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ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2009; September vol. 66 (No. 9): pp. 683-772.

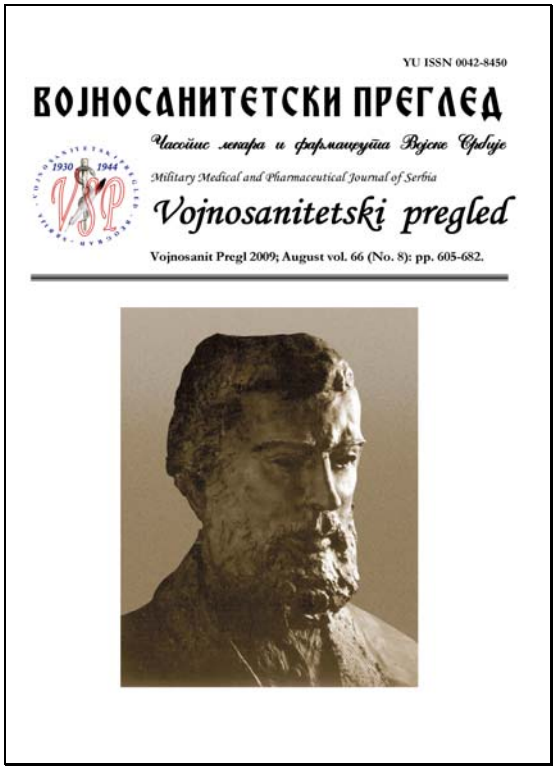

VOJNO-SANITETSKI PREGLED

MJESEČNIK LIJEKARA NARODNO-OSLOB. VOJSKE JUGOSLAVIJE

Ovaj broj posvećujemo

GOD. I SEPTEMBAR 1944 BROJ 1

IZDAJE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1944 – 2009.

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ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Први број *Војносанитетског прегледа* изашао је септембра месеца 1944. године

Часопис наставља традицију *Војно-санитетског гласника*, који је излазио од 1930. до 1941. године

ИЗДАВАЧ
Управа за здравство Сектора за материјалне ресурсе МО Србије

Адреса редакције: Војномедицинска академија, Институт за научне информације, Црнотравска 17, поштански фах 33–55, 11040 Београд, Србија. Телефони: главни и одговорни уредник 3609 311, технички секретар 3608 943, редакција 3609 902 и 3609 179, претплата 3608 997. Факс 2669 689. E-mail: **vmaini1@EUnet.yu** (главни и одговорни уредник) и **vmaini@hotmail.com** (редакција).

Радове објављене у „Војносанитетском прегледу“ индексирају: Science Citation Index Expended (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Садржаје објављују Giornale di Medicine Militare и Revista de Medicina Militara. Приказе оригиналних радова и извода из садржаја објављује International Review of the Armed Forces Medical Services.

Часопис излази дванаест пута годишње. Претплате: жиро рачун код Управе за јавна плаћања у Београду бр. 840-941621-02 – ВМА (за Војносанитетски преглед), ПИБ 102116082, или на девизни рачун код Народне банке број: 54104-ознака валуте-549. Годишња претплата: 4 000 динара за грађане Србије, 8 000 динара за установе из Србије и 150 € (у динарској противвредности на дан уплате) за претплатнике из иностранства. Копију уплатнице доставити на горњу адресу.

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YU ISSN 0042-8450 vol. 66 No. 9, 2009

VOJNOSANITETSKI PREGLED

The first issue of *Vojnosanitetski pregled* was published in September 1944
The Journal continues the tradition of *Vojno-sanitetski glasnik* which was published between 1930 and 1941

PUBLISHER

Health Department, Sector for Material Resources, Ministry of Defence, Serbia

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Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expended (SCIE) Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.
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S A D R Ž A J / C O N T E N T S

U septembru ove godine navršava se 65 godina kontinuiranog izlaženja Vojnosanitetskog pregleda (levo – naslovna strana broja 1 iz 1944; desno – naslovna strana broja 8 iz 2009).

This September, it is 65 years of continuous publishing of *Vojnosanitetski pregled* (left – cover page of the first issue from 1944; right – cover page of the eight issue from 2009).

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

Šezdesetpeti rođendan Vojnosanitetskog pregleda

Sixty-Fifth Anniversary of the *Vojnosanitetski pregled*

Silva Dobrić

Vojnomedicinska akademija, Institut za naučne informacije, **Beograd, Srbija**
Military Medical Academy, Institute for Scientific Information, **Belgrade, Serbia**

Ove godine, u septembru, navršava se 65 godina kontinuiranog izlaženja Vojnosanitetskog pregleda (VSP), časopisa lekara i farmaceuta Vojske Srbije. Prvi broj časopisa (slika 1) izišao je za vreme Drugog svetskog rata, 1944. godine u Bariju (Italija) jer su se, u to vreme, na našim prostorima odvijale završne bitke za oslobođenje zemlje od fašističkog okupatora. Međutim, već u decembru iste godine izišao je drugi broj VSP u tek oslobođenom Beogradu. Inicijativu za pokretanje jednog stručnog, vojnomedicinskog časopisa dao je general-major dr Gojko Nikoliš (slika 2), u to vreme na dužnosti glavnog referenta saniteta Vrhovnog štaba Narodnooslobodilačke vojske i partizanskih odreda Jugoslavije, uvidevši potrebu za stalnim stručnim usavršavanjem i razmenom iskustava pripadnika vojnog saniteta. Dr Nikoliš je bio i prvi glavni i odgovorni urednik VSP. Časopis je već imao preteču u predratnom Vojno-sanitetskom glasniku koji je počeo da izlazi 1930. godine kao stručno glasilo Sanitetskog odeljenja Ministarstva vojske i Mornarice Kraljevine Jugoslavije (slika 3). Vojno-sanitetski glasnik izlazio je sve do početka Drugog svetskog rata (poslednji broj objavljen je u januaru 1941. godine) i bio je izuzetno cenjen u medicinskim krugovima tog vremena. Međutim, radikalni raskid s prošlošću koji je kod nas bio prisutan u gotovo svim sferama života u posleratnom periodu, nije mimoišao ni stručne časopise, tako da se tek od 2002. godine (vol. 59) u impresumu VSP pominje da časopis nastavlja tradiciju svog slavnog pretka Vojno-sanitetskog glasnika.

Već prvih godina postojanja časopisa uvodi se praksa tzv. tematskih brojeva, kasnije suplementi, posvećenih raznim značajnim događajima. Tako je u 1950. godini broj 3–4 posvećen „otvorenju Vojno-medicinske akademije Jugoslovenske Armije“, a broj 3–4 za 1953. „osnivaču i dosadašnjem odgovornom uredniku, general-potpukovniku dr Gojku Nikolišu“.

U br. 1–2 iz 1955. pojavljuje se iscrpno Uputstvo saradnicima sa prilogom o jeziku i pravopisu. U broju 7–8 za 1955. prvi put u impresumu navode se članovi redakcije

This September, it is 65 years of continuous publishing of *Vojnosanitetski pregled* (Military Medical Journal), a journal for physicians and pharmacists of Serbian Army. The first issue of the journal (Figure 1) was published during World War II (WWII), 1944, in Bari (Italy) because that time the final struggles for liberation from fascist occupation were fought in the territory of the former Yugoslavia. Yet, the next issue was printed in December that year in just liberated Belgrade. An initiative for foundation of a military medical and pharmaceutical journal was given by Major General Dr. Gojko Nikoliš (Figure 2), at that time the Head of the Military Medical Service of the General Staff of the Yugoslav People´s Army. He recognized the need for permenent education and professional experiences exchange among the members of Military Medical Corps. Dr. Nikoliš was, in the same time, the first Editor-in-Chief of the journal. The *Vojnosanitetski pregled* had the pre-war predecessor the *Vojnosanitetski glasnik* (Military Medical Herald) founded in 1930 by the Medical Department of the Ministry of Army and the Navy of the Kingdom of Yugoslavia (Figure 3). The *Vojno-sanitetski glasnik* was published up to the beginning of WWII (the last issue in January, 1941). It was highly esteemed in the contemporary medical community. However, radical breaking with the past in that time in our country unfortunately affected professional journals, and, because of that, not earlier than 2002 (vol. 59) in the Heading of the *Vojnosanitetski pregled* was written that it is continuing the tradition of a famous predecessor, the *Vojno-sanitetski glasnik.*

Even in the first years of its ”life“, the practice of the so-called thematic issues (later supplements), dedicated to various significant events, was introduced. Thus, the issue 3-4 in 1950 was dedicated to the ”opening of Military Medical Academy of the Yugoslav Army“), and the issue 3-4 in 1953 to ”the founder and until recently Editor-in-Chief Lieutenant General Dr. Gojko Nikolioš“.

In the issue 1-2, in 1955, an extensive ”Instructions for Authors“ with an article on Language and Grammar, and in the issue 7-8, also in 1955, for the first time, the names of

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VOJNO-SANITETSKI PREGLED

MJESEČNIK LJEKARA NARODNO-OSLOB. VOJSKE JUGOSLAVIJE

UREDNIŠTVO:

Ovaj broj posvećujemo

junačkim bolničarkama, ljekarima i svima sanitetskim radnicima naše vojske, palim u borbi ili ubijenim od zločinačke fašističke ruke stojeći postojano na mjestima svojih svetih dužnosti; svima ranjenicima naše vojske čiji nas besprimjerni heroizam čelići, preporadja i potiče ka novim dostignućima

GOD. I SEPTEMBAR 1944 BROJ 1

IZDAJE SANITETSKO ODJELJENJE VRHOVNOG ŠTABA NOV I PO JUGOSLAVIJE

Sl. 1 – Naslovna strana prvog broja Vojnosanitetskog pregleda (septembar, 1944)

Fig. 1 – Cover page of the first issue of the *Vojnosanitetski pregled* (September 1944)


САНИТЕТСКО ОДЕЉЕЊЕ МИНИСТАРСТВА ВОЈСКЕ И МОРНАРИЦЕ
SANITETSKO ODELJENJE MINISTARSTVA VOJSKE I MORNARICE

КЊИГА I № 1—2 БЕОГРАД 1930 BEOGRAD № 1—2 KNJIGA I

ВОЈНО-САНИТЕТСКИ ГЛАСНИК
VOJNO-SANITETSKI GLASNIK

УРЕДНИК
Dr. JOP. T. СТАЈИЋ

UREDNIK
Dr. JOR. T. STAJIĆ

TOME I № 1—2 1930 № 1—2 VOLUME I

REVUE DE MEDECINE MILITAIRE
BEOGRAD YOUGOSLAVIE

REVIEW OF MILITARY MEDECINE
BEOGRAD YUGOSLAVIA

Sl. 2 – Naslovna strana prvog broja *Vojno-sanitetskog glasnika* (1930)

Fig. 2 – Cover page of the first issue of the *Vojnosanitetski glasnik* (1930)

Sl. 3 – Dr Gojko Nikoliš (1911–1995), lekar, istoričar, učesnik Španskog građanskog rata i Narodnooslobodilačkog rata na prostorima bivše Jugoslavije, general JNA, član Srpske akademije nauka i umetnosti, narodni heroj Jugoslavije, osnivač i prvi glavni i odgovorni urednik Vojnosanitetskog pregleda.

Fig. 3 – Dr Gojko Nikoliš (1911–1995), a physician, historian, participant in the Spanish Civil War and the People′s Liberation War in former Yugoslavia during the Second World War, General of the Yugoslav People′s Army, the Yugoslav People′s Hero, member of the Serbian Academy of Science and Art, founder and the first Editor-in-Chief of the *Vojnosanitetski pregled*.

časopisa, kasnije veoma značajni lekari i farmaceuti. Tako su tzv. stručnu korekturu tada obavljali, između ostalih, potpukovnik dr Antun Gašparov, osnivač naše gastroenterologije i major mr ph. Zlatko Binenfeld, jedan od značajnijih jugoslovenskih toksikologa. Lektor za strane jezike bila je vojni službenik dr Ines Veslej-Tanasković (Ines Wesley), tvorac jugoslovenske naučne informatike, a lektor za srpskohrvatski jezik vojni službenik Srđa Petrović.

