was indirectly confirmed in the case of an animal model. Surgically caused mitral insufficiency with consequent left ventricular dysfunction in dogs was ameliorated with the use of beta blockers [20].

Benefits of pharmacological reduction of heart rate

Two groups of drugs, based on application over decades, have proved their unequivocal role in the reduction of RHR. These medications are beta blockers and non-dihydropiridines.

The influence of beta-blockers on the reduction of RHR and mortality of patients with acute myocardial infarction and heart failure have been previously confirmed [19–22]. Data analysis of six studies which included 1,427 patients with acute myocardial infaretion showed that infarction size reduction in beta-blocker group of patients was in direct relation with the reduction of heart rate [21]. The analysis of 11 placebo-controled trials showed that there was a significant correlation between the long-term use of beta blockers after acute myocardial infarction and the reduction in RHR and mortality [22].

A meta-analysis of randomized clinical trials which included patients with previous myocardial infarction suggested that the benefit from the application of these two groups of drugs was proportional to the reduction of RHR. This meta-analysis showed that the reduction for each 10 beats per minute reduced the relative risk of cardiac death by 30%, the risk of sudden death by 30% and the risk of all-cause mortality by 20% [23].

In patients with stable angina, later appearance of ischemia during the stress test, correlated with the reduction of heart rate during the test [19].

Numerous studies confirmed the relationship between the reduction of RHR and outcomes in patients with heart failure. A recent meta-analysis of 35 studies which included patients with chronic systolic heart failure (n = 22,926) found a strong correlation between RHR and analyzed all-cause mortality ($p = 0.004$), and also between the change in RHR and the change in the left ventricular ejection fraction ($p < 0.001$) [23]. As a result, it was suggested that RHR lowering effect of beta-blockers was a major contributor to the clinical benefit associated with these agents. A study of 152 patients with heart failure who were receiving beta-blocker therapy showed that higher beta-blocker doses provided additional clinical benefits among patients with persistently elevated RHR [24]. These results suggest that the magnitude of reduction in RHR may be more important than achieving the target dose of beta-blocker therapy in patients with heart failure [24].

Whether to use beta-blockers as first-line agents in the treatment of arterial hypertension is a dilemma that has marked the last decade. Opinions about the role of beta-blockers in the reduction of RHR in patients with arterial hypertension are divided. Despite the lack of data about the reduction of RHR in patients with arterial hypertension, Consensus Document of the European Society of Hypertension suggests that, "heart rate reduction by antihypertensive agents may have beneficial effects" [25]. However, Bangalore et al. [26] have found quite the opposite effect. Meta-analysis of 60,000 patients included in 9 major clinical trials which determined the effectiveness of beta-blockers in the treatment of arterial hypertension showed that greater RHR reduction increased the risk of cardiovascular events [26]. The benefit of drug-induced bradycardia was less beneficial than bradycardia generated spontaneously because of the dyssynchrony of the reflected pulse wave and the outgoing pressure wave. The pulse wave dyssynchrony explains the beta-blocker-hypertension paradox. Hypertension paradox and pseudoantihypertensive effect of beta-blockers were examined in patients who were receiving atenolol, so these conclusions could not be unconditionally accepted, especially since we know that beta-blockers with vasodilatative effects equally effectively reduce the brachial and central pressure in the aorta.

The new specific RHR-lowering agent-ivabradine acts directly on the sinoatrial node by inhiting the I_f current of cardiac pacemaker cells, not affecting other cardiac ionic currents when used in therapeutic concentrations. The study BEAUTIFUL which included patients with coronary artery disease and the left ventricular systolic dysfunction showed the risk reduction of the coronary heart disease by 22%, of fatal and non-fatal myocardial infarction by 36% and the need for revascularization by 30% [27]. It is also expected that trials which are ongoing or will be conducted will prove cardioprotective efficacy of ivabradine in other cardiovascular diseases.

Conclusion

It is evident that RHR represents a strong predictor of mortality in the general population and in patients with arterial hypertension, coronary artery heart disease and heart failure. However, the dilemma whether rapid RHR is just a predictor or a risk factor still remains. In clinical practice, RHR has not been accepted as a classic cardiovascular risk factor. The gap between the epidemiological data and clinical practice can be explained by the fact that the clinical benefit of RHR reduction has not been proved in non-cardiologic patients.

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CASE REPORTS

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Penetrating wound of the heart manifested with peripheral embolism – case report

Ustrelna povreda srca manifestovana perifernom embolijom

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Abstract

Introduction. Heart injuries can be classified as penetrating and non-penetrating (blunt). Penetrating wounds are usually caused by stabbing with a piercing object, weapon or projectiles – missiles. The right atrium is damaged in most cases, because of its anatomical position – making the most of the anterior side of the heart. Morbidity caused by stabbing injuries to the heart is 20%–30%, while piercing wounds cause 30%–60% of deaths. **Case report.** A 28-year-old patient was admitted to our clinic with acute ischemia of the extremities. Angiography revealed a bullet in the right common femoral artery, occluding it. The patient denied having any piercing or shooting wound to his leg, but he said that four years before he had been shot to his chest. Echocardiography revealed an atrial septal defect of secondary type. An event reconstruction revealed that, four years after shooting, the bullet was displaced from the heart to the right common femoral artery. **Conclusion.** This case report is unique because of the rare type of injury, time that passed from the injury, the way bullet entered the artery (*via* atrial septal defect) and especially the success of both surgical procedures (embolectomy and repair of atrial septal defect).

Key words:
wounds, penetrating; embolism, paradoxical; heart septal defects; leg; diagnosis; embolectomy; treatment outcome.

Apstrakt

Uvod. Povrede srca mogu biti penetrantne (probojne) i nepenetrantne (tupe). Penetrantne povrede su najčešće izazvane ubodnim ranama šiljatog oružja ili oruđa i projektilima. Najčešće je povređena desna komora, pošto ona zauzima veći deo prednje strane srca. Smrtnost kod ubodnih rana srca je 20–30%, a kod prostrelnih 30–60%. **Prikaz bolesnika.** Bolesnik, star 28 godina, primljen je u kliniku sa znacima akutne ishemije ekstremiteta. Angiografski je utvrđeno da se u desnoj zajedničkoj femoralnoj arteriji nalazi puščano zrno koje je okludiralo arteriju. Bolesnik nije imao nikakvu prostrelnu, niti ustrelnu ranu u predelu noge. Od bolesnika je dobijen anamnestički podatak da je četiri godine ranije imao ustrelnu ranu u predelu grudnog koša. Ehokardiografski pregled je ukazao na postojanje atrijalnog septalnog defekta tipa *secundum*. Rekonstrukcijom događaja utvrđeno je da je puščano zrno nakon četiri godine od povređivanja dospelo u zajedničku femoralnu arteriju. **Zaključak.** Embolija femoralne arterije puščanim zrnom koja je nastala kod prikazanog bolesnika predstavlja svojevrstan raritet u pogledu dugog vremena koje je proteklo od ranjavanja, načina dospevanja metka (preko atrijalnog septalnog defekta) i, posebno, uspeha obe hirurške intervencije (embolektomije i korekcije atrijalnog septalnog defekta).

Ključne reči:
rana, penetrantna; embolija, paradoksalna; srce, septum, defekti; noga; dijagnoza; embolektomija; lečenje, ishod.

Introduction

Heart trauma presents one of the most serious and often fatal conditions in cardiac surgery. The first heart trauma described was by the Egyptians 5,000 years ago in the Edwin Smith Surgical Papyrus. Heart injuries had always and still do present a great challenge for surgeons and other doctors [1].

The number of heart injuries has grown widely over the years mainly due to the growing number of traffic and industry accidents, increased violence with the use of fire weapons. The frequent use of invasive cardiology procedures

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in every day clinical practice has also led to the increased number of heart injuries. In the USA, heart injuries became the third cause of overall mortality, after malignant and cardiovascular diseases, about 30,000 people die every year due to injuries of the heart and large blood vessels, which accounts for 25% of all deadly injuries [2], and nearly 10% of these die from the penetrating heart injuries [3].

The first successful suture of the stabbing wound of the heart was performed in Germany by Billroth's assistant L. Rhen in 1896, while the first successful treatment of the heart wound in the USA was performed by Hill in 1902 [4, 5].

Case report

A 28-year-old patient was admitted to our clinic with the acute ischemia of the right leg. He complained of pain, loss of motor activity and sensibility, which developed suddenly few hours prior to admission. Clinical evaluation revealed a cold, pulseless leg, with the loss of motor activity and sensibility. A pedal pulse, as well as popliteal and femoral pulse, could not be palpated. Cardiac examination showed no atrial fibrillation, personal history did not reveal any cardiac morbidity.