Od 1957. odgovorni sekretar, u to vreme dr Ivo Pavletić, postaje ujedno i glavni urednik Redakcije, dakle tehničkog dela, dok je odgovorni urednik i dalje bio dr Gojko Nikoliš. Od 1960. godine uvodi se funkcija glavnog i odgovornog urednika, a od naredne 1961. godine, osnivanjem Instituta za vojnomedicinsku dokumentaciju (sada Institut za naučne informacije), načelnik Instituta postaje ujedno i glavni i odgovorni urednik VSP, kako je i danas. U to vreme, časopis je već imao prepoznatljivu fizionomiju, a apstrakti radova objavljivali su se na više stranih jezika (ruski, engleski, nemački i francuski).

Povodom 25-godišnjice izlaženja časopisa izdata je kompletna bibliografija originalnih radova 1944–69, a časopis je odlikovan Ordenom za vojne zasluge sa velikom zvezdom što je bio dokaz prepoznavanja njegove uloge i značaja u razvoju sanitetske službe (slika 4).

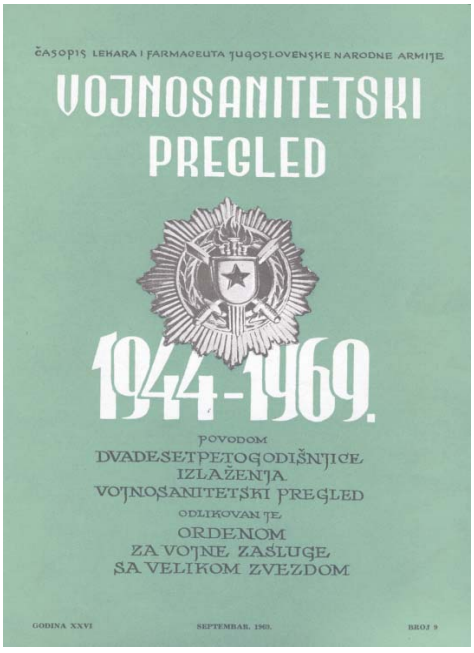
U periodu od osnivanja časopisa do 1972. godine izlazilo je i po 12 brojeva godišnje, što je bio pokazatelj velikog priliva radova. Od 1973. prelazi se na izdavanje šest brojeva u godini i to se održavalo sve do 2005. godine, kada se ponovo prešlo na izlaženje svakog meseca (trenutno je VSP jedini biomedicinski časopis u Srbiji sa takvom dinamikom izlaženja). U tom periodu časopis je u nekoliko navrata menjao izgled naslovne strane, ali uz stalno unapređenje kvaliteta sadržaja. Od 2006. godine časopis poprima sadašnji izgled sa naslovnom stranom na kojoj se objavljuju slike povezane sa sadržajem tog broja ili slike iz istorije medicine (slika 5).

members of the editorial staff of the Journal (later significant physicians and pharmacists) occured. Thus, the co-called expert proof-reading was performed, among others, by Lieutenant Colonel Dr. Antun Gašparov, the founder of domestic gastroenterology, and Major Zlatko Binenfeld, BPharm, one of the most significant Yugoslav toxicologists. The proofreaders for foreign languages and Serbo-Croatian were Dr. Ines Wesley, the author of Yugoslav Scientific Informatics, and Srđa Petrović, respectively.

In 1957, the "responsible secretary" of the Journal, in that time Dr Ivo Pavletić, became also the Chief of the Editorial Staff, while dr Gojko Nikoliš was still the Chief Editor of the journal. In 1960 the position of the Editor-in-Chief was established, and next year (1961), when the Institute for Military Medical Documentation (now the Institute for Scientific Information) was founded and the Editorial Staff of the *Vojnosanitetski pregled* became the part of the Institute, its Head was nominated as the Editor-in-Chief of the Journal which became a regular practice. In that time, the journal had recognizable appearance, and abstracts of articles in severeal foreign languages (English, Russian, German, French) were published.

The 25th Anniversary was marked by a complete bibliography of original articles published from 1944-1969, and the Journal was decorated by the Order of Mylitary Merits with the Grand Star (Figure 4).

The Journal had 12 issues in the volume from its inception indicating the high influx of articles. From 1973 six issues were published annually, but from 2005 publishing of 12 issues each year was renewed (presently the *Vojnosaniitetski pregled* is the only medical Journal in Serbia with that frequency of publishing). During this period cover page of the Journal has been changed many times, with constant improvement of the quality of its contents. Since 2006 the Journal has got a cover page with images suggesting the contents of a particular issue (Figure 5).



Sl. 4 – Naslovna strana jubilarnog broja VSP iz 1969. posvećenog 25-godišnjici izlaženja
Fig. 4 – Cover page of the jubilee issue of the *Vojnosanitetski pregled* in 1969 dedicated to its 25th Anniversary

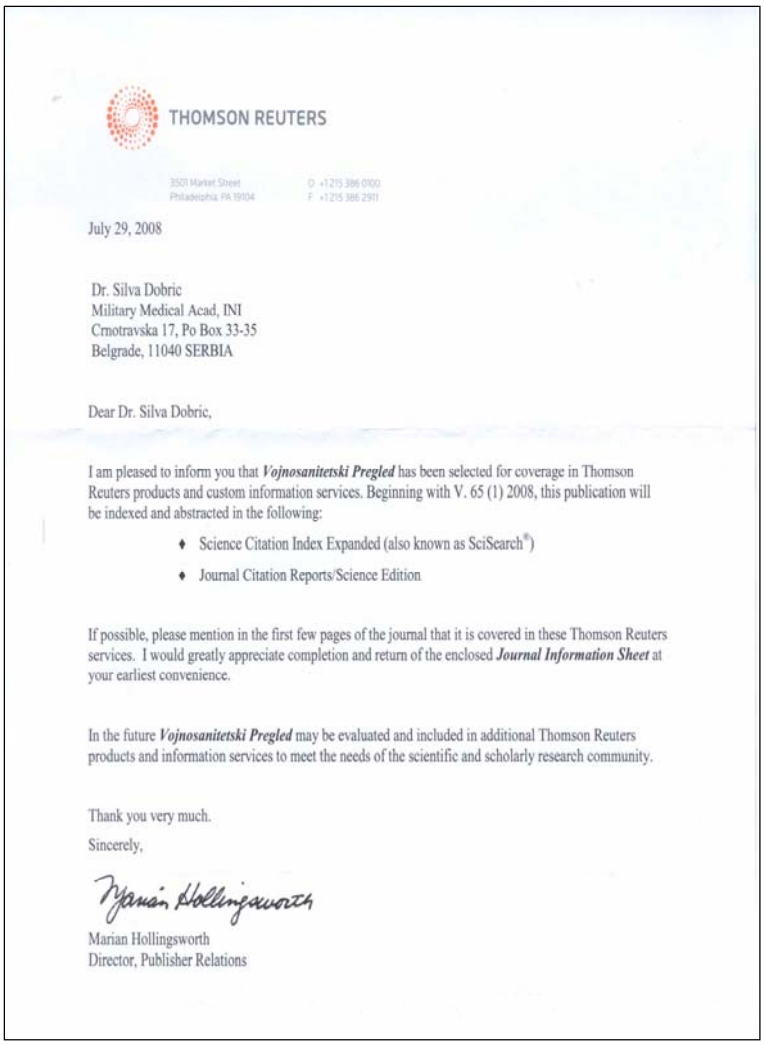
Sl. 5 – Izgled naslovne strane VSP iz različitih perioda njegovog izlaženja
Fig. 5 – Cover pages of the *Vojnosanitetski pregled* from different periods

Časopis je već od 1950. godine ušao u sistem citiranja nekoliko poznatih apstraktnih i citatnih časopisa i njihovih elektronskih baza. To su, u prvom redu, Index Medicus, indeksni časopis Nacionalne medicinske biblioteke SAD, i njegova elektronska baza MEDLINE, zatim Excerpta Medica i njena elektronska baza EMBASE, Chemical Abstracts, Biological Abstract, Interantional Pharmaceutical Anbstracts i još šest drugih sekundarnih publikacija. Od tog vremena, pa do danas sadržaj svakog broja VSP objavljuju Giornale di Medicina Militare i Revista de Medicina Militara, a prikaze originalnih radova i izvoda iz sadržaja International Review of the Armed Forces Medical Services. Od 2002. godine VSP se nalazi u sistemu praćenja baze EBSCO, preko koje se radovi objavljeni u njemu mogu dobiti u punom tekstu. Pored toga, časopis se razmenjuje sa 40 međunarodnih i 36 domaćih časopisa.

Iako je VSP uvek zauzimao značajno mesto u domaćoj biomedicinskoj publicistici, želja njegovog uredništva i izdavača bila je dobijanje međunarodnog statusa i renomea. Ka tom cilju krenulo se 2002. godine proširenjem Uređivačkog odbora u koji su ušla najpoznatija imena srpske medicine. Među njima, prvi put posle 1944. godine, kada ih je bilo dve (dr Julka Mešterović-Pantić i dr Danica Perović), našlo se i pet žena, četiri pripadnice vojnog saniteta (prof. dr Mirjana Životić Vanović, doc. dr Silva Dobrić, doc. dr Ljiljana Pavlica i naučni saradnik dr sc. med. Radojka Bokun) i jedna iz civilnih struktura (prof. dr Darinka Bošković), dok ih u sadašnjem sazivu Uređivačkog odbora ima čak osam, uključujući i glavnu i odgovornu urednicu časopisa. Krug recenzenata se takođe proširio na više od 100 stručnjaka iz različitih oblasti medicine, farmacije i stomatologije, uz pooštravanje kriterijuma za prihvatanje radova. Redovnost izlaženja, u vreme kada je izlaženje drugih domaćih časopisa kasnilo i po nekoliko meseci, obezbedili su sve veći priliv radova i iz tzv. civilnih struktura, što se, takođe, odrazilo na kvalitet radova publikovanih u VSP. Velika zasluga za ovo pripada tadašnjem glavnom i odgovornom uredniku prof. dr Vladimiru Tadiću koji je bio *spiritus movens* ovih promena. Tokom 2005. godine, kada je na čelo uredništva došao doc. dr Mile Ignjatović, završeno je i konstituisanje međunarodnog uređivačkog odbora, čime su se stekli i formalni uslovi za ulazak na međunarodnu scenu. Časopis je obogaćen novim rubrikama (pisma uredništvu, komentari, kritički osvrti i sl), dobio je logo i novi, moderniji, a po mnogima, i lepši izgled. Ovo, kao i stalno pozivanje autora, da svoje radove objavljuju na engleskom jeziku u cilju povećanja „vidljivosti“, rezultovalo je uključenjem VSP u *Science Citation Index Expended* (SCIE), čuvenu bazu naučnih časopisa Instituta za naučne informacije (the *Institute for Scientific Information* – ISI), sada *Thomson Reuters*, iz Filadelfije. Vest o ovome stigla je na e-mail redakcije VSP početkom juna 2008, a krajem jula stigla je i zvanična potvrda prijema i SCIE (slika 6). Na taj način, VSP je postao prvi domaći časopis iz oblasti humane medicine koji je ušao u društvo najprestižnijih naučnih časopisa sveta.

As early as in 1950 the Journal was indexed by a few well-known abstarct and indexed journals and their electronic databases, for example *Index Medicus* (MEDLINE), *Excerpta Medica* (EMBASE), *Chemical Abstracts*, *Biological Abstract, Interantional Pharmaceutical Anbstracts* and six other secundary publications. Ever since that time the contents of any issues of the Journal have been published in the *Giornale di Medicina Militare* and the *Revista de Medicina Militara*, while the abstracts of original articles in the *International Review of the Armed Forces Medical Services*. Since 2002 the *Vojnosanitetski pregled* has been included in the EBSCO base which provides free on-line approach to the journal contents and taking over the articles in the full text to its subscribers. Furthermore, the Journal is exchanged with 40 foreign and 36 domestic medical journals.

Although the *Vojnosanitetski pregled* has always had a significant position among domestic medical scientific Journals, the Editorial Board and the Publisher tend to obtain an international recongnition and reputation. This was a reason to widen Editorial Board in 2002 with Serbian most eminent medical experts. For the first time after the first issue in 1944, when among editors two women had been included (Dr. Julka Mešterović-Pantić and Dr. Danica Perović), the Editorial Board was proud to include five women, four from Military Medical Service (Prof. Mirjana Životić Vanović, Assist. Prof. Silva Dobrić, Assist. Prof. Ljiljana Pavlica and Assist. Prof. Radojka Bokun) and one from a civil medical institution (Prof. Darinka Bošković). Presently, there are eight women in the Editorial Board of the Journal including its Editor-in-Chief. The number of per-reviewers has also been increased by more than 100 scientists from various fields of medicine, pharmacy and dentistry, and the selection criteria for publishing have got more strict. Regularity in publishing in the time when publishing of other domestic medical journal is late even for several months, resulted in an incraesing influx of manuscripts from the so-called civilian institutions which, in turn, had favourable impact on the quality of articles published in the *Vojnosanitetski pregled*. The great merit for that belongs to Colonel Prof. Vladimir Tadić, at that time the Editor-in-Chief of the Journal, the *spiritus movens* of these changes. Within 2005, when Colonel Assist. Prof. Mile Ignjatović took over the Editor-in-Chief function, establishing of the Internation Editorial Board was finished providing formal conditions for the inclusion into international journal family. The Journal was enriched by new types of articles (e.g. Letters to the Editor, Comments, Critical Views, etc.), logo, and new, more modern, and, in the opinion of many readers, better appearance. That, as well as permanent invitations to authors to prepare their manuscripts in English in order to increase ”visibility“, resulted by inclusion of the *Vojnosanitetski pregled* into *Science Citation Index Expended* (SCIE), famous base of scientific journals of the Institute for Scientific Information (ISI), now *Thomson Reuters*, from Philadelphia, USA. The Editorial Staff of the Journal received e-mail with this information at the beginning of June, 2008, and at the end of July, received an official letter from Thomson Reuters (Figure 6). Thanks to that, the *Vojnosanitetski pregled* turned to the first domestic clinically oriented medical journal that was included into the group of the most influential scientific journals.



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July 29, 2008

Dr. Silva Dobric
Military Medical Acad, INI
Crnotravska 17, Po Box 33-35
Belgrade, 11040 SERBIA

Dear Dr. Silva Dobric,

I am pleased to inform you that ***Vojnosanitetski Pregled*** has been selected for coverage in Thomson Reuters products and custom information services. Beginning with V. 65 (1) 2008, this publication will be indexed and abstracted in the following:

- Science Citation Index Expanded (also known as SciSearch®)
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Thank you very much.

Sincerely,

Marian Hollingsworth
Director, Publisher Relations

Sl. 6 – Obaveštenje o prijemu VSP u *Science Citation Index Expended* (SCIE)
Fig. 6 – Information on inclusion of the *Vojnosanitetski pregled* into the *Science Citation Index Expended* (SCIE)

Ovo je rezultiralo dodatnim interesovanjem biomedicinskih stručnjaka iz zemlje, ali i inostranstva da svoje radove publikuju u VSP, tako da se broj pristiglih radova u redakciju VSP višestruko povećao u odnosu na period pre ulaska u SCIE. Ilustracije radi, dok je u prvih šest meseci 2008. godine u redakciju časopisa došlo 126 radova, a zaključno sa 31.12.2008. godine 314 radova, dotle je u proteklom šestomesečnom periodu (01.01.2009-30.06.2009) primljeno 250 radova, dakle 100% više nego u istom periodu prošle godine, odnosno skoro 80% ukupnog prošlogodišnjeg broja, od čega više od 75% od autora iz civilnih zdravstvenih i akademskih institucija. Ovakav trend prisutan je od 2006. godine i, prema svim pokazateljima, izgleda da će se i nastaviti, što dovoljno govori o ugledu koji VSP ima u domaćoj stručnoj javnosti. Takođe, porastao je i broj pretplatnika časopisa, što je rezultovalo povećanjem tiraža na 1 000 primeraka.

Od prošle godine časopis je dostupan on-line preko sajta Vojnomedicinske akademije što je dodatno doprinelo njegovoj sve većoj vidljivosti i dostupnosti zainteresovanima.

Budući da je VSP tek od 2008. godine u sistemu praćenja citatnih baza ISI, još uvek nema određen impakt faktor

Consequently, the number of domestic and foreign biomedical scientists submitting their articles for publishing in the *Vojnosanitetski pregled* increased highly as compared with the period before coverage by SCIE. For example, in the first half of 2008, the editorial staff of the Journal received 126 manuscripts, and by the end of the year (December 31, 2008) 314 ones, in the period from January 1, 2009 to June 30, 2009, the number was 250, that is 100% more than in the same period of the last year or almost 80% of the total number of manuscripts received during last year. Of these manuscripts more than 75% were sent by authors from civil institutions. This trend has been observed from 2006, and, it seems to be continued implaying a high reputation of the Journal among domestic scientists. Accordingly, the number of journal subscribers has increased leading to the increasing printing (at the moment 1,000 copies per issue).

Last year the Journal started on-line edition at the web site of the Military Medical Academy (MMA), Belgrade. This has additionally increased visibility and availability of the journal.

Due to the fact that the *Vojnosanitetski pregled* has been covered by SCIE just from 2008, its impact factor (numerical indicator of influence of particular journal on its scientific field) has

(numerički pokazatelj uticaja određenog časopisa na oblast koju pokriva), ali se na osnovu izveštaja stručnih službi baze EBSCO, preko koje je VSP dostupan u punom tekstu, o broju pristupa člancima objavljenim u njemu, može pretpostaviti da VSP već ima određen uticaj (nadamo se ne mali) na oblast biomedicinskih nauka. Naime, samo u prvom kvartalu ove godine (period januar-mart) zabeležena su 2 902 pristupa VSP i preuzimanja pojedinih članaka iz njega, dok je u čitavoj prošloj godini taj broj iznosio 2 340. Dakle, samo u prva tri meseca ove godine bilo je 562 pristupa radovima iz VSP više, nego tokom svih 12 meseci prošle godine! Nadajmo se da će se ovaj trend nastaviti i ubuduće.

Od 1995. godine, u sklopu proslave Dana Vojnomedicinske akademije (2. mart) Uredništvo i izdavač VSP dodeljuju specijalnu nagradu autoru koji je u prethodnoj godini objavio najviše radova na stranicama VSP, kao priznanje za doprinos razvoju naučne misli u oblasti biomedicine i podizanje ugleda časopisa. Interesantno je da su svi dosadašnji dobitnici ove nagrade pripadnici vojnog saniteta, iako je poslednjih godina, kao što je napred spomenuto, trend da najveći broj autora koji objavljuju u VSP dolazi iz civilnih ustanova. Imena dosadašnjih dobitnika nagrade Autor godine VSP naveden je u tabeli 1.

not yet been determined. However, according to the information from EBSCO (a base providing full text articles from the *Vojnosanitetski pregled* in pdf format to its subscribers) on the number of approaches to the articles published in the Journal (so-called hits) it could be assumed that the *Vojnosanitetski pregled* already has some impact (hope no low) on the filed of biomedical sciences. Namely, only in the first quarter of this year (January-March) 2,902 hits were recorded, while in the whole last year this number was 2,340. So, there were 562 hits more in the first three months of this year in relation to those reached during all 12 months in 2008. We hope this trend continues in the future!

Since 1995, on celebrating the Day of Military Medical Academy (March 2), the Editorial Board and the Publisher of the *Vojnosanitetski pregled* have awarded a special prize to the author with the highest number of articles published in the Journal during the previous year as a recognition of his/her contribution to the development of biomedical science and increasing of the Journal's prestige. It is interesting that all the previous winners of this prize were the members of Serbian Military Medical Service, although last years, as above mentioned, there was a tendency of increasing number of authors from the so-called civil medical institutions. The names of the previous Authors of the Year of the *Vojnosnitetski pregled* are given in table 1.

Tabela 1

Autori godine Vojnosanitetskog pregleda

Table 1

Authors of the Year of the *Vojnosanitetski pregled*

Godina Year	Autor Author	Institucija Institution
1995	Zoran Roganović	Klinika za neurohirurgiju, VMA Clinic for Neurosurgery, MMA
1996	Zoran Roganović	Klinika za neurohirurgiju VMA Clinic for Neurosurgery, MMA
1997	Miomir Cvetinović	Klinika za maksilofacijalnu hirurgiju, VMA Clinic for Maxillofacial Surgery, MMA
1998	Ranko Raičević	Klinika za neurologiju VMA Clinic for Neurology, MMA
1999	Ranko Raičević	Klinika za neurologiju VMA Clinic for Neurology, MMA
2000	Ranko Raičević	Klinika za neurologiju VMA Clinic for Neurology, MMA
2001	Mile Ignjatović	Klinika za opštu i vaskularnu hirurgiju VMA Clinic for General and Vascular Surgery, MMA
2002	Ranko Raičević	Klinika za neurologiju VMA Clinic for Neurology, MMA
2003	Ljubomir Panajotović	Klinika za plastičnu hirurgiju VMA Clinical for Plastic Surgery, MMA
2004	Goran Brajušković	Institut za patologiju VMA Institute for pathology, MMA
2005	Marija Toskić-Radojičić	Institut za farmaciju VMA Institute for Pharmacy, MMA
2006	Goran Brajušković	Institut za patologiju VMA Institute for Pathology, MMA
2007	Snežana Đorđević	Centar za kontrolu trovanja VMA Poison Control Centre, MMA
2008	Boris Ajdinović	Institut za nuklearnu medicinu VMA Institute for Nuclear Medicine, MMA

Na kraju, treba istaći da su svi dosadašnji uspesi VSP rezultat predanog rada plejade urednika, članova uredništva, recenzenata i redakcije časopisa od samog početka njegovog

It should be emphasized that all the present successes of the *Vojnosanitetski pregled* are the result of devoted work of numerous editors, members of ediatorial board and staff, reviewers

izlaženja. Od osnivanja do danas časopis je uređivalo 12 glavnih i odgovornih urednika (tabela 2). Svako od njih dao je svoj doprinos razvoju i unapređenju časopisa, a generacijama koje slede ostaje da taj put nastave i ubuduće.

from the very beginning of the Journal printing. From the foundation to now the Jornal has been edited by 12 Editors-in-Chief (Table 2). Each of them have contributed to its development and improvement, hoping that their followers will go on that way.

Tabela 2

Glavni i odgovorni urednici Vojnosanitetskog pregleda od osnivanja do danas

Table 2

Editors-in-Chief of the *Vojnosanitetski pregled* from the foundation to now

Period	Ime i zvanje/Name and title
1944–1952	general-major / Major General Dr. Gojko Nikoliš
1953–1954	general-major / Major General Dr. Đura Mešterović
1955–1960	general-potpukovnik /Lieutenant General Dr. Gojko Nikoliš
1960–1962	pukovnik / Colonel Dr. Ivo Pavletić, hirurg/ surgeon
1963–1971	general-major / Major General Dr. Žarko Cvetković, hirurg /surgeon
1971–1979	pukovnik / Colonel Dr. Božidar Nikolić, epidemiolog/ epidemiologist
1979–1990	pukovnik / Colonel Dr. Vladimir Đergović, hirurg / surgeon
1990–1995	pukovnik/ Colonel Dr. Čedomir Marković
1995–2000	pukovnik prim./ Colonel Dr. Dušan Milić, anesteziolog / anesthesiologist
2000–2005	pukovnik / Colonel Prof. Dr. Vladimir Tadić, farmakolog-toksikolog/ pharmacologist-toxicologist
2005-2006	pukovnik / Colonel Assist. Prof. Dr. Mile Ignjatović, hirurg/ surgeon
2006-	vojni službenik Prof. Dr. Silva Dobrić, spec. kliničke farmacije / Clinical pharmacist

Velika zasluga, svakako, pripada i autorima VSP koji su kroz proteklih 65 godina svojim znanjem i iskustvom ispunili njegove stranice i učinili ga prepoznatljivim daleko izvan granica naše zemlje.

Na kraju, pozivam sve vas, prijatelje i poštovaoce VSP, da mu povodom ovog velikog jubileja, 65 godina postojanja, poželimo još mnogo, mnogo uspešnih i srećnih godina!

The great merit, certainly, is shared by the authors of the *Vojnosanitetski pregled* who for the previous 65 years have covered its pages by their knowledge and experience making it well-known abroad.

At the end, I invate you, the friends and the loyal readers of *Vojnosanitetski pregled*, that on the occasion of its great jubilee, 65 years of publishing, all together wish it go on for many successful and happy years!

V I V A T, F L O R E A T, C R E S C A T
V O J N O S A N I T E T S K I P R E G L E D!