Due to unknown etiology of ischemia, angiography was indicated, which revealed a bullet in the right common femoral artery (Figure 1). There was no penetrating bullet wound

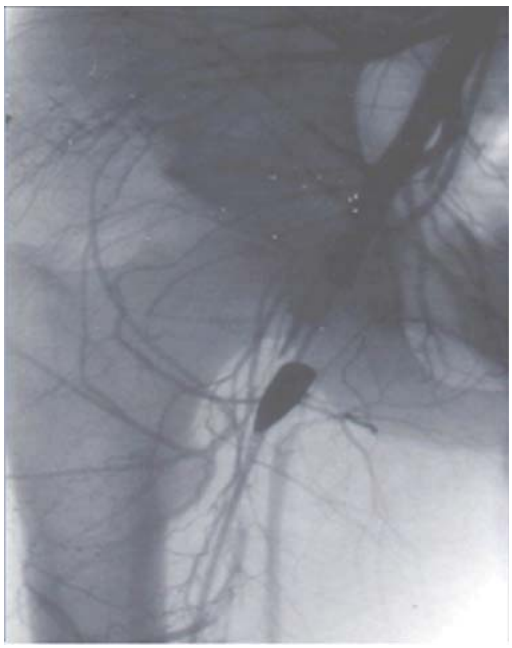

Fig. 1 – Angiography: the bullet in the common femoral artery

of the leg. The patient said that he had been wounded four years ago at the battlefield, that is, he had been shot by a sniper to the right side of the chest. He was then admitted to the army hospital and treated for the right hemothorax, which was subsequently drained. During his hospitalization, the chest x-ray disclosed the bullet (Figure 2). After the drainage of the hemothorax, patient was feeling well and discharged. Now, four years after the shooting, he was admitted for the

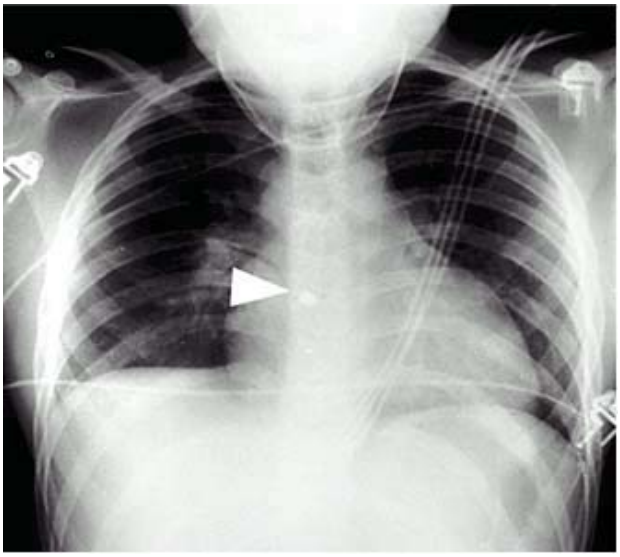

Fig. 2 – Chest radiography: a bullet in the heart

acute ischemia of the right leg, and an angiography revealed a bullet in the right common femoral artery. By the time-event reconstruction we concluded that the bullet entered the brachiocephalic vein, and then reached the right atrium through the superior vein cava. The transthoracic echocardiography showed the atrial septal defect type secundum, so it was evident that the bullet passed through the atrial septal defect, entered the left heart and was dislodged to the right common femoral artery. The bullet was in the heart 4 years before and it caused paradoxal embolization of the right common femoral artery.

Following admission, surgical embolectomy of the bullet from the right common femoral artery was performed, and 10 days after embolectomy, an atrial septal defect was repaired on-pump using the patch technique. The recovery was uneventful and the patient was discharged.

Discussion

The incidence of heart trauma has increased eight times in the past 30 years. About 70% of penetrating injuries are caused by stabbing, out of which 11% are alive at the arrival to hospital. The use of firearms is the cause of 30% of heart injuries, and about 40% of gunshot wound victims come to hospital alive [1, 4–6]. Due to the anatomical position of the heart, penetrating injury affects the right ventricle in 40%–45% of patients, the left ventricle in 30%–35%, the right atrium in 15% and the left atrium in 5% [3].

Clinical presentation of penetrating heart injuries includes hypovolemia due to bleeding and sings of cardiac tamponade (hypotension, elevated central venous pressure and muffled heart sounds) [7]. Some of the patients with penetrating injuries do not have symptoms that point to cardiac involvement [8], especially when patients are as young as our patient was, doctors do not consider the possibility of a heart problem. Therefore, prompt and adequate diagnostics and surgical intervention are essential. Preoperative diagnostics depends on hemodynamic stability of the patient, *i.e.* ade-

quate diagnostics is possible only in hemodynamically stable patients, while unstable patients, with growing hemothorax, heart tamponade, or active bleeding require urgent thoracotomy or medial sternotomy [1]. Echocardiography, as fast, accurate and noninvasive procedure, is essential in early diagnosis and evaluation of heart injury [7], while heart catheterization is a valuable but time-consuming diagnostic tool, and is not necessary in the initial phase of the heart injury diagnostics [1]. In this case report, leg ischemia of unknown etiology led us to perform angiography, which revealed the true cause of the problem – bullet in the artery, and then with the time-event reconstruction and performed echocardiography examination we were able to successfully establish proper order of events which led to this complication and its successful treatment. We think that echocardiographic examination is nessecery not only in all stable patients with heart injures in initial assessment and planning further management, but also in patients with chest trauma as signs of heart injury might not be visible at the beginning.

Foreign body embolization is a rare complication of penetrating wounds with bullets being the commonest of them [9–11]. A bullet accesses the vessel lumen either by direct propulsion or by erosion of vessel wall. Arterial bullet emboli are four times more frequent than venous [12]. All this emphasizes the rare nature of our patient who had embolization from the brachiocephalic vein through the superior vein cava to the right atrium and then paradoxical embolization through atrial septal defect. By now only a few similar cases have been reported in the literature [9, 13–15].

Conclusion

This case report is unique because of the rare type of injury and a long interval (four years) from the injury to paradoxical embolism and surgical treatment. A bullet embolus should be suspected in any patient who has a gunshot wound without an exit wound. If by any chance the shooter had been closer to the target – our patient – or if the bullet's caliber had been bigger or the bullet had entered at a different angle, this wound would have been fatal. Fortunately, all these unusual circumstances were in favor of the presented patient and helped him survive.

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CASE REPORT

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Uncommon metastatic site from breast cancer

Retko mesto metastaze karcinoma dojke

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Abstract

Introduction. Breast cancer is one of the most common malignancies in women and the main leading cause of cancer death. The most frequent sites of metastases from breast cancer are bones, lungs, the central nervous system, the liver and soft tissue. Colonic metastases from breast cancer are rare. **Case report**. We presented a 70-year-old woman with bulky obstructing lesion of sigmoid colon. A physician in charge on our department examined the patient and past history of breast cancer was found up. Surgery was performed with removal of sigmoid colon and three of six lymph nodes were positive. Pathological examination, including immunohistochemical stains, confirmed the diagnosis of metastatic breast cancer to sigmoid colon. The multidisciplinary oncology team suggested postoperative chemotherapy. The patient received four cycles of chemotherapy with paclitaxel followed by anastrozole. On the first control visit no disease activity was detected. **Conclusion.** In patients with the past history of breast cancer the symptoms of hematochezia or anemia may indicate colonic metastases.

Key words:
breast neoplasms; neoplasm metastasis; colonic neoplasms; diagnosis, differential.

Apstrakt

Uvod. Karcinom dojke jedan je od najčešćih karcinoma kod žena i vodeći uzrok smrti od malignih bolesti. Karcinom dojke najčešće metastazira u kosti, pluća, centralni nervni sistem i jetru. Metastaze u debelo crevo su jako retke. **Prikaz bolesnika.** Prikazali smo bolesnicu, staru 70 godina, sa dijagnozom opstruktivne infiltracije sigmoidnog dela kolona. Lekar koji je pregledao bolesnicu dobio je podatak da je bolesnica operisala karcinom dojke. Bolesnica je operisana, urađena je resekcija sigmoidnog dela kolona, i od pregledanih šest limfnih čvorova u tri su se nalazila žarišta metastaza. Patološkohistološkim pregledom, uključujući imunohistohemijsku analizu, potvrđena je dijagnoza metastatskog karcinoma dojke u sigmoidni kolon. Multidisciplinarni onkološki tim predložio je postoperativnu hemioterapiju. Bolesnica je primila četiri ciklusa hemioterapije sa paklitakselom i nakon toga nastavila terapiju anastrazolom. Na prvom kontrolnom pregledu nisu viđeni znaci aktivnosti maligne bolesti. **Zaključak.** Kod bolesnica sa ranije postavljenom dijagnozom karcinoma dojke, sa simptomatologijom krvi u stolici ili prisutnom malokrvnošću treba misliti i na mogućnost pojave metastaza karcinoma dojke u debelo crevo.

Ključne reči:
dojka, neoplazme; neoplazme, metastaze; kolon, neoplazme; dijagnoza, diferencijalna.

Introduction

Breast cancer is one of the most common malignancies in women and the main cause of cancer-related deaths [1]. When breast cancer is diagnosed at an early stage, the survival rate is higher; however, recurrences and metastases are quite common. Breast cancer usually metastasizes to the lymph nodes, lung, bone, liver, and brain. There are few reports of breast cancer metastasizing in the gastrointestinal tract (stomach and small intestine) while colonic metastases are extremely rare [2, 3]. Other unusual locations of breast cancer metastases may include eyes, urinary bladder, and skin.

Colonic metastases from breast cancer are rare and their nonspecific clinical presentation may be easily mistaken as a second primary colonic carcinoma; it may impair the clinical diagnosis and delay the treatment resulting in earlier mortality [4, 5].

Case report

At the beginning of 2010, a 70-year-old woman visited our Institute complaining of hematochezia. The results of blood count test and complete check-up were normal and the result of rectal examination was negative. The findings of

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colonoscopy examination showed circumferential bulky obstructing lesion in sigmoid colon. It was not possible for colonoscope to pass through the stenosis. Analysis of the biopsy material confirmed the presence of adenocarcinoma of the colon (HG3, NG3) (Figure 1). The patient underwent

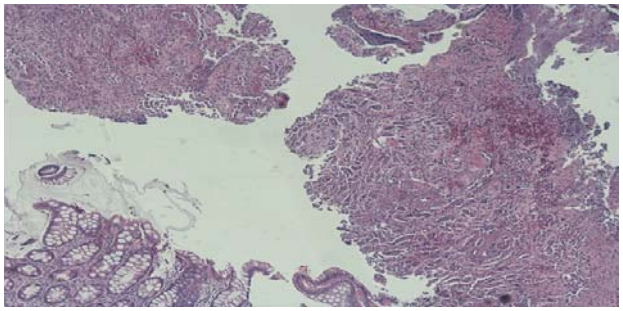

Fig. 1 – Endoscopic biopsy: metastatic adenocarcinoma in the specimen of the large intestine mucus (HE, ×40)

surgery and resection of sigmoid colon with end-to-end anastomosis. The results of pathological examination including immunohistochemical staining, confirmed the diagnosis of metastatic breast cancer to sigmoid colon (CK20-, CK7-, CK8+, CK18+, ER+, PR+). Six lymph nodes were identified and three of them were metastatic. These findings were similar to those of the prior breast cancer specimen (Figures 2 and 3). Cancer cells invaded the whole intestinal wall from