ORIGINAL ARTICLES UDC 616.12–008.331.1–052:612.766.1

Impact of acute exercise on antioxidant enzymes activity and lipid status in blood of patients with hypertension

Uticaj akutnog izlaganja fizičkom naporu na aktivnost antioksidativnih enzima i lipidni status u krvi bolesnika sa hipertenzijom

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Abstract

Background/Aim. Many studies support the hypothesis that oxidative stress is involved in the pathogenic process of a variety of diseases including hypertension. In humans, hypertension is also considered a state of oxidative stress that can contribute to the development of arteriosclerosis and other hypertension-induced organ damage. The aim of this study was to evaluate an influence of acute physical exercise on antioxidative enzymes activity and lipid status in patients with hypertension. **Methods.** Fourty patients with hypertension and 20 age-matched controls were included in the study. To assess an influence of acute exercise on lipids and antioxidative enzymes activity the following parameters were determined at rest and immediately after the acute cardiopulmonary exercise cycloergometer test: triglycerides (TG), total cholesterol, low density cholesterol (LDL), oxidised LDL cholesterol (OxLDL), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and plasminogen activator inhibitor (PAI). **Results.** In basal condition, hypertensive patients compared to the control group had increased, but not significantly, level of Ox LDL (88.61±14.06 *vs* 79.00±29.26 mmol/L), PAI (3.06±0.56 *vs* 2.6±0.35 U/mL) and activity of GSH-Px (50.22±15.20 *vs* 44.63±13.73 U/g Hb). After acute exercise test, there was significantly greater level of Ox LDL (79.0±29.26 *vs* 89.3±29.07 mmol/L; $p < 0.05$) only in the control group. GSH-Px activity was significantly decreased only in hypertensive patients after acute exercise (50.22±15.2 *vs* 42.82±13.42 U/g Hb; $p < 0.05$), but not in the controls. **Conclusion.** No significantly elevated Ox LDL, GSH-Px and PAI-1 levels were found in hypertensive patients during basal condition in comparison with healthy subjects. Decreased GSH-Px activity was associated with those in acute exercise only in hypertensive patients. It could be an important indicator of deficiency of physiological antioxidative defense mechanism in hypertensive patients during an acute exercise.

Key words:
hypertension; exercise; oxidoreductases; triglycerides; cholesterol; lipoproteins, ldl.

Apstrakt

Uvod/Cilj. Mnoga ispitivanja podupiru hipotezu da je oksidativni stres uključen u patogenezu različitih bolesti uključujući i hipertenziju. S druge strane smatra se da je hipertenzija kod čoveka stanje oksidativnog stresa koje sudeluje u razvoju arterioskleroze i drugih poremećaja izazvanih hipertenzijom. Cilj ove studije bio je da se proceni uticaj akutnog fizičkog napora na aktivnost antioksidativnih enzima i lipidni status kod bolesnika sa hipertenzijom. **Metode.** U ispitivanje bilo je uključeno 40 bolesnika sa hipertenzijom i 20 zdravih osoba iste starosti. Kod njih su u stanju mirovanja, kao i neposredno posle aerobnog treninga (ergometrijskog testa) određivani sledeći parametri: trigliceridi (TG), ukupni holesterol, lipoproteini male gustine (LDL), oksidisani LDL holesterol (Ox LDL), superoksid dismutaza (SOD), glutation peroksidaza (GSH-Px), inhibitor aktivatora plazminogena (PAI). **Rezultati.** U bazalnim uslovima bolesnici sa hipertenzijom u odnosu na kontrolnu grupu imali su viši nivo Ox LDL (88,61±14,06 *vs* 79,00±29,26 mmol/L), PAI (3,06±0,56 *vs* 2,6±0,35 U/mL) i aktivnost GSH-Px (50,22±15,20 *vs* 44,63±13,73 U/g Hb), koji nije dostigao nivo statističke značajnosti ($p > 0,05$). Tokom ergometrijskog testa uočen je statistički značajan porast koncentracije Ox LDL u odnosu na bazalni nivo (79,0±29,26 *vs* 89,3±29,07 mmol/L, $p < 0,05$) samo u kontrolnoj grupi. Aktivnost GSH-Px statistički je značajno opala samo kod bolesnika sa hipertenzijom nakon sprovedenog ergometrijskog testa (50,22±15,2 *vs* 42,82±13,42 U/g Hb; $p < 0,05$), ali ne i kod ispitanika kontrolne grupe. **Zaključak.** Nisu nađeni značajno viši nivoi Ox LDL, PAI-1 i GSH-Px u bazalnim uslovima kod bolesnika sa hipertenzijom u odnosu na ispitanike kontrolne grupe. Nakon fizičke aktivnosti kod bolesnika sa hipertenzijom uočeno je statistički značajno sniženje aktivnosti GSH-Px. Ovo bi mogao biti važan pokazatelj nedostatka fiziološkog mehanizma antioksidativne odbrane kod bolesnika sa hipertenzijom izloženih akutnom fizičkom naporu.

Ključne reči:
hipertenzija; vežbanje; oksidoreduktaze; trigliceridi; holesterol; lipoproteini, ldl.

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Introduction

Many studies support the hypothesis that oxidative stress is involved in the pathogenic process of a variety of diseases including hypertension [1, 2]. In humans, hypertension is also considered a state of oxidative stress that can contribute to the development of arteriosclerosis and other hypertension-induced organ damage [3].

Lipid peroxidation and reduced antioxidant defense mechanisms are important factors affecting oxidation of lipoproteins and thereby the progression of arteriosclerotic disease [1, 3].

An enhanced oxidative stress has been observed in hypertensive patients as indicated by increased free radicals production, lipid peroxidation and diminished antioxidant status [3–5]. Assessment of antioxidant activities and lipid peroxidation byproducts in hypertensive subjects indicates an excessive amount of reactive oxygen species (ROS) and a reduction of antioxidant mechanism activity in both blood and several other cellular systems including not only vascular cells but also those found in circulating blood [3, 6].

Experimental and clinical evidence has demonstrated impairment of endothelium function caused by oxidative products in patients [3].

Antioxidant system includes non-enzymatic components and enzymatic ones such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) [1, 2].

It is known that exercise induces oxidative stress. There are many studies on exercise training and hypertension, but very few on exercise-induced oxidative stress and antioxidant activities in hypertensive patients [5–7]. It has been shown that reduction of superoxide radicals by infusion of superoxide dismutase (SOD) significantly decreases blood pressure in spontaneously hypertensive rats [7].

Exercise, paradoxically, is a well recognized model of oxidative stress and also an important therapeutic tool in hypertensive patients. Reduction of activity of antioxidant system could be a cause of increased oxidative state during exercise. Since physical activity protects against the development of cardiovascular disease (CVD) and modifies risk factors as plasminogen activator inhibitor (PAI), a regular exercise program seems to be desirable. There is a biochemical paradox: considerable amounts of oxygen are necessary to obtain a good performance and a satisfactory cardiopulmonary status, while an excess of oxygen or a defective metabolism of it could be harmful [8, 9] .

In relation to antioxidant enzymes, an increase of SOD and GSH-Px activities has been observed in skeletal muscle, heart and liver during a single bout of acute exercise [10] . It is important that physical training induces enhancement of muscular and liver antioxidant enzymes, mainly GSH-Px, facilitating the removal of reactive oxygen species and the reduction of oxidative stress levels [8].

The aim of this study was to estimate lipid oxidation and antioxidant parameters during basal conditions and after submaximal exercise test in a group of untreated hypertensive subjects, compared with gender- and age-paired healthy controls.

Methods

The study population consisted of consecutive outpatients from the Endocrinology and Cardiology Departments of University Clinical Center "Dr Dragiša Mišović", Belgrade. We evaluated 40 patients with hypertension (20 males and 20 females), aged 51.19±8.37 years and 20 age- and gender-matched controls (healthy, normotensive nonsmokers). Exclusion criteria were secondary arterial hypertension, diabetes, coronary artery disease, rhythm disturbances, cerebrovascular disease, chronic obstructive lung disorder or severe renal failure. Essential hypertension was defined according to the criteria of the VI Joint National Committee WHO grade I – II, non treated for hypertension.

For providing an objective assessment of exercise capacity and impairment we applied cardiopulmonary exercise cycle ergometer test (Jaeger Oxycon Delta ER - 900). All study subjects underwent a symptom-limited incremental test protocol with 25W increments each 3 minutes. Test was designed to be progressive and incremental in order to elicit the important parameters: VO_2 max (mL/min) - maximal O_2 uptake; FAI index (%) - maximal O_2 uptake compared to predictive value; VO_2/Kg (mL/Kg/min) - uptake related to body weight; VE (L/min) - ventilation per minute; RER - respiratory exchange ratio anaerobic threshold; T - time to anaerobic threshold (min). Heart rate and rhythm were continuously monitored using a 12 lead electrocardiogram. Blood pressure was measured before each load change. Gas analyses and flow probes were calibrated before each test. Gas exchange data were collected in a breath by breath manner and averaged into 30-second time period. All parameters were calculated as highest 30-second time period recorded before volitional fatigue was reached. Test lasted from 3 to 12 min depending on physical condition. Blood pressure was measured with a mercury sphygmomanometer, with a patient in the sitting position after a 5-minute rest.

This investigation was approved by the Ethical Committee of University Clinical Centre "Dr Dragiša Mišović", Belgrade.

Lipid parameters triglyceride, total cholesterol, HDL and LDL cholesterol, oxidized LDL cholesterol (mmol/L) were measured from serum.

Triglycerides (TG) were measured by an enzymatic colorimetric method (Elitech).

HDL-cholesterol was measured after precipitation of LDL and VLDL by phosphotungstic acid (Serbolab).

LDL-cholesterol was calculated according to the Friedwald formula.

Oxidised LDL-cholesterol was measured by the Elisa method (Mercodia) from serum.

Plasminogen activator inhibitor-type 1 (PAI-1) (U/mL) was measured by the spectrophotometer method using a commercial kit (Behring).

Superoxide dismutase (SOD) (U/g Hb) was measured by the enzymatic colorimetric method from erytrocyte after centrifugation of 0.5 mL of whole blood for ten minutes at 3 000 rpm and then aspiration off the plasma. Erytrocytes were washed 4 times with 3 mL of 0.9% Na Cl solution and centrifuged for 10 minutes at 3 000 rpm after each wash. The

washed centrifuged erytrocytes should then be made up to 2.0 mL with cold redistilled water, mixed and left to stand at +4 C° for 15 minutes. The lysat was diluted with Ransot sample diluent, so that the % of inhibition fell between 30% and 60%.

The activity of SOD was measured at 500 nm with a commercially available kit (Randox Laboratories, kit Ransod superoxide dismutase) by testing the inhibition degree of a tetrazolium salt oxidation reaction. The coefficient of variability between assays was 4.2%.

The activity of GSH-Px (U/g Hb) was evaluated by a commercial kit (Ransel glutathione peroxidase, Randox Laboratories) in erythrocytes at 340 nm by measuring the decrease of NADPH absorbancy. The coefficient of variability between assays was 4%.

All data were expressed as mean ± standard deviations (SD).

Statistical analysis was done by a Statistical Package for the Social Sciences Program (SPSS). Comparisons of all measurements were made with the paired Student's *t*-test and Mann-Whitney *U* test. Simple and multiple linear regression analysis determined all correlations.

Differences between groups were considered significant at $p < 0.05$.

Results

All demographics and biochemical parameters are shown in Tables 1 and 2. Table 2 shows that during basal condition, oxidised LDL cholesterol (Ox LDL), GSH-Px and PAI-1 were increased, but not significantly, in the hypertensive patients as compared to those of the controls.

There was no change in SOD activity between hypertensive and healthy subjects, before and after the exercise (Table 2). The patients with hypertension had significantly decreased levels of GSH-Px after exercise ($p < 0.05$). Ox LDL cholesterol was significantly increased during acute exercise only in the healthy subjects ($p < 0.05$) (Table 2).

Peak oxygen uptake (VO_2) was significantly greater in the healthy group ($p < 0.01$). There were no significant differences between hypertensive patients and healthy subjects for exercise time and ventilation per minute (VE). There was a negative correlation between VO_2 peak and Ox LDL before exercise ($r = -0.65$, $p < 0.05$) (Table 3).

Systolic and diastolic blood pressure were significantly higher during exercise in the hypertensive group ($p < 0,01$) (Table 4). There was no correlation between blood pressure (BP) and antioxidant enzymes (GSH-Px and SOD) activity.

Table 1

Clinical and biochemical parameters in the hypertensive patients and the control group

Parameters	Control group (healthy subjects) (n = 20)	Hypertensive group (n = 40)
Female/male	10/10	20/20
Body mass index (kg/m^2)	25.01 ± 1.90	26.82 ± 3.14
Glycemia (mmol/L)	5.08 ± 0.68 – rest	5.41 ± 0.95 – rest
	4.92 ± 0.74 – exercise	5.39 ± 0.87 – exercise
Tryglycerides (mmol/L)	1.74 ± 0.9 – rest	2.08 ± 1.35 – rest
	1.98 ± 0.8 – exercise	2.22 ± 1.09 – exercise
Total cholesterol (mmol/L)	5.57 ± 1.67 – rest	6.62 ± 0.78 – rest
	5.9 ± 1.88 – exercise	6.78 ± 0.69 – exercise
LDL cholesterol (mmo/L)	3.61 ± 1.56 – rest	4.42 ± 0.82 – rest
	3.55 ± 1.55 – exercise	4.65 ± 0.64 – exercise
PAI-1 (U/mL)	2.6 ± 0.35 – rest	3.06 ± 0.56 – rest
	2.22 ± 0.65 – exercise	2.87 ± 0.93 – exercise

Table 2

Indicators of oxidative stress and antioxidative defense before and after the acute exercise in the hypertensive and the control group

Indicators	Hypertensive group (n = 40)		Control group (n = 20)	
	rest	exercise	rest	exercise
Ox LDL (mmol/l)	88.61 ± 24.06	95.3 ± 22.51	79.0 ± 29.26	89.3 ± 29.07*
SOD (U/g Hb)	904.7 ± 99.66	928.08 ± 73.66	877.14 ± 153.18	895.0 ± 193.49
GSH-Px (U/g Hb)	50.22 ± 15.2	42.82 ± 13.42*	44.63 ± 13.73	43.97 ± 25.97*

* $p < 0.05$ *vs* the basal value (at the rest)

Table 3

Respiratory and cardiovascular post-exercise data in the hypertensive and the control group

Variable	Hypertensive group	Control group
VO_2 peak (mL/min)	20.55 ± 6.73	26.35 ± 10.53*
VE (L/min)	53.72 ± 14.07	52.00 ± 9.89
Exercise time (min)	13.58 ± 4.78	11.05 ± 1.48

* $p < 0.01$ vs the hypertensive group; VO2 oxygen uptake; VE = ventilation per minute

Table 4

Blood pressure before and during the exercise in the hypertensive and the control group

Blood pressure – BP (mmHg)	Hypertensive group		Control group	
	Rest	During exercise	Rest	During exercise
Systolic BP	139.65 ± 22.96	206.8 ± 22.9*	122.37 ± 12.09	128.0 ± 30.64
Diastolic BP	90.3 ± 12.04	103.75 ± 11.89*	80.0 ± 9.36	73.6 ± 16.56

*$p < 0.01$ vs the basal value (at the rest)

Discussion

There are some contradictory results in the literature regarding oxidative stress parameters and lipids in hypertensive patients during acute exercise. The oxidation of LDL cholesterol is considered the key event in initiation of arteriosclerosis [9, 10]. In our study OxLDL was increased but not significantly in hypertensive patients in basal condition, compared to the control group. On the other hand, we found increased Ox-LDL after the exercise test only in the healthy subjects. Our results are consistent with those of other studies on oxidative stress [10, 11]. It has been proposed that oxidative stress may be associated with the pathogenesis of hypertension and its complications [11, 12].

In this study we observed an increase in GSH-Px activity in the hypertensive patients compared with the controls during basal condition. In relation to acute exercise, a decrease in GSH-Px was observed only in the hypertensive patients. This finding is in accordance with that of Redon et al [3]. There was no significant change in SOD activity in basal condition and after exercise, in both groups (hypertensive patients and controls). A possible explanation for these findings is that the rise in some enzyme activities in the patients with hypertension could be a compensatory mechanism of the body to prevent tissue damage [13, 14].

Our results suggest that there seems to be an imbalance between erytrocyte oxidant and antioxidant systems in patients with hypertension. This disturbance of the oxidative metabolism may affect endothelial cell functions and contribute to the development and maintenance of cardiovascular complications during hypertension. Reduced levels of GSH-Px after acute bouts of exercise are related to an extensive number of metabolic and gene expression disturbances [15–17]. Whether a lower GSH-Px activity is a cause or a consequence of an increased oxidative status, needs further evaluation [3].

The absence of a relationship between the BP values and antioxidant parameters in the group of hypertensive subjects may indicate that factors other than BP values alone, such as an enhanced activity of angiotensin II or hyperinsulinemia, may be responsible for altered oxidative state in blood, which is in accordance with the previous studies [18, 19].

In this study we found elevated concentrations in plasma of PAI-1 only in patients with hypertension, in basal condition. An acute exercise decreased the level of PAI-1 only in the healthy subjects, but not significantly. It has been shown that an increased PAI-1 may contribute to acceleration of atherosclerosis in condition characterized by insulin resistance [20, 21].

The evidence of a high oxidative profile during exercise in hypertension is not directly related to an increase risk of CVD [22]. An increase of antioxidant enzyme activity (GSH-Px), related to the intensity of exercise after different levels of training has also been described [23]. Accordingly, after a regular physical training program an improvement in the counterbalance of the oxidative stress could be expected.

Conclusion

It can be concluded that acute exercise induces an effect well counterbalanced only in the healthy subject, but not in the hypertensive patients.

REFERENCES

1. *Berry C, Brosnan MJ, Fennell J, Hamilton CA, Dominiczak AF.* Oxidative stress and vascular damage in hypertension. Curr Opin Nephrol Hypertens 2001; 10(2): 247–55.
2. *Zalba G, San José G, Moreno MU, Fortuño MA, Fortuño A, Beaumont FJ,* et al. Oxidative stress in arterial hypertension: role of NAD(P)H oxidase. Hypertension 2001; 38(6): 1395–9.
3. *Redón J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A,* et al. Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension 2003; 41(5): 1096–101.
4. *Wu L, Juurlink BH.* Increased methylglyoxal and oxidative stress in hypertensive rat vascular smooth muscle cells. Hypertension 2002; 39(3): 809–14.
5. *Moore K, Roberts LJ 2nd.* Measurement of lipid peroxidation. Free Radic Res 1998; 28(6): 659–71.
6. *Cracowski JL, Baguet JP, Ormezzano O, Bessard J, Stanke-Labesque F, Bessard G,* et al. Lipid peroxidation is not increased in patients with untreated mild-to-moderate hypertension. Hypertension 2003; 41(2): 286–8.
7. *Steinberg D, Witztum JL.* Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? Circulation 2002; 105(17): 2107–11.
8. *Chisolm GM, Steinberg D.* The oxidative modification hypothesis of atherogenesis: an overview. Free Radic Biol Med 2000; 28(12): 1815–26.
9. *Cai H, Harrison DG.* Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000; 87(10): 840–4.
10. *Lerman LO, Nath KA, Rodriguez-Porcel M, Krier JD, Schwartz RS, Napoli C,* et al. Increased oxidative stress in experimental renovascular hypertension. Hypertension 2001; 37(2 Part 2): 541–6.
11. *Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M.* Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci U S A 1991; 88(22): 10045–8.
12. *Giugliano D, Ceriello A, Paolisso G.* Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? Metabolism 1995; 44(3): 363–8.
13. *Villa-Caballero L, Nava-Ocampo AA, Frati-Munari A, Ponce-Monter H.* Oxidative stress, acute and regular exercise: are they really harmful in the diabetic patient? Med Hypotheses 2000; 55(1): 43–6.
14. *Sen CK.* Oxidants and antioxidants in exercise. J Appl Physiol 1995; 79(3): 675–86.
15. *Ji LL.* Antioxidant enzyme response to exercise and aging. Med Sci Sports Exerc 1993; 25(2): 225–31.
16. *Palanduz S, Ademoğlu E, Gökkuşu C, Tamer S.* Plasma antioxidants and type 2 diabetes mellitus. Res Commun Mol Pathol Pharmacol 2001; 109(5-6): 309–18.
17. *Mena P, Maynar M, Gutierrez JM, Maynar J, Timon J, Campillo JE.* Erythrocyte free radical scavenger enzymes in bicycle professional racers. Adaptation to training. Int J Sports Med 1991; 12(6): 563–6.
18. *Nordt TK, Schneider DJ, Sobel BE.* Augmentation of the synthesis of plasminogen activator inhibitor type-1 by precursors of insulin. A potential risk factor for vascular disease. Circulation 1994; 89(1): 321–30.

19. *Astley S, Langrish-Smith A, Southon S, Sampson M*. Vitamin E supplementation and oxidative damage to DNA and plasma LDL in type 1 diabetes. Diabetes Care 1999; 22(10): 1626–31.
20. *Bayhan G, Atamer Y, Atamer A, Yokus B, Baylan Y*. Significance of changes in lipid peroxides and antioxidant enzyme activities in pregnant women with preeclampsia and eclampsia. Clin Exp Obstet Gynecol 2000; 27(2): 142–6.
21. *Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr, Liu K*. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA 2003; 290(23): 3092–100.
22. *Paterna S, Parrinello G, Amato P, Bologna P, Fornaciari E, Follone G*, et al. Can losartan improve cardiac performance during the treadmill exercise test in hypertensive subjects? Drugs Exp Clin Res 2002; 28(4): 155–9.
23. *Nuttall SL, Dunne F, Kendall MJ, Martin U*. Age-independent oxidative stress in elderly patients with non-insulin-dependent diabetes mellitus. QJM 1999; 92(1): 33–8.

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Uzroci slabljenja vida kod uveitisa

Causes of visual loss in uveitis

Zora Stanković

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Apstrakt

Uvod/cilj. Epidemiološka studijska ispitivanja slepila kod radnoaktivne grupe stanovnika traže tačno definisanje prave veze uveitisa i oštećenja vida. S obzirom na to da u tercijarne ustanove uglavnom dolaze, ostaju i leče se bolesnici sa težim oblicima uveitisa, cilj rada bio je da se utvrdi da li godine života, pol, godine početka uveitisa, dužina trajanja oslabljenog vida i uzroci koji do toga dovode imaju uticaja na stepen oštećenja vida kod bolesnika sa različitim vrstama uveitisa. **Metode.** Podaci su bili prikupljeni iz medicinske dokumentacije 237 bolesnika lečenih u Odeljenju za uveitise Instituta za očne bolesti u Beogradu u periodu mart 2005 – mart 2008. godine. **Rezultati.** Smanjenje oštrine vida (≤ 0,3) nađena je kod 161/237 (67,9%) bolesnika, od kojih je kasnije njih 85 imalo oštrinu vida ≤ 0,1. Od uveitisa su najčešće obolevali radno aktivni bolesnici (do 60 godina starosti) (173/237; 73%). Najveći procenat bolesnika sa oslabljenjem vida postojao je kod obolelih od panuveitisa (77/94; 81,91%). Godine početka uveitisa i pol bolesnika nisu imali statistički značajan uticaj na slabljenje vida. Cistoidni edem makule (CMO) (43/161; 26,7%), katarakta (28/161; 17,39%) i kombinacija CMO i katarakte su najčešći uzroci pada vida (34/161; 21,1%). **Zaključak.** Faktori rizika za teško slabljenje vida (≤ 0,1) su panuveitis, bilateralna inflamacija, produženo trajanje redukcije vida i veći broj recidiva. Glavni uzroci slabljenja vida kod 65,2% naših bolesnika bili su CMO i katarakta.

Ključne reči:
uveitis; vid, oslabljeni; faktori rizika.

Abstract

Background/Aim. Epidemiological studies of blindness in a working age population require a precise definition of the true connection of uveitis and visual damage. Since most patients with more severe types of uveitis are hospitalized in tertiary referral uveitis service, our aim was to determine whether age, sex and age of onset of uveitis, as well as duration of visual loss and its causes influence the degree of visual damage in patients with different types of uveitis. **Methods.** The data were collected from medical records of 237 patients at the Department for Uveitis of the Institute for Eye Diseases in Belgrade over a three-year period (March 2005 to March 2008). **Results.** Visual acuity reduction (≤ 0.3) was found in 161/237 (67.9%) patients, 85 of whom had visual acuity of ≤ 0.1 later. Working age patients (up to 60 years of age) most often suffered from uveitis (173/237; 73%). The highest noumber of patients with visual loss was in the group suffering from panuveitis (77/94; 81.91%). The age of onset of uveitis and sex have no statistically significant influence on visual loss. The most common causes of visual loss (34/161; 21.1%) were cystoid macular oedema (CMO) (43/161; 26.7%), cataract (28/161; 17.39%) and combination of CMO and cataract. **Conclusion.** The risk factors for severe visual loss (≤ 0.1) are panuveitis, bilateral inflammation, prolonged visual reduction and a significant number of relapses. The main causes of visual loss in 65.2% of our patients were CMO and cataract.