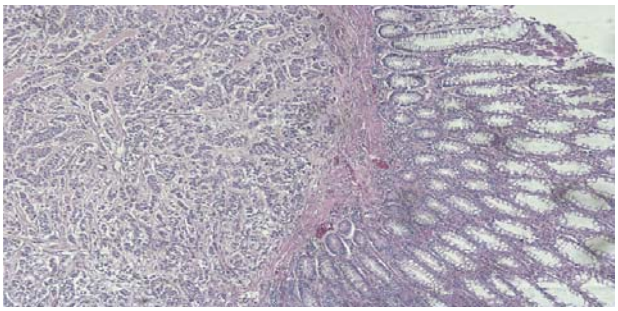

Fig. 2 – Breast cancer metastasis in large intestine wall; atypical tumor cells abundant in eosonophil cytoplasm and pleomorphic nuclei arrange in trabecular cluster (HE, ×40)

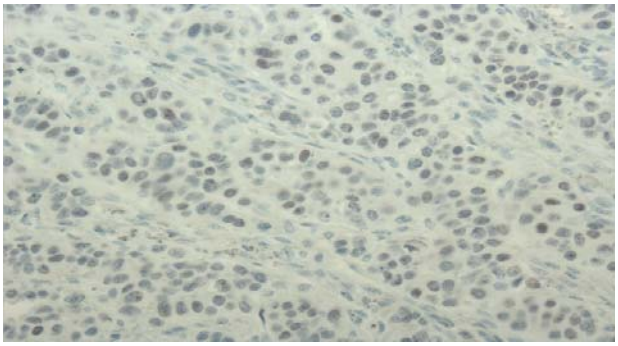

Fig. 3 – Immunophenotype of metastatic colonic cancer; estrogen receptor+ (immunohistochemical analysis, B-SA ×200)

mucosa to the serosa and surrounding fat tissue and infiltrated into the posterior wall of the urinary bladder. The multidisciplinary oncology team suggested postoperative chemotherapy. The patient received four cycles of chemotherapy with paclitaxel, followed by anastrozole. The first control visit showed no disease progression.

The patients past medical history was marked by breast exulcerated cancer in her left breast without palpable axillar lymph nodes in 2007. Using core biopsy the following diagnosis was established: ductal invasive carcinoma HG 2 with the invasion of capillaries, lymph ducts, and perineural area. At that time, the patient was treated with four cycles of neoadjuvant chemotherapy (5-fluorouracil, adriamycin, cyclophosphamide), which resulted in partial clinical response. Chemotherapy was followed by left mastectomy and ipsilateral axillary lymph node dissection and the excision of infiltrated region of pectoralis major on June 9, 2008. Histopathological examination of surgical specimen confirmed the presence of grade II invasive ductal carcinoma (4 cm × 3 cm) with skin invasion and 10 lymph nodes without metastases (G2, pT4N0) and the infiltration of muscle and perineural area. Immunohistochemistry tests for estrogen and progesterone receptors showed positive staining for both receptors (Figure 4). There was no evidence of distant metastases at the time of surgery. Multidisciplinary oncology team considered the patient to be at high risk for disease recurrence and suggested further treatment with radiotherapy (TD 50 Gy in 25 fractions) and adjuvant chemotherapy (cisplatin, cyclophosphamide, methotrexate, and 5-fluorouracil) for six months, which was followed with tamoxifen therapy until the beginning of 2010.

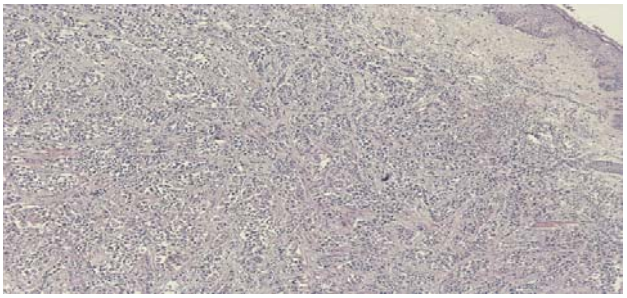

Fig. 4 – Primary breast cancer (HE, ×40)

Discussion

Metastatic involvement of the large bowel is rare. The incidence of metastatic breast cancer involving the colon is unknown, but an autopsy series reported the frequency of colonic involvement of metastatic breast cancer to be 8%, not including serosal implants [6]. The disease-free interval between primary breast cancer and gastrointestinal involvement varies from synchronous presentation up to 30 years, the median interval between diagnosis and presentation of metastases is six to eight years [2]. The symptoms may vary from asymptomatic abdominal masses to those mimicking ulcerative colitis [7]. Anorexia, hematochezia, and positive fecal occult blood testing are common presenting symptoms [4]. These non-specific findings often mimic other gastrointestinal diseases such as colorectal cancer, inflammatory bowel disease, ischemic colitis and, diverticulitis.

Differentiating primary colon cancer from metastatic breast cancer to the colon may be challenging. In patients with prior histories of breast cancer, second primaries of the gastrointestinal tract are more common than metastatic disease [8]. Immunohistochemistry has aided in differentiating the tumor site of origin. Hormone receptors, such as estrogen and progesterone ones, are utilized to differentiate breast *versus* gastrointestinal primary cancer [9], but these receptors may be positive in 20% to 28% of primary gastric carcinomas [10]. The more common antigen markers include cytokeratins (CK) 7 and 20 [11, 12].

In the presented case, the histological subtype of metastatic breast cancer was invasive ductal carcinoma (IDC). Infiltrating lobular carcinoma was found to metastasize more frequently to the gastrointestinal tract, peritoneum, and retroperitoneum than the IDC [13]. Metastatic disease involving the colon may be viewed as a systemic visceral disease, which should be treated with chemotherapy. Pathological analysis and repetition of endoscopy are necessary for the early and accurate diagnosis [14].

Conclusion

Radiologists and endoscopists should pay a special attention to patients with the history of lobular breast cancer and newly identified GI malignancies that may, among other diseases, be the metastases from breast cancer.

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CASE REPORT

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Congenital upper eyelid coloboma with ipsilateral eyebrow hypoplasia

Urođeni defekt gornjeg kapka sa istostranom hipoplazijom obrve

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Abstract

Introduction. Coloboma is a Greek word, which describes the defect of all layers of the organ, and it can be congenital or as the result of an injury, operation, or some disease. Congenital upper eyelid coloboma is a rare anomaly, with the unknown incidence. The size of the defect is different, but it always involves all layers of the eyelid. This malformation is more frequent at the upper eyelid, and unilaterally, at the junction of the medial two thirds. Sometimes, it can also involve the eye, and may be a component of many syndromes (Goldenhar, Fraser, Manitoba, CHARGE, Cat eye). **Case report.** We are describing the case of the upper eyelid coloboma with the rare eyebrow anomaly at the three- month old girl, and the result of reconstruction. The baby was treated conservatively with lubricants and overnight patching. Pentagonal excision of the defect was performed in general anesthesia. Three layers of the eyelid were prepared: the skin, muscle and tarsoconjunctival layer. Because of orbicularis muscle malposition, reinsertion and reposition of the muscle fibres were performed. Then, lateral canthotomy was made and the suture of three layers of the eyelid. Catgut suture 7–0 was used for the conjunctiva and muscle. Nylon 6–0 was used for skin suture. Z-plasty was done on the upper part of the pentagonal excision in order to reduce skin tension at the suture line. The operation lasted about 60 minutes and the hospitalization three days. The occlusive dressing was applied for two days. The stitches were removed after seven days. The postoperative swelling of the upper and lower eyelid disappeared in five days. There were no complications in the postoperative period. **Conclusion.** The main principle of the treatment of eyelid coloboma is surgical reconstruction of all layers of the eyelid, in optimal period, using different surgical methods, which depends on the size of the defect. An early diagnosis is of the greatest importance, as well as the treatment of associated anomalies. Complications of the upper eyelid coloboma depend on the size of the defect, presence of the eye anomalies and the method of reconstruction.

Key words:
eye abnormalities; eyelids; coloboma; eyebrows; reconstructive surgical procedures; treatment outcome.

Apstrakt

Uvod. Kolobom je grčka reč koja opisuje defekt svih slojeva organa, a može biti kongenitalni ili posledica povrede, operacije ili neke bolesti. Kongenitalni kolobom gornjeg očnog kapka je retka anomalija, sa nepoznatom incidencijom. Veličina defekta je različita, ali uvek uključuje sve slojeve kapka. Ova malformacija je češća na gornjem kapku i jednostrano, na spoju medijalne dve trećine. Nekada, može da zahvati oko, a može biti i sastavni deo mnogih sindroma (Goldenhar, Fraser, Manitoba, CHARGE, Cat eye). **Prikaz bolesnika.** U radu je opisan kolobom gornjeg očnog kapka udružen sa retkom anomalijom obrve kod devojčice stare tri meseca, kao i postrekonstruktivni rezultat. Beba je lečena konzervativno lubrikantima i u toku noći primenom zavoja. Petougaona ekscizija defekta sprovedena je u opštoj anesteziji. Ispreparisana su tri sloja kapka: koža, mišić i tarzokonjuktivalni sloj. Zbog malpozicije orbikularnog mišića urađena je reinsercija i repozicija mišićnih vlakana. Učinjena je, zatim, lateralna kantotomija i sutura očnog kapka u tri sloja. Ketgut 7–0 je korišćen za suturu konjunktive i mišića, a najlon 6–0 je korišćen za kožu. U gornjem delu ekscizione rane urađena je Z-plastika u cilju smanjenja napetosti kože duž suturne linije. Operacija je trajala 60 minuta, a hospitalizacija 3 dana. Okluzivni zavoj bio je postavljen 2 dana. Šavovi su uklonjeni nakon 7 dana. Postoperativni otok gornjeg i donjeg kapka iščezao je nakon 5 dana. Nije bilo komplikacija u postoperativnom periodu. **Zaključak.** Osnovni princip lečenja koloboma očnih kapaka je hirurška rekonstrukcija svih slojeva kapka, u optimalnom periodu, korišćenjem različitih hirurških metoda, u zavisnosti od veličine defekta. Rana dijagnoza je od najvećeg značaja, kao i tretman udruženih anomalija. Komplikacije koloboma gornjeg očnog kapka zavise od veličine defekta, prisustva anomalija očiju i metode rekonstrukcije.

Ključne reči:
oko, anomalije; očni kapci; oko, defekt; obrve; hirurgija, rekonstruktivna, procedure; lečenje, ishod.

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Introduction

Coloboma, a Greek word, meaning defect is ysed for a defect of all the layers of the eyelid. Coloboma may be congenital or a result of injury, operation, or some disease.

Congenital upper eyelid coloboma is a rare anomaly of unknown incidence. The size of the defect varies, but it always involves all the layers of the eyelid. This malformation is more frequent in the upper eyelid, unilaterally, and at the junction of the medial two thirds. Sometimes a defect can involve eye, and may be a component of many syndromes (Goldenhar, Fraser, Manitoba, Charge, Cat eye). The main principle of the treatment is surgical reconstruction of all eyelid layers in optimal period, using different surgical methods, which depends on the size of the defect. An early diagnosis is of the greatest importance, as well as the treatment of associated anomalies. Complications of untreated upper eyelid coloboma depend on the dimensions of the defect, the presence of eye anomalies and the method of reconstruction.

We presented a 3-month-old girl with upper eyelid congenital coloboma and the eyebrow anomaly, and the result of the reconstruction. The main purpose of this report was to describe a rare, combined congenital malformation and the patient's condition after surgical treatment, as well a, to paint out the importance of multidisciplinary approach in the early diagnosis and the treatment of this anomaly.

Case report

A 3-month-old girl was referred to the Plastic Surgery Unit by the ophthalmologist. The main diagnosis was congenital upper right eyelid coloboma. Coloboma was on the medial third of the upper eyelid. The girl had ipsilateral eyebrow hypoplasia and malposition. The rest of the physical examination was normal. There was no family history of similiar or other congenital anomalies (Figure 1).

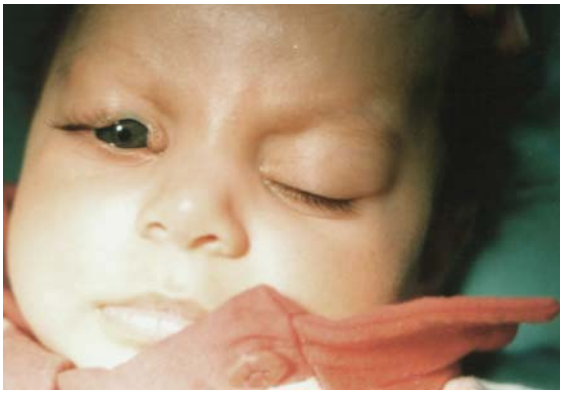

Fig. 1 – A three-month-old girl before surgical treatment

The baby was treated conservatively with lubricants and overnight patching. The pentagonal excision of the defect was performed in general anesthesia. The three layers of the eyelid were prepared: the skin, muscle and the tarsoconjunctival layer. Because of the malposition of the orbicularis muscle, reinsertion and reposition of the muscle fibres were performed. Then, lateral canthotomy was made and suture of the three layers of the eyelid. Catgut suture 7–0 was used for the conjunctiva and muscle. Nylon 6–0 was used for skin suture. Z-plasty was done on the upper part of pentagonal excision in order to reduce skin tension at the suture line. The operation took about 60 minutes and the hospitalization three days. The occlusive dressing was applied for two days. Stitches were removed after seven days. The postoperative swelling of the upper and lower eyelid disappeared in five days. There were no complications in the postoperative period. The girl underwent a regular control by the plastic surgeon and the ophthalmologist. Correction of eyebrow deformity was recommended in a later period (Figure 2).

Fig. 2 – The result of surgical treatment after 3 years

Discussion

Congenital eyelid coloboma was first described by Walter Eyre Lambert in 1901 considering the anomaly of the upper left eyelid. It is supposed that this malformation derives from the incomplete fusion of the mesodermal clefts during the gestation period, under the influence of PAX2 gene [1]. It is possible that many factors, such as radiation, may have some influence on the development of the eyelid. Upper eyelid coloboma is a rare congenital anomaly of unknown incidence.

Grover et al. [2] reported his results of a retrospective study which covered the period of 18 years and 51 patients with congenital coloboma of both eyelids. Upper eyelid coloboma was more frequent (74.5%), and defect of the eyelid was less than 40% in 57.9% patients. In our hospital the incidence of this malformation is about 1 : 9000 during a 5-year-period. There are no relevant data about sex, race and size distribution of this anomaly. Coloboma is the most frequent at the junction of the medial two thirds of the upper eyelid, and laterally in the lower eyelid. There are also some reports about bilateral upper eyelid coloboma [3].

Congenital upper eyelid coloboma is sometimes associated with other anomalies. Cryptophthalmos is present in the Fraser syndrome [4] and in Manitoba Oculotrichial syndrome (MOTA) [5, 6]. CHARGE syndrome is described as a syndrome with eyelid coloboma, lip and/or palate cleft, ear

anomaly, choanal athresia, brain and cardiovascular anomalies and slow psycho- somatical development [7]. Goldenhar syndrome Oculo Auriculo Ventebral (OAV) syndrome includes upper eyelid coloboma, ear, nose, palate, lip and mandibular hypoplasia, and eye lipodermoid cyst, as well as strabismus [6, 8]. In some cases, coloboma may involve eye (iris, lens, choroidea, retina, optical nerve) – Cat eye syndrome. Nouby [9] indicated in his study that 3 out of 26 children with eyelid coloboma had cryptophthalmos and 11 were found with some facial anomalies, like first cleft syndrome. Nouby made the classification of eyelid coloboma: coloboma without cryptophthalmos, coloboma with partial cryptophthalmos, coloboma with total criptophthalmos, classical cryptophthalmos and severe cryptophthalmos (severe nose deformities and lower eyelid ectropion). Lower eyelid coloboma is a rare anomaly, but it is usually a part of the Treacher Collins syndrome.

Eyelid coloboma treatment is surgical and depends on the size of the defect [10]. A team approach is necessary for the early diagnosis and treatment of accompanied anomalies, and sometimes there is a need for genetics consultation. The ophthalmological examinations of the newborn with eyelid coloboma must include the anterior segment (symblepharon, conjunctival caruncular malformation, keratopathy, choroidal coloboma, eyelid lypodermoid cyst), as well as the posterior segment (retinal and optical nerve coloboma). Computed tomography (CT) is reserved for Treacher Collins syndrome, for patients with lower eyelid coloboma.

The optimal period for the operation depends on the size of the defect. If coloboma is smaller, operation can be delayed until the school time [11], but if the defect is larger, operation must be done as soon as possible in order to prevent corneal lesions. In the meanwhile, topical lubricants and wet dressing are recommended. Surgical methods depend on the size of defects, but excision and reconstruction of all eyelid layers remain necessary. There are many surgical methods that can be used: direct suture, local, regional and composite skin flaps [12]. Sometimes, there is a need for two-stage operation. Skin or other flaps are necessary when the defect involves more than 40% of the upper eyelid. The most common methods in those cases are Cuttler-Beard, modified Hughes technique, Tensel or modified Tensel flap and full, thickness cross-flap from the lower eyelid.

Conclusion

We presented a very rare congenital, combined upper eyelid anomaly. In this case, there was no need for the use of a flap, but we performed lateral canthotomy and Z-plasty, because of the borderline defect size. In our opinion, the desinsertion and reposition of the orbicularis muscle are very important, like in cleft lip operations. Also, pentagonal excision may have some advantages on simple V-excision, because suture line is at the right angle and at the eyelid border. Reconstruction of eyebrow deformity can be performed later, using some of the numerous known surgical methods.

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HISTORY OF MEDICINE

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The Spanish Flu – Part I: the first wave

Španska groznica – I deo: prvi talas

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Key words:
influenza, human; world war I; disease outbreakes; history, 20th century; serbia.

Ključne reči:
grip, humani; prvi svetski rat; epidemije; istorija, 20-ti vek; srbija.

Introduction

The Spanish Flu is a term which denotes an influenza pandemic which emerged in 1918. This disease has numerous synonyms: the Spanish Flu, La Grippe espagnole, the Spanish Influenza and it is also possible to encounter throughout the world such names as the Spanish Lady or the Purple Death. The latter name resulted from the specific skin colour in the most severe cases of the diseased, who by the rule also succumbed to the disease, and is also at the same time the only one which does not link this disease with the Iberian peninsula. This name is actually the most correct.

The disease was named Spanish due to the complex war circumstances. Spain was not a participant in the war, thus “the new disease” was written about freely in that country. On the contrary, due to the strong censorship of the press of the warring sides, very little was written about this disease. Therefore, a wrong impression resulted from reading the Spanish press, that the disease had emerged there first. It was mentioned in Spain on May 22, 1918 for the first time [1]. The “ABC” Madrid journal published that a disease similar to influenza had been present in the country since the beginning of May. A week later, the Spanish king Alfonso XIII, the Spanish prime minister and some other members of the government got sick and the pandemic was named Spanish for good [*].

The Spanish Flu was also written about in the Serbian press in May 1918. “The Serbian Newspaper” which was published on Corfu, conveyed in the period May 15/28, 1918[†] the writings of the French press, which discussed the reasons for the lessening in intensity of the German offensive: “In discussing the anticipated German offensive, papers ascertain that the German infantry is still not making any attempts and believe that the cause of this is either a drop in the morale in the German army, which has already lead to riots, or an influenza epidemic, for which there are proofs that it is strongly raging in the German army.” [3].

The information about the presence of influenza in the German army was correct and later, even Erich Ludendorff (1865–1937), a German military commander, wrote about the negative impact of this disease on the German offensive [4].

„The Serbian Newspaper“ wrote in the period October 23 / November 5, 1918 at the peak of the second, deadliest wave of the pandemic:

„Various countries have been assigning the origin of this imposing guest to each other for quite some time, and at one point in time they agreed to assign its origin to the kind and neutral Spain, which had been fighting off this honour just as much as German submarines, so imposing in their search for hospitality off Spanish shores. Finally and with great difficulty, they freed Spain from this stain, as it was ascertained that the flu had existed in Germany before it appeared in Spain. Besides, it is absolutely not unnatural that a world war should give a world disease, nor illogical that this disease be started by the country which had also started the war“ [5].