Key words:
uveitis; vision, low; risk factors.

Uvod

Uveitis je termin koji se koristi da opiše intraokularne inflamatorne bolesti koje mogu nastati u bilo kom uzrastu, ali predominantno pogađaju grupu radnoaktivnih osoba [1]. Prosečna godišnja prevalencija uveitisa je 14–17 na 100 000 stanovnika, sa maksimumom u grupi između 20 i 50 godina starosti, posle čega opada [2–6]. Postoje geografske varijacije u totalnoj populacionoj prevalenciji obolelih od uveitisa: 38 na 100 000 u Francuskoj, oko 200 na 100 000 u Americi i otprilike 730 na 100 000 u Indiji [2, 4]. Pošto se kod nas uglavnom ispituje patofiziologija i etiologija uveitisa, nemamo precizne podatke o prevalenciji ovog oboljenja u Srbiji.

Uveitis može uzrokovati značajno slabljenje vida i predstavlja peti po redu uzrok gubitka vida u razvijenom svetu (refraktivne greške, glaukom, dijabetička retinopatija, senilna degeneracija makule), učestvujući u otprilike 10–15% uzroka totalnog slepila. S obzirom na to da je većina obolelih iz radnosposobne grupe stanovništva, potencijalni socijalni i ekonomsku troškovi su ogromni.

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Cilj ove retrospektivne studije bio je da se ispita stepen, trajanje i uzroci slabljenja vida kod bolesnika obolelih od uveitisa, jer se pretpostavilo da je upravo to ključ za bolje razumevanje ove bolesti ne samo sa ugla oftalmološkog, već i sa socioekonomskog aspekta.

Metode

U trogodišnjem periodu (mart 2005–mart 2008), prikupljeni su podaci iz medicinske dokumentacije 237 bolesnika lečenih u Odeljenju za uveitise Instituta za očne bolesti u Beogradu. Svi bolesnici prošli su oftalmološki pregled: oštrina vida, pregled na biomikroskopu, očni pritisak (IOP) i biomikroskopija zadnjeg pola Goldmanovim staklom sa tri ogledala. Podaci su, takođe, sadržali pol, godine života, dužinu trajanja oboljenja i uzroke slabljenja vida.

Bolesnici sa stalnim oštećenjem vida idenifikovani su na osnovu postojanja ireverzibilnih promena, kao što su makularni ožiljak ili atrofija, lamelarne rupture makule, atrofije optikusa, itd. Anatomska strana inflamacije korišćena je za klasifikaciju uveitisa prema preporukama *International Uveitis Study Group* [7]. Oštrina vida prema Snellenu bila je beležena na svakom pregledu. U svrhu ove studije, slabljenje vida bilo je definisano kao korigovana oštrina vida od < 0,3. Bolesnici sa oštećenjem vida bili su podeljeni u dve podgrupe: one sa umerenim slabljenjem vida (0,1–0,3) i one sa teškim smanjenjem oštrine vida označenom kao slabljenje vida ≤ 0,1. Kao dodatak stepenu smanjenja vida, takođe, uračunata je i dužina trajanja gubitka vida. Kako stepen oštrine vida kod uveitisa može varirati u zavisnosti od težine samog oboljenja i pratećih sekvela, totalno trajanje gubitka vida računato je dodavanjem trajanja svake individualne epizode.

Uticaj pola, tipa uveitisa, godina starosti i godina u kojima je počelo slabljenje vida analiziran je pomoću binarne regresije, dok je odnos između trajanja i težine slabljenja vida analiziran uz pomoć *t*-testa i Mann-Whitney testa.

Rezultati

U studiju je bilo uključeno 237 bolesnika sa uveitisom, prosečne starosti 49 (opseg 7–82) godina i srednjim trajanjem oboljenja od 38 ± 51,33 meseca (opseg 3–264 meseca). Bilo je 146 (61,6%) žena i 91 (38,4%) muškarac. Od ukupnog broja bolesnika, 161 (67,9%) imao je smanjenje vida ≤ 0,3. Od ovih bolesnika 76 (47,2%) imalo je umereno slabljenje vida (0,1–0,3), a 85 (52,8%) težak stepen smanjenja oštrine vida (< 0,1). Određeni stepen permanentnog oštećenja vida nađen je kod 43/161 (26,7%) bolesnika. Od ovog broja, 11 je imalo unilateralno, a 32 bilateralno oštećenje.

Od 237 bolesnika hroničnu intraokularnu inflamaciju imalo je njih 80 (33,75%), što je rezultiralo smanjenjem vida (umerenim ili jakim) kod 50 (62,5%). Umereno slabljenje vida bilo je prisutno kod 14/50 (31%) bolesnika, a 36/50 (69%) imalo je teško smanjenje oštrine vida. Bilateralna inflamacija postojala je kod 159/237 (67,1%) bolesnika, od kojih je 114/159 (71,7%) imalo umereno ili teško slabljenje vida; 35/114 (30,7%) bolesnik izgubio je vid na jednom oku, a 79/114 (69,3%) na oba oka. Od tih 79 bolesnika sa bilateralnim gubitkom vida, 58 (73,41%) pokazivalo je težak gubitak vida, koji spada pod kriterijume za legalno slepilo u mnogim delovima sveta.

Srednja dužina trajanja gubitka vida bila je 22,6 meseci za bolesnike sa umerenim smanjenjem oštrine vida, a 24,2 meseci za one sa teškim gubitkom vida. Kod bolesnika kod kojih je vid oslabio samo na jednom oku, srednja dužina smanjenja vida bila je 21 mesec, a čak 45,1 mesec kod onih sa bilateralnom bolešću.

Prema preporukama *International Uveitis Study Group*, za klasifikaciju uveitisa korišćena je anatomska strana inflamacije. U tabeli 1 prikazan je ukupan broj bolesnika obolelih od različitih vrsta uveitisa. Iz ove tabele, takođe može se videti odnos vrste uveitisa prema broju bolesnika sa značajnim slabljenjem vida, odnosno prema stepenu slabljenja vida. Gubitak vida najčešće se javljao kod bolesnika sa panuveitisom (77/94; 81,91%), a zatim kod onih sa prednjim uveitisom (41/71; 57,75%). Od bolesnika sa prednjim uveitisom, 33 je imalo akutni, a 38 hronični prednji uveitis. Smanjenje oštrine vida bilo je mnogo češće i teže u podgrupi sa hroničnim prednjim uveitisom.

U tabeli 2 dati su podaci o godinama starosti bolesnika i učestalosti panuveitisa i pojave obostranog slabljenja vida. Kod bolesnika mlađih od 40 godina života (n = 81; 34,18%), i u grupi od 40 do 60 godina (n = 92; 38,82%), njih 41%, odnosno 46,8% imalo je panuveitis, dok je 25,6% u prvoj, tj. 28,2% u drugoj grupi imalo bilateralno smanjenje oštrine vida. Od ukupnog broja naših bolesnika, manje od trećine činile su osobe preko 60 godina starosti (n = 64; 27%). Kod njih incidencija panuveitisa (45%) bila je slična onoj kod bolesnika iz radnoaktivne grupe stanovništva, ali se prevalencija bilateralnog oštećenja vida povećala na čak 49%.

Tabela 1

Dijagnoza kod bolesnika sa oslabljenim vidom

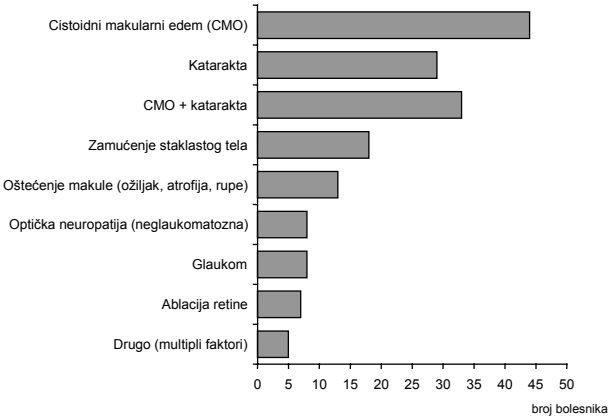
Dijagnoza	Ukupno bolesnika (n = 237)	Bolesnici sa oslabljenim vidom (n = 161) n (%)	Stepen oslabljenog vida	
			Umereni (n = 76) n (%)	Teški (n = 85) n (%)
Panuveitis	94	77 (81,91)	36 (46,76)	41 (53,24)
Prednji uveitis	71	41 (57,75)		
akutni	33	17 (51,51)	8 (47,10)	9 (52,90)
hronični	38	24 (63,16)	10 (41,67)	14 (58,33)
Intermedijalni uveitis	30	16 (53,33)	10 (62,50)	6 (37,50)
Fuchov heterohromni uveitis	11	8 (72,72)	3 (37,50)	5 (62,50)
Zadnji uveitis	21	12 (57,14)	6 (50,00)	6 (50,00)
Sklerouveitis	10	7 (70,00)	3 (42,86)	4 (57,14)

Tabela 2

Odnos godina starosti bolesnika i učestalosti panuveitisa i pojave obostranog slabljenja vida

Godine života	Broj bolesnika (%)	Panuveitis (%)	Bilateralno slabljenje vida
< 40	81 (34,18)	41,00	25,60
40–60	92 (38,82)	46,80	28,20
> 60	64 (27,00)	45,00	49,00

Na slici 1 može se videti da su kod 161 bolesnika sa značajnim smanjenje oštrine vida, glavni uzroci povećanja bili cistoidni edem makule (CMO) (n = 43; 26,7%), katarakta (n = 28; 17,39%), i kombinacija CMO i katarakte (n = 34; 21,1%). Drugi uzroci kao što su glaukom, pojasasta degeneracija, teški vitritis, ablacija retine, optička neuropatija, formiranje epiretinalne membrane i submakularna fibroza, zajedno su uzrokovali slabljenje vida kod 56 (34,78%) bolesnika.



Sl. 1 – Uzroci slabljenja vida kod bolesnika sa značajnim smanjenjem oštrine vida

Statistička analiza pokazala je da su panuveitis ($p = 0,05$) i starije životno doba ($p = 0,02$) značajni preduslovi za pojavu gubitka vida. Godine života u kojima se javlja uveitis i pol bolesnika nisu imali statistički značajan uticaj na slabljenje vida. Bolesnici sa produženim trajanjem smanjenja oštrine vida ($p = 0,05$) i sa bilateralnom inflamacijom ($p = 0,05$), imali su mnogo veći rizik od gubitka vida.

Diskusija

Od 237 bolesnika, 161 (67,9%) imao je slabljenje vida ≤ 6/18, od čega njih 50 (45%) bilateralno. Ovo je više nego u ranijim izveštajima [1, 8, 9] i može biti uzrokovano našom definicijom gubitka vida kao korigovane oštrine vida od ≤ 6/18, jer smo pošli od toga da redukcija oštrine vida ovog nivoa mnogo više utiče na svakodnevne životne potrebe. Naš stav podržan je studijom Evansa i sar. [10], koji oštećenje vida definišu kao vid od ≤ 6/18. Većina drugih studija koristi WHO definiciju gubitka vida [1, 8, 11, 12]. U tercijarnim zdravstvenim ustanovama, većina bolesnika po svemu sudeći pati od teških, često bilateralnih uveitisa. Sličan primer viđa se u većini studija specijalizovanih centara, kod kojih je panuveitis najčešća dijagnoza [13, 14]. Međutim, u populacionim studijama, najčešći tip uveitisa je prednji uveitis [15, 16]. Skorašnja studija koju su sproveli Taylor i Keeffe [17] sugeriše da se ekonomsko slepilo dešava kada oštrina vida oslabi na 6/12, dok oštrina vida ispod ovog nivoa ugrožava sposobnost osobe da vozi i funkcioniše na radnom mestu. Ovo je podržala studija Westa i sar. [18] po kojima oštrina vida od 20/30 ugrožava čitanje.