It would also have been wrong to name the disease as German. The world war brought a world disease, which

[*] Giving wrong names to diseases is not a novelty in the history of pandemics. A syphilis epidemic broke out in Naples in 1494 which was transmitted from the New World. The French named it the Italian, and the Italians the French disease and only some time later did Fracastoro name it syphilis [2].

[†] It should be borne in mind that the Julian calender was used in the Kingdom of Serbia also during World War One. The use of the Gregorian calender (only for secular purposes) began on January 23, 1919 in the newly formed state of the Kingdom of Serbs, Croats and Slovenes.

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started on the territory of another power which was to have a determining impact on the outcome of World War One. It is believed today that the Spanish Flu originated in the United States of America [4]. Only nowadays do we know that this disease was caused by the influenza virus A of H1N1 antigenic characteristics.

The spread and consequences of the Spanish Flu

The first pandemic wave appeared in the spring of 1918, and is usually described as a mild one because of the rare deaths. The second wave, extremely deadly, came in the autumn of 1918. The third wave took place in the winter of 1919. The disease did not spare any part of our planet. The disease caused death on all meridians, destroying complete families, leaving indelible wounds on the souls of the survivors. It is believed that a third of the world's population of that time, around five hundred million people, had a clinically expressed disease. Around fifty million people died [6]. The Spanish flu claimed five times more lives than World War One!

When American authors wish to make a striking illustration of the number of victims of this pandemic just in their country, then they say that the Spanish flu claimed more lives than was the total of the war losses of the American army in World War One, World War Two, the Korean and Vietnam wars altogether [7]. The high death rate was to be the basic characteristic of the second wave. The number of deaths is in itself scary, but the most susceptible age group makes this disease particularly tragic. People at the height of their vitality, aged between 20 and 40 died most frequently of the Spanish Flu! The American neurosurgeon Harvey Williams Cushing (1869–1939), who himself had the Spanish Flu, described its victims as „doubly dead in that they died so young" [4].

However, despite such a high death rate, there is practically nothing left of the memory of the Spanish Flu in the collective memory of humankind. This pandemic is therefore often called the forgotten pandemic.

The American historian Alfred W. Crosby, the author of the book „America's Forgotten Pandemic" (1990), states how many details on the Spanish Flu could be found in the most renowned world encyclopedias. He found three sentences in the Encyclopedia Britannica. In the Encyclopedia Americana one, indicating only that the disease had killed 21 million people. The information on the number of victims given there, is significantly below the actual number.

The 1918–1919 flu pandemic had also some other specificities. One of them was already the three pandemic waves in the course of just one year. It is not known which features of the virus of that time made this possible. Another one is the struggle of the scientists of that time to find an efficient vaccine against the Spanish Flu. Medicine had advanced tremendously following the discoveries made by Pasteur and efficient vaccines existed already against various other diseases, thus the hope of scientists that the discovery of a vaccine would defeat the pandemic was not altogether groundless.

It was believed that the flu was caused by the Pfeiffer bacillus – *Haemophilus influenzae*. This wrong view about the cause of the disease made the efforts of scientists vainly. The suspicion about the Pfeiffer bacillus causing the pandemic occurred already while it lasted. Dr. Aleksa Savić (1878–1928), wrote in 1918 about the experiments made by the team of the French scientist Charles Jules Henri Nicolle (1866–1936):

„By experiments made on monkeys and humans, they determined that the disease is transmitted exclusively by secretions from lungs and lung ducts of the diseased, and that the disease is not transmitted by injecting blood taken from patients. According to their view, the cause of the flu is such a tiny microorganism, that it cannot be seen by the currently available methods of observation" [8].

Scientists were full of energy, fortitude and good intentions in 1918, but also not aware of their practically hopeless position. There are even today numerous difficulties in the production of a vaccine against the influenza virus, which is antigenically unstable. The present day science has advanced so much, that the remaining genetic material of the virus was looked for and found in the preserved tissues of the Spanish Flu victims. The virus was then put together and finally even made alive! Every fragment of the Spanish Flu virus genome is known today, each one of its nitrogenous bases! However, the virus itself, is still a mystery. It is still not completely clear, which of its features enabled it to kill millions of people at the height of their vitality. The present day scientists are trying to understand the genetic basis of the contagiousness and deadliness of the influenza virus, in order to protect humankind with this knowledge against similar future pandemics. Thus, the enlivening of the Spanish Flu virus represents another specificity.

The Spanish Flu pandemic is a subject which is not easy to investigate. On one hand there is a shortage of sources, which is the consequence of the reality of war of that time. Not much was written about the disease while Great War lasted and even if it was, only favourable reports about the reduction in the number of deaths or about some efficient vaccines were highlighted. The presentation of the actual situation was avoided (and even forbidden). It is therefore difficult to reconstruct the events of that time, particularly in the war stricken environments. On the other hand, people were dying throughout the world, there are graves of the Spanish Flu victims everywhere, which speak a lot for themselves, but even they cannot fully present the time itself, when the pandemic lasted. There is another difficulty. Although many people survived the Spanish Flu pandemic, they in particular are the one who said almost nothing about the disease. This is a world phenomenon. The pain caused by the loss of the dearest ones remains in the soul, it is not even talked about. Nothing can bring back the dead. Thus, what presents a particular difficulty in studying the Spanish Flu pandemic is the general oblivion, so we can quote here the sentence from the novel „Fortress" by Meša Selimović: „What is not written does not exist. It is dead and gone."

Medical statistics in war conditions could not have been precise enough, therefore there is not a complete statistic

presentation of the pandemic. However, there is a certain number of documents left, based on which it is possible to conclude indirectly what was happening throughout the world at that time. Thus the combination of the preserved medical records, statistical data, photos, noted down memories and newspaper articles collected from various parts of the world, present today a reliable manner of getting the right picture of the Spanish Flu pandemic.

The records made by Serbian doctors, newspaper articles, photographs with some later writings, were used in this paper. A particularly important source was the book by John M. Barry „The Great Influenza: The Story of the Deadliest Pandemic in History“ [4].

The author of this paper made his contribution to the reconstruction of the picture of the Spanish Flu pandemic, by noting down the memories of the pandemic in the Tovariševo village in Vojvodina.

However, it must be said straight away that even the oldest residents of the above mentioned village, born only a few years after the pandemic, did not know much about the pandemic. They were told that a „terrible disease“ raged at that time, that people just „dropped dead“ of it, that „six coffins were taken out of one street in one day“. A man whose father had died of the Spanish Flu, did also not say more than a few sentences about the disease.

It is possible to find data in church books about tens of very young people having died of this disease in Tovariševo. This village is certainly a miniature example that the mortality caused by the Spanish Flu can still be investigated even today. Church and municipal books are a valuable source of data.

The first wave

There are several theories about where the pandemic influenza virus from 1918 appeared first. Many scientists looked for the pandemic source in China, because earlier experience showed that flu mainly came from the Far East. However, epidemiological data did not confirm such assumptions. Olson et al. [9] believe that there are strong proofs that an early pandemic wave was present in New York already in February 1918. These explorers found that a greater death rate was observed in this very period among young people, caused by flu, which is already a feature of the pandemic virus. According to them, the virus came onto the American soil from Europe. The British scientist John S. Oxford, believes that the disease appeared first in a big British military base in the north of France already back in the winter of 1916. [10]. This assumption is based on the appearance of severe respiratory infections in this base, which were recorded under the name of „purulent bronchitis“. The disease was followed by high temperature, coughing, and the presence of heliotrope cyanosis and a high death rate made the „purulent bronchitis“ very similar to the most severe form of the Spanish Flu. Signs of bronchopneumonia were found by clinical examination, whereas histological research confirmed „acute purulent bronchitis“. A similar appearance of the purulent bronchitis was noted down in March 1917 also among British soldiers in a base near London. The disease would appear all of a sudden, followed by a high temperature, rapid breathing and heliotrope cyanosis of the face, lips and ears, a sign which was to be an indication to doctors during the Spanish Flu pandemic, that death was near. The author of this hypothesis believes that it took more than two years for this disease to start spreading throughout the planet, because of the lack of intensive transport during World War I, and that the demobilization in the autumn of 1918 created ideal conditions for the flourishing of the pandemic. Many scientists consider this kind of explanation as unconvincing. Oxford included also in his work the photographs of the soldiers on the Western Front, showing them plucking turkeys and feeding swine, which indicates the closeness of people and animals, which had a big role in the appearance of pandemic flu viruses.

The American author John M. Barry, who studied the 1918 flu pandemic for years, presented the hypothesis about the appearance of the disease at the beginning of 1918 in the Haskell County in Kansas [4]. People and animals were in close contacts in this extremely rural area. Dr. Loring Miner was a doctor in this spacious, sparsely inhabited area. At the end of January 1918 patients started calling on him, complaining of strong headaches, muscle pain, high temperature and unproductive cough. Dr. Miner knew well the flu symptoms, but he noticed in all these cases an expressed intensity of the symptoms. His patients started dying in this isolated area. Miner informed the competent health authorities about this, but the answer was not adequate.

The local newspaper „The Santa Fe Monitor“ brought numerous news in the course of the first half of February 1918 about the Haskell County inhabitants falling ill with pneumonia or about their recovery. The names and surnames of the diseased were given. For example this paper wrote on February 14, 1918:

„Mrs. Eva Van Alstine is sick with pneumonia. Her little son Roy is now able to get up ... Ralph Lindeman is still quite sick... Mertin, the young son of Ernest Elliot, is sick with pneumonia ... We are pleased to report that Pete Hesser’s children are recovering nicely...“.

„The Santa Fe Monitor“ wrote on February 21, 1918: „Most everybody over the country is having lagrippe or pneumonia“.

It is possible to follow the data about the infrequent but existing transport between the Haskell County and the American military base Camp Funston, to which the recruited young men went in this County. Names are given of the soldiers who went home from this base for a visit, only to return to Funston at the end of February 1918. There were around 56,000 soldiers in that camp at the time. The first case of a diseased suffering from the flu was registered on March 4, 1918. In the following three weeks 1,100 soldiers were so ill, that they had to be admitted to hospitals for treatment, whereas thousands of others had the disease and recovered without being admitted to hospitals. Pneumonia developed in 237 soldiers, and the number of deaths amounted to 38. This was a far greater number of deaths,

than was expected from a „common“ influenza epidemic, yet still insufficient to be given attention to, in that significant war year (Figure 1).