Studije Rothova i sar. [8] kao i Bodaghi i sar. [14] istraživale su incidenciju i etiologiju slepila u sličnim grupama bolesnika, ali nisu prikazale trajanje oštećenja vida ili dokumentovale privremeni gubitak vida koji je verovatno redukovao kvalitet života i snizio ekonomsku produktivnost ovih bolesnika. Naši podaci pokazuju da je gubitak vida kod uveitisa pre svega privremeno, ponekad teško oštećenje vida, koje traje nedeljama i mesecima, pa čak i godinama, primarno prouzrokovano CMO, kataraktom ili kombinacijom ova dva. U većini formi uveitisa, oštećenje vida ne dešava se od jedne epizode uveitisa; češće recidivirajuće epizode inflamacije uzrokuju kumulativno oštećenje. Međutim, neki bolesnici sa teškom bolešću mogu razviti uporni CMO i u ranim stadijumima, dok bolesnici sa Behçetovom bolešću mogu razviti težak gubitak vida tokom par dana, uprkos intenzivnoj imunosupresivnoj terapiji.

Etiologija inflamacije, ukoliko je znamo, takođe mora biti uzeta u obzir, jer nemaju svi tipovi uveitisa isti uticaj na vid. Stanja kao što su Behçetova bolest i *birdshot retinochoroidopathy* imaju mnogo lošiju prognozu u poređenju sa Fuchs' heterohromnim uveitisom, gde je vidna prognoza mnogo bolja, čak iako se katarakta razvija kod većine bolesnika i uzrokuje redukciju vida dok se ne primeni operacija katarakte.

Bolesnici sa bilateralnom intraokularnom inflamacijom imali su lošiju vidnu prognozu u poređenju sa drugim grupama ($p = 0,05$); srednje trajanje slabljenja vida bilo je duže, više od dva puta (45,1 mesec) u poređenju sa bolesnicima koji su imali unilateralnu inflamaciju (21 mesec). Naše iskustvo sugeriše da kod ovih bolesnika postoji tendencija u razvoju mnogo teže inflamacije koja otežava kontrolu same bolesti. Panuveitis je bila najčešća dijagnoza, a posle njega sledе prednji uveitis, intermedijalni i zadnji uveitis. Bodaghi i sar. [14] u svojoj studiji na 927 bolesnika sa teškim uveitisom takođe su pokazali da je panuveitis najčešća dijagnoza koju sledi prednji uveitis. Oni su zaključili da se rezultati njihove studije ne mogu primeniti na opštu populaciju, pošto u tercijarne ustanove uglavnom dolaze, ostaju i leče se bolesnici sa težim oblicima uveitisa. Ovaj zaključak odnosi se i na našu kohortu. Rothova i sar. [8] pokazali su takođe da panuveitis ima najgoru prognozu, što se slaže sa našim rezultatima.

Godine početka uveitisa nisu imale statistički značajan uticaj na slabljenje vida kod naših ispitanika; ovo može biti vezano za činjenicu da nijedan bolesnik nije imao juvenilni reumatoidni artritis, poznat kao uzrok slabljenja vida kod dece [19]. Starenje ima nepovoljan uticaj na oštrinu vida ($p = 0,019$). Ovo je verovatno posledica povećane prevalencije panuveitisa i bilateralnih inflamacija kod bolesnika pre-

ko 60 godina, mada Darell i sar. [2] nisu pokazali da godine života predstavljaju faktor rizika. Nijedan od naših bolesnika nije imao senilnu degeneraciju makule, ali mogućnost da pojava senilne katarakte doprinosi slabljenju vida, ne može da se isključi iz ove grupe bolesnika.

Uočena je jaka veza između trajanja oslabljenog vida i stepena njegovog smanjenja ($p = 0,05$), tj. produženo trajanje slabijeg vida bilo je snažno povezano sa njegovom lošijom oštrinom.

Katarakta i CMO odvojeno ili zajedno uzrokuju slabljenje vida kod 65,2% bolesnika u našoj studiji, što se slaže sa ispitivanjima koja su vršili Bodaghi i sar. [14]. U ispitivanjima uzroka slabljenja vida, Rotova i sar. [8] prikazali su da je CMO najčešći uzrok ovog slabljenja (26% bolesnika), dok odmah iza sledi katarakta kod 582 bolesnika sa intraokularnom inflamacijom (19% bolesnika) [8]. Mada operacija katarakte daje odličnu prognozu kod većine tipova uveitisa, usvojeno je da oko mora biti bez inflamacije najmanje tri meseca pre operacije (Fucksov heterohromni uveitis je najočitiji izuzetak), inače bolesnik može patiti od prolongiranog smanjenja oštrine vida, uprkos uspešnoj operaciji katarakte.

Poslednjih godina može se videti značajno napredovanje u lečenju uveitisa, ali uprkos tome, slabljenje vida nastaje kod više od 35–40% bolesnika [8, 9]. Pregledi literature pokazuju da postoji samo par baza podataka o incidenciji i prevalenciji gubitka vida i slepila kod uveitisa. Ovo iznenađuje s obzirom na očigledni socioekonomski značaj ove bolesti. Većina studija ispituje uzroke slepila posmatrane kod starijih bolesnika, ne klasifikujući uveitise kao odvojeni entitet. Epidemiološka studijska ispitivanja slepila kod radnoaktivne grupe stanovnika traže tačno definisanje prave veze uveitisa i vidnog oštećenja.

Zaključak

Dve trećine bolesnika sa uveitisom razvija umereno (0,3–0,1) ili teško (< 0,1) smanjenje oštrine vida. Od bolesnika kojima zbog uveitisa slabi vid, njih 26,7% ima permanentno oštećenje vida. Radnoaktivni bolesnici (do 60 godina starosti) najčešće obolevaju od uveitisa. Godine bolesnika kada počne uveitis i pol nemaju statistički značajan uticaj na slabljenje vida.

Bolesnici sa bilateralnim uveitisom imaju težu inflamaciju, dva puta duže trajanje slabljenja vida i lošiju prognozu. Najčešći oblik uveitisa kod hospitalizovanih bolesnika je panuveitis, kod kojeg je gubitak vida najveći. Glavni uzroci slabljenja vida kod 65,2% bolesnika sa uveitisom su CMO i katarakta. Faktori rizika od teškog gubitka vida ($\leq 0,1$) su panuveitis, bilateralna inflamacija, produženo trajanje redukcije vida i veći broj recidiva.

Pošto je većina obolelih iz radnosposobne grupe stanovništva, socijalni i ekonomski troškovi su ogromni, zbog čega naš dalji rad na otkrivanju, lečenju i borbi protiv posledica uveitisa ima još veći značaj.

L I T E R A T U R A

1. *Suttorp-Schulten MS, Rothova A.* The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol 1996; 80(9): 844–8.
2. *Darrell Rw, Wagener Hp, Kurland Lt.* Epidemiology of uveitis. Incidence and prevalence in a small urban community. Arch Ophthalmol 1962; 68: 502–14.
3. *Mortensen KK, Sjolie AK, Glodschmidt E.* Uveitis, eine epdemiologische Unterschung. Dtsch Ophthalmol Ges 1981; 78: 97–101.
4. *Vadot E, Barth E, Billet* R Epidemiology of uveitis: preliminary results of a study in the Savoy. In: *Saari K,* editor. Uveitis Update. Amsterdam: Elsevier; 1984. p. 13–6.
5. *Baarsma GS.* The epidemiology and genetics of endogenous uveitis: a review. Curr Eye Res 1992; Suppl 11: 1–9.
6. *Tran VT, Auer C, Guex-Crosier Y, Pittet N, Herbort CP.* Epidemiology of uveitis in Switzerland. Ocul Immunol Inflamm 1994; 2: 169–76.
7. *ten Doesschate J.* Causes of blindness in The Netherlands. Doc Ophthalmol 1982; 52(3–4): 279–85.
8. *Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A.* Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol 1996; 80(4): 332–6.
9. *Couto C, Merlo JC.* Epidemiological study of patients with uveitis in Buenos, Argentina. Amsterdam, New York: Kugler Publications; 1993.
10. *Evans JR, Fletcher AE, Wormald RP, Stirling S, Smeeth L, Breeze E,* et al. Prevalence of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. Br J Ophthalmol 2002; 86(7): 795–800.
11. *Kotaniemi K, Aho K, Kotaniemi A.* Uveitis as a cause of visual loss in arthritides and comparable conditions. J Rheumatol 2001; 28(2): 309–12.
12. *Rosner RS.* Uveitis and blindness. Med Trial Tech Q 1967; 14(2): 39–42.
13. *Merrill PT, Kim J, Cox TA, Betor CC, McCallum RM, Jaffe GJ.* Uveitis in the southeastern United States. Curr Eye Res 1997; 16(9): 865–74.
14. *Bodaghi B, Cassoux N, Wechsler B, Hannouche D, Fardeau C, Papo T,* et al. Chronic severe uveitis: etiology and visual outcome in 927 patients from a single center. Medicine (Baltimore) 2001; 80(4): 263–70.
15. *McCannel CA, Holland GN, Helm CJ, Cornell PJ, Winston JV, Rimmer TG.* Causes of uveitis in the general practice of ophthalmology. UCLA Community-Based Uveitis Study Group. Am J Ophthalmol 1996; 121(1): 35–46.
16. *Päivönsalo-Hietanen T, Vaahtoranta-Lehtonen H, Tuominen J, Saari KM.* Uveitis survey at the University Eye Clinic in Turku. Acta Ophthalmol (Copenh) 1994; 72(4): 505–12.
17. *Taylor HR, Keeffe JE.* World blindness: a 21st century perspective. Br J Ophthalmol 2001; 85(3): 261–6.
18. *West SK, Rubin GS, Broman AT, Muñoz B, Bandeen-Roche K, Turano K.* How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. Arch Ophthalmol 2002; 120(6): 774–80.
19. *Cunningham ET Jr.* Uveitis in children. Ocul Immunol Inflamm 2000; 8(4): 251–61.

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Association between obesity and socioeconomic factors and lifestyle

Udruženost gojaznosti sa socioekonomskim faktorima i stilovima života

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Abstract

Background/Aim. The prevalence of overweight and obesity is increasing at an alarming rate and it is a manifestation of the epidemics of a sedentary lifestyle and excessive energy intake. The aim of this study was to determine the prevalence of overweight and obesity in the population of the Province of Vojvodina, Serbia, and to examine the association between obesity and socioeconomic and lifestyle factors. **Methods.** A cross-sectional study conducted in the Province of Vojvodina in 2006 involved 3 854 participants aged 20 years and over (1 831 men and 2 023 women). The study was a countinuation of the baseline study conducted in 2000 (n = 2 840, 1 255 men and 1 585 women). The main outcome measures were overweight and obesity (Body Mass Index – BMI ≥ 25 kg/m^2), sociodemographic factors, including nutrition habits – having breakfast everyday and television watching frequency. **Results.** The prevalence of overweight and obesity in both sexes in 2006 was 57.4% (35.7% were overweight and 21.7% obese). The prevalence of overweight was higher in men (41.1%) than in women (30.9%) ($p < 0.001$) while obesity was higher in women (23.1%) as compared to men (20.2%) ($p = 0.035$). For both sexes, overweight rates were highest at the age 60–69 (men 44.8% and women 39.1%) while obesity rates were peaked to men aged 50–59 (25.1%) and women aged 60–69 years (37.8%). Increasing ageing, males, rural population, single examinees, lower educational level, improved income, examinees that never/sometimes have breakfast and frequently watch TV were associated with obesity. **Conclusions.** The population of Vojvodina, with 23.1% obese women and 20.2% obese men is one of severely affected European populations. High prevalence of obesity requires urgent public health action. Healthy lifestyle, balanced nutrition with low energy intake and increased physical activity have to be promoted within a prevention strategy and obesity management.

Key words:
obesity; body mass index; risk factors; prevalence; socioeconomic factors; yugoslavia.