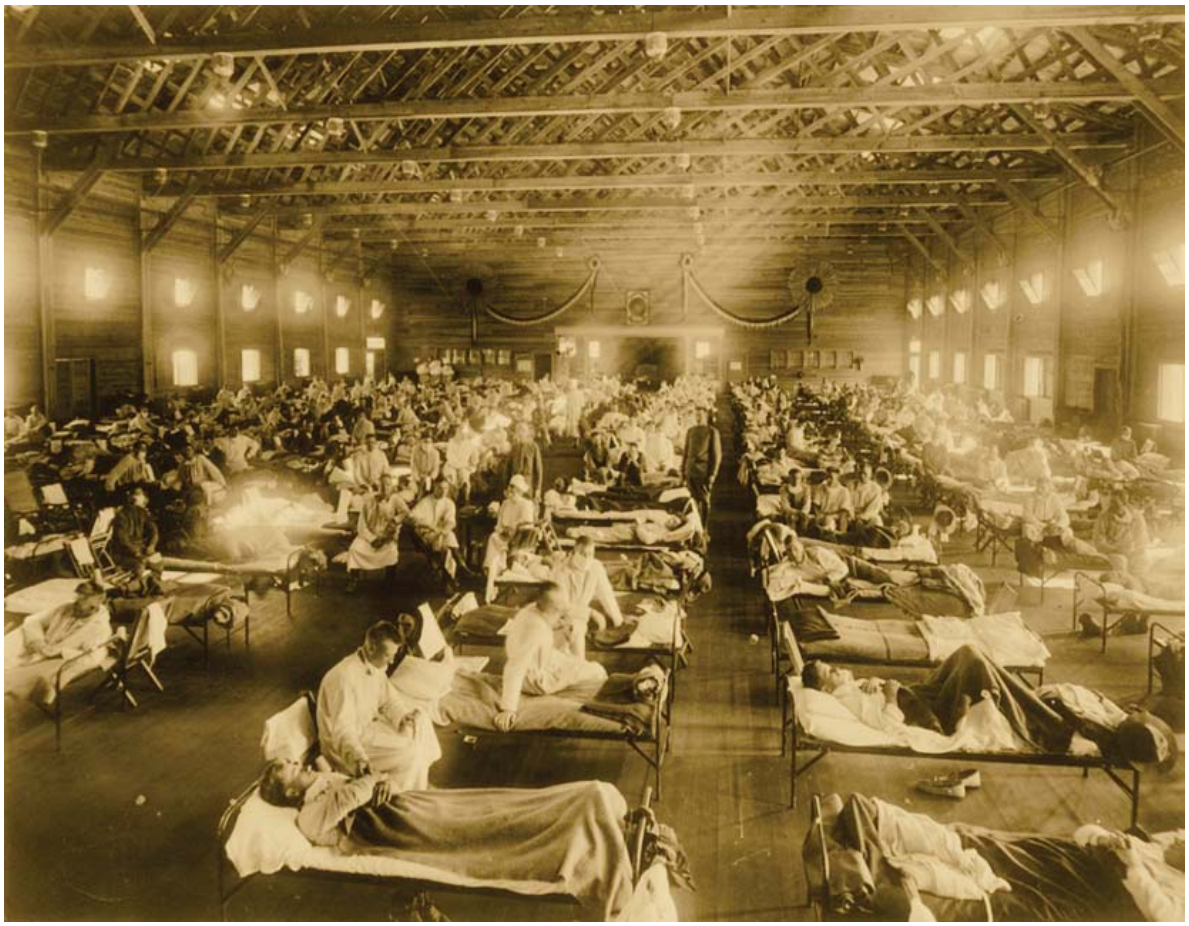

Fig. 1 – The ill-stricken with the influenza in Camp Funston in the US state Kansas (the photo was probably taken in the course of the first wave of the Spanish Flu)

While the flow of people between the Haskell County and the Funston base was relatively weak, the transport among individual American military bases, or between them and Europe, was very lively. Railway transport was dominant on the American continent and between America and Europe ship transport. The latter was so intensive in that war year that, judging by the number of passengers, it could be compared with the present day air transport!

Contacts between the military and civil population were also numerous. That is the reason why influenza appeared rapidly in 24 of the 36 major military bases in the country, and 30 of 50 major American towns, mainly those which were in the vicinity of military bases, had an increased number of death cases. Since the entry of the United States in the war (1917) the influx of American soldiers into Europe increased. At the beginning of 1918 Germany was preparing a big spring offensive on the Western Front. Hundreds of thousands of soldiers were withdrawn from the preceding Eastern Front, since they were not needed there, considering the fall of the Russian empire. At the same time, hundreds of thousands of American soldiers were arriving into Europe. They were supposed to be the turning point factor, enabling the Allies to resist German attacks and then win the war. However the pandemic influenza virus strain came along with the American soldiers into Europe.

The French town Brest was the first place in Europe where the flu caused by this virus appeared. The disease appeared in that port on the coast of the Atlantic already at the beginning of April. Tens of thousand of American soldiers who disembarked in Brest, brought to Europe, besides faith in allied victory, without intending to do so, the tiny „weapon“, which was to prove more efficient in destroying human lives than all technical wonders, brought already by World War One. The flu spread rapidly from Brest onto its surroundings in concentric circles. It should be pointed out, however, that the disease manifested itself everywhere at this stage in a mild form. There were death cases, but they were very rare.

The disease appeared in the Serbian army on Corfu. Dr. Aleksandar Radosavljević (1877–1956) states:

„At the beginning of April in 1918 some sudden diseases appeared in a bakers troop of our army. About 150 people fell ill in two days, 95 of which were bedridden with a high temperature, headache, pain throughout the body, sweating and coughing. The disease appeared due to a contact of our soldiers with French bakers, who had arrived by ship from Thessaloniki.This severe condition lasted 3–4 days, followed by recovery or death. The epidemic struck

soon also the other military units, even the civilians, with complications of pneumonia. In May 1918 the epidemic flourished in even greater proportion and the death rate caused by this disease was even greater.“ [11].

It is possible to find information in „The Serbian Newspaper“ about one Serbian soldier, a conscript of the craftsmen and bakers troop on Corfu, dying on April 7/20 in 1918 in the French Naval Hospital „Achileon“ [12]. The cause of death was not indicated, although the circumstances indicate that it was most likely the Spanish Flu. The disease appeared in the Serbian army, thus, very early, before it even got the Spanish name, even before it spread from Brest to Paris.

The influenza was present in Paris already at the end of April, and it arrived in Italy at just about the same time. The first cases were found in the British army mid April. Then, the disease started intensifying.

The same disease appeared in German troops, also at the end of April. It had an impact on the combat power of German forces, just as was the case with the Allies, which had a particular significance, if we bear in mind that that was a period of an extremely strong German offensive, which even threatened to make Germany the winner of the Great War. The famous American doctor Harvey Cushing wrote in his diary directly from the frontline:

„The expected third phase of the great German offensive gets put off from day to day... When the next offensive will come off no one knows. It probably won't be long postponed . I gather that the epidemic of grippe which hit us rather hard in Flanders also hit the Boche worse, and this may have caused the delay.“ [4].

Erich Ludendorff, the chief commander of the German forces, blamed also the flu for the failure of the German offensive, pointing out that: „It was a grievous business having to listen every morning to the chiefs of staff's recital of the number of influenza cases, and their complaints about the weakness of their troops“ [4].

The disease appeared in the neutral Spain only in May. It was most likely brought by Spanish and Portuguese workers, who travelled by train to France and back. The first news on the epidemic appeared in the „ABC" Madrid Journal on May 22, 1918. The journal wrote about the presence of a disease similar to influenza, which was spreading from the beginning of May. A large number of people gathered on squares in the course of the third week of May for the traditional Madrid annual festivities (Fiesta de San Isidro Labrador), which was favourable for the spread of the infection. The disease was still presented as a two-or three-day fever, with gastrointestinal symptoms, weakness, but very low mortality. An announcement was made on May 28, 1918 about king Alfonso XIII falling ill, followed by the prime minister and several other members of the government cabinet. Many workers were absent from work because they were ill, and some public services, like the post office and banks, were forced to shut down [1].

The new disease was openly written about in Spain, whereas war practice in the countries participating in the war imposed that weaknesses of the countries were not to be brought out in the press. The mortality level as a consequence of this disease in Spain, was low at first and ranged from 0.04 to 0.65 death cases per 1,000 inhabitants. As the flu arrived in Spain from France, it is known in this country as the French flu.

The spread of the disease continued. The flu appeared only scarcely in a more severe form. The British soldiers transmitted the disease to England in June, thus the number of death cases caused by the flu in England, Scotland and Wales in that month and in the following July, started to grow. As of June the disease became more intensive in Germany. Denmark and Norway were stricken in July. Holland and Sweden in August.

A group of Danish scientists, who studied the statistical data from 1918 and 1919, concluded that the lethality was greater during the first pandemic wave from July till August, than in the second wave from October 1918 till January 1919. Denmark was unique in this respect [13].

The disease appeared in Croatia at the beginning of July. It was present in Dalmatia and Bosnia mid July [14]. That first wave of the Spanish Flu was quite certainly also present in the occupied Serbia at that time, but there is no data about this.

This disease became more and more severe as time went by. Doctor V.S.S. whose initials were only given in a recent piece of writing by a group of Serbian authors, wrote the following on the Thessaloniki front:

„As a troop doctor of the First Yugoslav Regiment, I saw at the beginning of June 1918 a sudden short-lasting attack of this epidemic, similar to some kind of assaulting atmospheric attack. The until then healthy regiment at the „Kotka“ position, was descending down to the lowlands to rest. Upon arrival into the village Donji Požar I fell ill, among the first ones, that very evening, and so did the almost the whole regiment the following day. Upon arrival into the village Gostoljube on the same day, I found the whole battalion in front of my regiment surgery, looking for medical help, coughing and sneezing as if upon order, everyone single one of them. The epidemic disappeared soon as silently as it had come, without causing any damage, several days after the arrival of the regiment onto the hill Pajik [15].

The Serbian doctors on the Thessaloniki front realized already at the end of June and beginning of July that the disease was becoming increasingly severe. Đorđe Vladisavljević, the head of the medical corps of the Supreme Command, wrote about febrile diseases, which were appearing in the Serbian military units in the course of May:

„Some of our doctors reported them as dengue or Pappataci fever, and the French ones as flu. It was only realized in June and July, when lung complications started to appear, with quite high death rates, that it was a question of influenza.“ [15].

The disease announced in some places even earlier its deadly potential. In France at the end of May, in a small base numbering 1,018 recruits – 688 were admitted to hospitals for treatment, of which 49 soldiers died. It is extremely concerning when 5% of the total number of manpower dies of a disease and particularly when this happens to young and strong people [4].

An American military paper wrote: „Pneumonias have been more common sequelae in July than in April.“ [4].

The disease arrived in Bombay end of May 1918, spreading from there throughout India via railway network. The disease was present in Shanghai end of May.

It arrived in New Zealand in September.

The first wave of the Spanish Flu can still be considered as a mild one. Millions of people fell ill, but complications and deadly outcomes were mainly rare. Thus, had it by any chance stayed just on this level, on the properties of this first mild wave, the Spanish Flu would have remained unnoticed, to be more precise, unrecorded in the history of the world.

There were underestimations of the disease as regards the description of the mild clinical course of this early wave. The famous British medical journal „The Lancet" wrote on July 13, 1918 that the existing epidemic could not be the influenza, because the symptoms, although very similar to influenza, were too mild, short lasting and complications were rare.

The British had thus, just like in at least another two later cases, completely underestimated the pandemic. The British command had proclaimed the end of the pandemic on August 10, 1918 and one medical journal wrote on August 20, 1918 that the influenza epidemic „has completely disappeared" in Britain [4].

Still, the first pandemic wave spread rapidly, although its real scope is difficult to estimate. Already during the second, deadlier wave, even without adequate statistics, the pandemic left deep traces throughout the planet, in the form of millions of graves. Not even two months after the text in the medical journal ''The Lancet", which wrote that this „mild" disease could not be influenza, a new opinion appeared throughout the world about the appearance of a „new" disease which, considering the severity of its clinical picture, complications and numerous death cases, could not be the flu.

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BOOK REVIEW / PRIKAZ KNJIGE

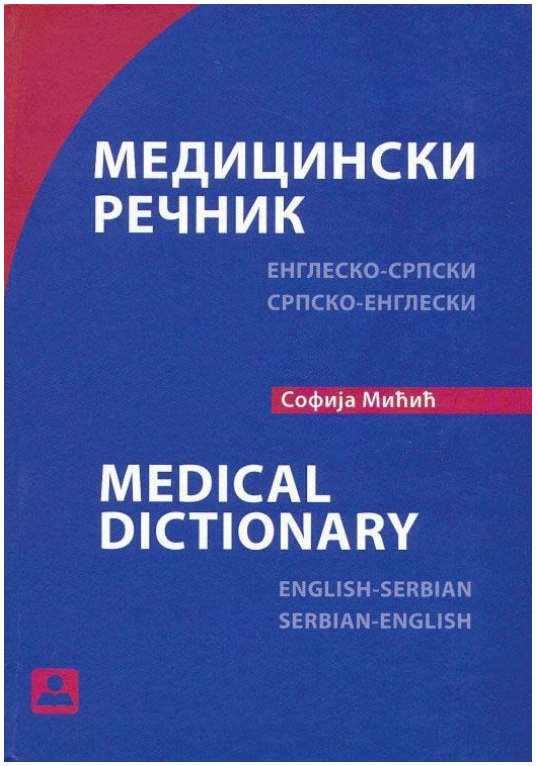
Title / Naslov:
Medical Dictionary, English-Serbian Serbian-English 2nd revised edition / Medicinski rečnik: englesko-srpski, srpsko-engleski, drugo dopunjeno izdanje

Author / Autor: **Dr. Sofija Mićić**

Publisher / Izdavač: **Serbian State Publisher of Textbooks, Belgrade / Zavod za udžbenike, Beograd**

Year / Godina: **2011**

879 pages, XVI pages of illustrations
40, 000 entries / 879 strana, XVI strana ilustracija
40 000 odrednica



The Medical Dictionary English-Serbian Serbian-English, 2nd revised edition (1st edition of the Dictionary, published in 2007, was awarded the City of Belgrade Prize for Education for 2007), Belgrade, publisher Serbian State Publisher of Textbooks, the author Prof. Dr. Sofija Mićić appeared after a few years of extensive and hard research within the Fulbright Postdoctoral Scientific Project at the Indiana University-Purdue University Indianapolis (IUPUI) and presented in the International Academic Center, 12 Dečanska Str., 1st floor) organized by the Fulbright Alumni Association of Serbia (FAAS).

Welcome speech was delivered by Prof. Sima Avramović, the Dean of the Faculty of Law, University Belgrade, the President of the FAAS. On the significance of this lexicographic project was discussed with inspiration and numerous words of praise and respect by the Academician Dragan D. Micić, pointing out and praising scientific/professional/ teaching engagement of the Author, then Prof. Slobodanka Đolić emphasizing the significance of correct translating both simple and complex terms and expressions from English to Serbian as being enormous contribution of this Dictionary, then Dr. Ivana Lazić-Konjik, and the Author herself – Sofija Mićić, the Doctor of Linguistic Sciences (Anglistics), an Asso-

Medicinski rečnik srpsko-engleski, englesko-srpski, 2. dopunjeno izdanje (1. izdanje ovog Rečnika, objavljeno 2007, nagrađeno je Nagradom grada Beograda, oblast Obrazovanje za 2007), Beograd, Zavod za udžbenike, autora prof. dr Sofije Mićić pojavio se posle nekoliko godina napornog istraživanja u okviru Fulbrajtovog posledoktorskog naučnog projekta na Indiana University-Purdue University Indianapolis (IUPUI) Indianapolis, USA i nedavno predstavljen u Međunarodnom akademskom centru (International Academic Center, Dečanska 12) u organizaciji Fulbright Alumni Association of Serbia (FAAS).

Pozdravni govor održao je prof. Sima Avramović, dekan Pravnog fakulteta, Univerziteta Beograd, predsednik FAAS. O značaju ovog leksikografskog poduhvata nadahnuto i s puno izraza hvale i poštovanja govorili su akademik Dragan D. Micić koji je istakao i pohvalio naučno-stručno-pedagoški rad autorke, prof. Slobodanka Đolić, naglašavajući značaj pravilnog prevođenja kako jednostavnih, tako i složenih termina i izraza sa engleskog na srpski jezik, što je veliki doprinos ovog Rečnika, dr Ivana Lazić-Konjik i autor, Sofija Mićić, doktor lingvističkih nauka (anglistika), profesor engleskog jezika na Medicinskom fakultetu, Univerziteta u Beogra-

ciate Professor of English Language at the Faculty of Medicine and at the Faculty of Stomatology, University Belgrade.

This bilingual dictionary, a total of 879 pages, except for vocabulary part (English-Serbian pages 9–448, Serbian-English pages 449–879) contains Preface (pages 5–6), a list of the used phonetic signs and symbols (for English Language) and abbreviations (pages 7–8), as well as a brief illustrated vocabulary inserted between the English-Serbian and the Serbian-English glossary paginated by the Roman numbers (I–XVI). Each of the 40,000 entries (lemmas) is supplied with a short grammatical data on the kind of word, expressive significance of lexeme, the field of use, and, that is most precious to any user of the Dictionary, there is a phonetic transcription of all the English entries due to the known difficulties with medical terms pronunciation. The Dictionary "Consistently applies the principle of finding out an optimal translated form, if any, or otherwise, of clearly marking the differences between many of them imposed as a solution" (Preface).

Publishing a dictionary such is this one is a highly attention-worthy event. Due to abrupt development of all the scientific fields, thus the development of biology and medicine, especially of molecular biology and genetics, mainly in English-speaking countries, a huge number of new words, new names and expressions are being forged. Anglicisms, so, enter scientific literature with no limits and noticeably – through the main door. Since a long time ago English Language has not been the property of one country only, but the language of understanding between the peoples (lingua franca).

The Author, Prof. Dr. Sofija Mićić within this large lexicographic project, by studying hundreds and thousands of examples of the use of words, except for major entries, medical terms, entered numerous phrases and collocations characteristic for medical field. As pointed out by Ivana Lazić-Konjik in her presentation of the Dictionary:„Many entries, increased by new meanings, collocations and idioms, are being introduced in the use, examples of sentences also given; many names referring new technologies, apparatures and laboratory procedures are at all new and are yet to be customized to Serbian Language Thus, the Dictionary gives certain solutions for new terminology, placing itself as normative for the field."

A special problem in compiling the Dictionary was the very fact that all those countless anglicisms were not adapted linguistically, nor standardized, neither their use standardized. No Serbian equivalents problem also appeared as a great one.

Sofija Mićić put a huge effort to keep Serbian vocabulary and Serbian Language by standardization of Serbian words instead of borrowings whenever it was possible, and in the Preface says: „For each foreign word we found Serbian one when it was possible, and when it was not possible, a foreign word was adequately allocated, which was a hard work to do."

That was the way, I want to strongly emphasize here, for Sofija Mićić, with great effort and zeal to maintain a long-standing tradition of Serbian Languages spoken and written by numerous giants of Serbian science – Dositej Obradović, Josif Pančić, Jovan Jovanović Zmaj, Laza K. Lazarević, Vladan Đorđević, Milutin Milanković – to mention but a few of them.

Certainly, praiseworthy is the effort made by Prof. Dr. Jovan V. Mićić, a Professor at the Medical Faculty, Univer-

du i u okviru nastave doktorskih studija Stomatološkog fakulteta Univerziteta u Beogradu.

Ovaj dvojezični rečnik, ukupno 879 strana, pored rečničkog dela (englesko-srpski 9–448 str, srpsko-engleski 449–879) sadrži Predgovor (5–6 str), spisak korišćenih fonetskih znakova i simbola (za engleski jezik) i skraćenica (7–8 str), kao i mali ilustrovani rečnik umetnut između englesko-srpskog i srpsko-engleskog ostraničen rimskim brojevima (I-XVI). Uz svaku (40 000) odrednicu (lemu) navodi se kratak gramatički podatak o vrsti reči, ekspresivnoj vrednosti lekseme, domenu upotrebe i drugo i, što je takođe važno svakom korisniku Rečnika, uz engleske odrednice dat je fonetski izgovor s obzirom na probleme sa izgovorom medicinskih termina. U Rečniku „Dosledno je poštovan princip da se nađe optimalan prevodni oblik, ako postoji, ili, ukoliko ne postoji, da se jasno označe razlike između više njih koji se nameću kao rešenje" (Predgovor).

Pojava ovakvog rečnika predstavlja događaj vredan pažnje. Usled naglog razvoja svih oblasti nauke, pa i biologije i medicine, a naročito molekularne biologije i genetike i to uglavnom u zemljama engleskog govornog područja, nastale su i brojne nove reči i mnoštvo naziva i izraza. Tako, anglicizmi suvereno i na velika vrata ulaze u naučnu literature. Engleski jezik već dugo više nije vlasništvo jedne zemlje, već pravi jezik sporazumevanja (*lingua franca*).

Autorka, prof. dr Sofija Mićić, u ovom opsežnom leksikografskom poduhvatu, proučavajući stotine i hiljade primera primene reči, pored glavnih odrednica, medicinskih termina, u Rečnik je unela i brojne izraze i kolokacije karakteristične za medicinsku oblast. Kako je to istakla Ivana Lazić-Konjik u svom izlaganju o Rečniku „Mnoge odrednice su, obogaćene novim značenjima, kolokacijama i idiomima, koje se tek uvode u upotrebu, a dati su i rečenični primeri; mnogi nazivi iz savremene tehnologije, aparature i laboratorijskih procedura sasvim su novi i trebalo ih je prilagoditi srpskom jeziku. Otuda su u Rečniku ponuđena neka rešenja za nove termine, te bi se mogao koristiti i kao normativan za oblast koju opisuje". Poseban problem tokom izrade Rečnika predstavljala je i činjenica da sve to mnoštvo anglicizama nisu jezički adaptirani, ni standardizovani, niti je njihova upotreba normirana. Ne mali problem bilo je i nepostojanje srpskih ekvivalenata.

Sofija Mićić uložila je veliki napor da sačuva srpsku leksiku i srpski jezik tako što je standardizovala srpske reči umesto tuđica kad god je to bilo moguće, u Predgovoru ističe: „Za svaku stranu reč potražili smo gde je moguće srpski naziv, a gde nije bilo moguće, adekvatno je obrađena strana reč, što je bio mukotrpan posao". Tako, što naročito želim ovde da istaknem, sa puno truda i pregnuća Sofija Mićić nastavlja viševekovnu tradiciju srpskog jezika kojim su govorili i pisali i brojni velikani srpske nauke – Dositej Obradović, Josif Pančić, Jovan Jovanović Zmaj, Laza K. Lazarević, Vladan Đorđević – da spomenem samo neke od njih. Svakako, hvale vredan je i trud prof. dr Jovana V. Mićića, profesora Medicinskof fakulteta u Beogradu, velikog poznavaoca stručnih, medicinskih reči srpskog jezika, oca autorke Rečnika, dr Sofije Mićić, koji se

sity Belgrade, also an expert on medical words in Serbian Language, the Father of Dr. Sofija Mićić who advocates for putting Serbian words back into use and steering clear of anglicisms when it is possible, and, in so doing, preserve lexical treasure and the dignity of Serbian Language.

Finally, although not less important, I would like to add that Prof. Dr. Sofija Mićić is an outstanding English Language Editor and the Editor of the Column "Language of Medicine in "Serbian Archives of Medicine" (the Journal of the Serbian Medical Society) and the Member of the Editorial Board of this our oldest medical journal. Dr. Sofija Mićić is the member of many Serbian and international associations of English Language teachers. It has to be underlined especially her membership in the Main Board of the Association of Fulbright Scholars of Serbia and the European Professional Development Committee (EPDC), as well as the European Medical Writers Association (EMWA). Dr. Sofija Mićić is the author of a great number of books and papers in Serbian and foreign scientific journals. Dr Sofija Mićić is mentioned as an eminent eminent researcher – expert on anglistics in the Serbian Encyclopedia, Vol. 1 (A–Beobob), p. 207, published by Serbian State Publisher of Textbooks, Belgrade, Serbian Academy of Sciences and Arts, Belgrade, and Matica Srpska, Novi Sad, 2010. Dr Sofija Mićić has delivered numerous lectures and her papers presentations at conferences in Serbia, Great Britain, Hungary, USA. Dr Sofija Mićić is the winner of the British Council Prize.

To all those who use this Dictionary each and any day, to the Editorial Staff of the "Vojnosanitetski Pregled", to the authors who write papers for medical journals, to all those who work in medical science and profession, to students of medicine, stomatology, biology, molecular biology remains to hope that this bilingual Medical Dictionary of the Author Sofija Mićić will be many more times republished increased and enriched and always keeping pace with further development of medical and other sciences.

Dragana Mučibabić, BA
Language Editor
"Vojnosanitetski Pregled"

zalaže za vraćanje srpskih reči u upotrebu i izbegavanje anglicizama gde je to moguće i, tako, čuva rečničko blago i dignitet srpskog jezika.

Najzad, iako ne manje važno, dodajem i da je prof. dr Sofija Mićić dugogodišnji uvaženi lektor i urednik rubrike „Jezik medicine" u „Srpskom arhivu za celokupno lekarstvo" i član Uređivačkog odbora ovog najstarijeg medicinskog časopisa u Srbiji. Prof. dr Sofija Mićić je član brojnih domaćih i međunarodnih udruženja profesora engleskog jezika. Posebno se ističe članstvo u Glavnom odboru Udruženja Fulbrajtovih stipendista Srbije i Evropskom odboru za profesionalni razvoj (EPDC) Evropske asocijacije za pisanje u medicini (EMWA). Takođe, autor je velikog broja radova u domaćim i stranim naučnostručnim časopisima i knjiga. Prof. Mićić navedena je kao istaknuti anglista u Srpskoj enciklopediji, tom 1 (A-Beob), str. 217, izdavači Srpska književna zadruga, Beograd, Srpska akademija nauka i umetnosti, Beograd i Matica srpska, Novi Sad, 2010. Održala je brojna predavanja i izlagala na konferencijama u zemlji, Velikoj Britaniji, Mađarskoj, Americi. Dobitnik je Nagrade Britanskog saveta zapadnog Balkana.

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Dragana Mučibabić, prof.
jezički redaktor
časopisa „Vojnosanitetski pregled"

ERRATUM

Dušan Škrbić, Goran Stojanović, Djordje Považan, Mirna Djurić, Živka Eri

The role of autofluorescence bronchoscopy in monitoring a tumorous lesion in the bronchial mucosa: a case report

Uloga **antifluorescentne** bronhoskopije u praćenju tumorskih lezija bronhijalne mukoze

Vojnosanit Pregl 2012; 69(6): 531–5.

Erratum in: Vojnosanit Pregl 2012; 69(9): 821.

Dušan Škrbić, Goran Stojanović, Djordje Považan, Mirna Djurić, Živka Eri

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Uloga **autofluorescentne** bronhoskopije u praćenju tumorskih lezija bronhijalne mukoze

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Poziv za reklamiranje u 2012. godini

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Primeri oblika referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

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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.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Tabele

Sve tabele štampaju se sa proredom 1,5 na posebnom listu hartije. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Za fus-notu koristiti sledeće simbole ovim redosledom: ***, †, ‡, §, ||, ¶, **, ††, ...** Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

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Examples of references:

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Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

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.

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Časopis „Vojnosanitetski pregled“ izlazi godišnje u 12 brojeva.

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Poreski identifikacioni broj (PIB) za ustanove	
Mesto	
Ulica i broj	
Telefon / telefaks	

Pretplata na časopis „Vojnosanitetski pregled“ (zaokružiti):

1. Lično. Dokaz o pretplati dostavljam uz ovu prijavu.
2. Za pripadnike MO i Vojske Srbije: Dajem saglasnost da se prilikom isplate plata u Računovodstvenom centru MO iz mojih prinadležnosti obustavlja iznos mesečne rate (pretplate).
3. Virmanom po prijemu profakture.

Datum _____	Potpis _____

VOJNOSANITETSKI PREGLED
VOJNOMEDICINSKA AKADEMIJA
Crnotravska 17, 11040 **Beograd**, **Srbija**
Tel/Fax: +381 11 2669689
vmaini1@EUnet.rs
vmavsp@hotmail.com

Časopis „Vojnosanitetski pregled“ izlazi godišnje u 12 brojeva.

Godišnja pretplata za 2012. godinu iznosi: 4 000 dinara za građane Srbije, 8 000 dinara za ustanove iz Srbije i 150 € za strane državljane i ustanove. Sredstva se uplaćuju na tekući račun Vojnomedicinske akademije Beograd kod Uprave za javna plaćanja u Beogradu broj: **840-941621-02 VMA (za Vojnosanitetski pregled ili za VSP)**, **PIB 102116082**. Uplatnicu (dokaz o uplati) dostaviti lično ili poštom (pismom, faksom, *e-mail*-om). Za zaposlene u MO i Vojsci Srbije moguća je i pretplata u 12 mesečnih rata putem trajnog naloga, tj. „odbijanjem od plate“. Popunjen obrazac poslati na adresu VSP-a.

PRIJAVA ZA PRETPLATU NA ČASOPIS „VOJNOSANITETSKI PREGLED“

Ime i prezime ili naziv ustanove	
Jedinstveni matični broj građana	
Poreski identifikacioni broj (PIB) za ustanove	
Mesto	
Ulica i broj	
Telefon / telefaks	

Pretplata na časopis „Vojnosanitetski pregled“ (zaokružiti):

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