Apstrakt

Uvod/Cilj. Prevalencija prekomerne telesne mase i gojaznosti alarmantno se povećava kao rezultat sve izraženijeg sedanternog načina života i povećanog energetskog unosa. Cilj rada bio je procena prevalencije prekomerne telesne mase i gojaznosti stanovništva Vojvodine i ispitivanje udruženosti gojaznosti sa socioekonomskim faktorima i stilom života. **Metode.** Urađena je studija preseka u 2006. godini na uzorku od 3 854 stanovnika Vojvodine (1 831 muškarac i 2 023 žene), starosti 20 i više godina. Studija je nastavak osnovne studije sprovedene u 2000. godini (n = 2 840, 1 255 muškaraca i 1 585 žena). Predmet istraživanja bili su prekomerna telesna masa i gojaznost (BMI ≥ 25 kg/m^2), sociodemografski faktori uključujući i navike u ishrani – svakodnevno doručkovanje i gledanje televizije. **Rezultati.** Prevalencija prekomerne telesne mase i gojaznosti kod oba pola u 2006. godini bila je 57,4% (35,7% bilo je sa prekomernom telesnom masom i 21,7% gojaznih). Prevalencija prekomerne telesne mase bila je viša kod muškaraca (41,1%) nego kod žena (30,9%) ($p < 0.001$), dok je gojaznost bila veća kod žena (23,1%) u poređenju sa muškarcima (20,2%) ($p = 0,035$). Kod oba pola procenat ispitanika sa prekomernom telesnom masom bio je najviši u kategoriji 60–69 godina (44,8% muškaraca i 39,1% žena), dok je procenat gojaznih muškaraca bio najviši u kategoriji 50–59 godina, a žena starosti 60–69 godina (37,8%). Starost, muški pol, seoska populacija, samci, niži nivo obrazovanja, viši prihodi, ispitanici koji nikad/ponekad doručkuju i učestalo gledanje televizije bili su udruženi sa gojaznošću. **Zaključak.** Stanovnici Vojvodine sa 23,1% gojaznih žena i 20,2% gojaznih muškaraca jedni su od najviše zastupljenih u populaciji Evrope. Visoka prevalencija gojaznosti zahteva hitnu javnozdravstvenu akciju. Zdrav način života, balansirana ishrana sa niskim energetskim unosom i povećana fizička aktivnost moraju biti promovisani u okviru strategije prevencije i kontrole gojaznosti.

Ključne reči:
gojaznost; telesna masa, indeks; faktori rizika; prevalencija; socijalni faktori; srbija.

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Introduction

Excess weight is a significant health problem worldwide. Globally, there are more than 1 billion overweight adults, at least 300 million obese [1]. Recent estimations have showed that the prevalence of overweight and obesity increases at alarming rates, both in developed and developing countries [2, 3].

Overweight and obesity are major risk for serious diet-related chronic diseases, including diabetes type 2, cardiovascular diseases, cerebro-vascular diseases, some cancers, psychosocial disturbances, osteoarthritis and increased risk ranged from premature death to serious chronic conditions that reduce the overall quality of life [4, 5]. The risk of associated disease increases with body mass index (BMI). There is also an evidence that obesity decreases longevity [6, 7].

Excess body weight poses one of the most serious public health challenges of the 21st century for the World Health Organization (WHO) – European Region. It is responsible for more than 1 million deaths and 12 million disability-adjusted life-years (DALYs) in the Region every year [4]. The body mass index is the most commonly used indicator of overweight and obesity as it provides useful estimations of weight – for – height at the population level. In developed countries, obesity is high and has a tendency of growing. In the United States the prevalence rate of obesity is 20% in men and 25% in women, in Canada 35% for men and 27% for women and in Europe ranges from 10–20% among men and 10–25% among women [8–10].

The prevalence of overweight and obesity in Province of Vojvodina (northern part of the Republic of Serbia with 2 031 992 inhabitants) in the 70-ties of the 20th century was 51.6% [11]. A study carried out in 2000 reported 58.5% adults with overweight and obesity, 23% of them were obese [12].

This article provides the most recent prevalence estimates of overweight and obesity based on the representative sample of the Province of Vojvodina in 2006 and examines the trend in overweight and obesity compared with 2000. This article discusses adults aged 20 years and over classified as overweight or obese according to their BMI, based on measured body height and body weight [13, 14]. Impact of education level, gender and age, income, type of settlements, nutrition habits – everyday having breakfast and watching television was explored.

Methods

The Ministry of Health of the Republic of Serbia carried out "The 2006 National Survey for the population of Serbia" (without data on Kosovo and Metohija). The study was conducted as a continuation of the baseline study 2000 in according with its methodology. Target population was an age group of 20 and above who were members of household (persons from particular institutions were not included – old people houses, social institutions, prisons, psychiatric institutions). Sample frame encompassess all households within the census for 2002 in Serbia.

A stratified two-stage sample of the population was used. In Serbia, six geographic areas were identified as main stratum in the sample – Vojvodina, Belgrade, Central, West, Eastern and South East Serbia. The further stratum classification was to the urban and rural areas. Two-stage sampling was conducted so that in the first stage census circles selected by the Propability Proportional Sampling were distinguished. In the second stage households were selected (10 households and 3 reserves from the list) by the Simple Random Sampling Without Replacement.

A sample was chosen as to reliable statistical evaluation for all characters whose frequency of appearance was above 5%. For the total population, relative error of 5% of evaluated proportions was anticipated. Concerning requirements for precise evaluation and the level of the obtained evaluation relialibility, the number of examinees that enable sufficient size of sample according to stratums was selected. The poll included 6 156 households in Serbia (14 522 adult persons aged 20 and above). The survey conducted in the Province of Vojvodina covered 1 810 households (1 060 in town and 750 in other settlements) when 3 854 adults were examined.

Measurement of body mass was performed using a decimal scale in kilograms, after taking off shoes and excess clothing. The weight was measured to the nearest 100 g. Height was measured to the nearest 0.1 cm, without shoes, using a specially mounted metal centimeter ruler. Body mass index was calculated as weight in kilograms, divided by height in m^2. Those with a BMI 25.0–29.9 kg/m^2 were classified as overweight, while those with BMI $\geq$ 30.0 kg/m^2 were classified as obese [13, 14]. Obesity was divided into three categories, with successive values representing escalating health risk [2]. People in class I (BMI 30.0 to 34.9 kg/m^2) had a high risk of developing health problems. For those in Class II (BMI 35.0 to 39.9 kg/m^2), the risk was very high, and in class III (BMI 40 kg/m^2 or more), extremely high [15].

Data on age and sex, education, marital status, types of settlements, household income, nutrition habits – regular having breakfast and watching TV were obtained by questionnaire.

Educational level was categorized as primary (elementary complete and incomplete school), secondary (secondary completed) and postsecondary (any college or university), marital status as being married or single while types of settlements as town and other settlements. Household income according to the wealth index was divided into five levels – the poorest (first level), poorer (second level), middle class (third level), richer (fourth level) and the richest (fifth level). Waching TV and regular having breakfast were estimated for the previous week.

The obtained data were statistically processed using the SPSS version 14.0. Statistical analysis was done using descriptive and inferential statistics. The results are given as mean ± SD and proportion. Differences in frequency were tested by χ^2 test. Differences between two sample means were tested by applying Student's *t*-test (for both *p* values < 0.05 were considered to be statistically significant). All the reported *p* values were two-tailed. In construction of a model to connect obesity and potential risk factors, multivariate logistic regression was used, where we analyzed the

effect of an independent variable if it is controlled for the other factors. Importance of each variable included in the model was verified by examination of the Wald statistics. Any variable whose univariable test (with dependent variable obesity) had $p < 0.10$ was a candidate for the multivariable model along with all variables of known clinical importance: sex, age, type of settlements, married status, education level, income, regular intake of breakfast, lunch, supper and snacks, physical activity in spare time, frequency of physical activity, watching TV (full model). Variables were selected by backward elimination (probability for removal was 0.25). Model fit was analyzed by using a classification table (cut-off 0.50), for calculation sensitivity and specificity.

Results

In 2006 a research carried out in Vojvodina estimated that more than one third of population aged 20 and more were overweight, while more than one fifth of population was obese.

The prevalence rate for overweight was 35.7% (95% CI: 34.1–37.2) and 21.7% for obesity (95% CI: 20.4–23.0). Rates of overweight and obesity vary depending on age and sex. The prevalence of overweight in men (41.1%) was higher than in women (30.9%) ($p < 0.001$) while the prevalence of obesity was 23.1% in women and 20.2% in men ($p = 0.035$). The prevalence of overweight and obesity defined by BMI showed an increase up to the age 69, and thereafter the prevalence decreased. For both sexes, overweight rates were lowest at the age 20–29 (29.6% – men and 11.5% – women) and highest at the age 60–69 (44.8% men and 39.1% women) while obesity rates were lowest at age 20–29 years (9.7% men and 7.7% women) and peaked to men aged 50–59 (25.1%) and women aged 60–69 years (37.8%) (Table 1, Figure 1).

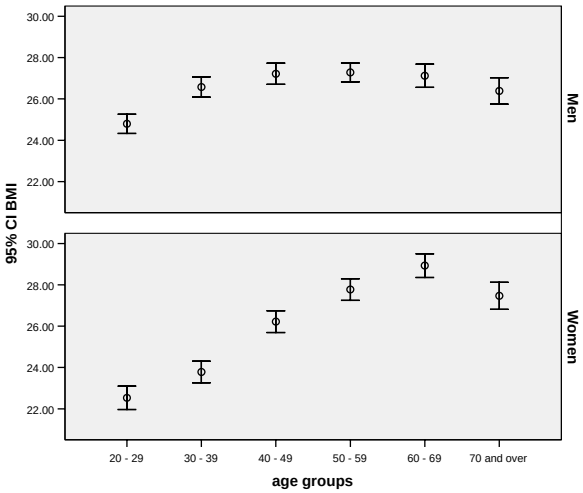

Fig. 1 – Mean Body Mass Index (BMI) by sex and age groups (bars = 95% Cis)

There were no statistically significant differences in overweight of adult population in the Province of Vojvodina in 2000 (35.2%) and in 2006 (35.7%), as well as obesity (23.2% in 2000 to 21.7% in 2006). An average BMI of adults was 26.66 ± 5.19 kg/m^2 in 2000 and 26.45 ± 4.96 kg/m^2 in 2006. Among obese people BMI varied greatly. In 2006, 15.6% of population had a BMI class I, 4.6% were class II, while 1.5% class III. There were no statistically significant differences in those three categories in 2000 and 2006 (Table 2).

Table 1

Age – specific prevalence (%) of overweight and obesity among men and women

Sex	Age – specific prevalence (%) of overweight*						Total
	20–29	30–39	40–49	50–59	60–69	> 70	
Men	29.6	43.1	43.9	42.9	44.8	42.4	41.1
Women	11.5	20.5	35.3	38.3	39.1	34.4	30.9
Total	20.7	32.1	39.5	40.5	41.6	37.6	35.7
Sex	Age – specific prevalence (%) of overweight*						Total
	20–29	30–39	40–49	50–59	60–69	> 70	
Men	9.7	17.7	24.5	25.1	23.0	19.4	20.2
Women	7.7	8.2	19.3	30.9	37.8	29.6	23.1
Total	8.7	13.1	21.9	28.1	31.3	25.5	21.7

* Overweight definied as body mass index (BMI) of 25.0–29.9 kg/m^2
\+ Obesity definied as BMI ≥ 30 kg/m^2

Table 2

Percentage distribution of body mass index (BMI) by sex, population aged 20 or older, Province of Vojvodina, 2000 and 2006

BMI	Both sexes		Men		Women	
	2000	2006	2000	2006	2000	2006
Underweight	2.4	2.5	1.0	1.2	3.5	3.7
Normal weight	39.2	40.0	37.5	37.5	40.4	42.3
Overweight	35.2	35.7	41.7	41.1	30.3	30.9
Obese Class I	16.5	15.6	15.7	15.8	17.0	15.5
Obese Class II	4.9	4.6	3.5	3.3	6.0	5.8
Obese Class III	1.8	1.5	0.6	1.0	2.8	1.9
Obese	23.2	21.7	19.8	20.2	25.8	23.1
Overweight and Obese	58.4	57.4	61.6	61.3	56.1	54.0
Average BMI (kg/m^2)	26.66	26.45	26.54	26.61	26.77	26.31

Statistically important decrease of the prevalence of overweight occurred in 2006 compared with 2000 among women aged 20–29 ($p = 0.027$) and obesity in women aged 50–59 ($p = 0.001$) and 70 and over ($p = 0.040$).

The association between obesity (including overweight BMI ≥ 25 kg/m^2) and potential risk factors is shown in Table 3.

Table 3

Association between overweight and obesity* and potential risk factors obtained by use of logistic regression

Explanatory variables	Unstandardized coefficient (B)	Wald statistics	*p*	(95% CI)
Sex				
women				1.000
men	0.411	29.013	< 0.001	1.509 (1.299–1.752)
Age		242.79	< 0.001	
20–29				1.000
30–39	0.514	14.402	< 0.001	1.672 (1.282–2.180)
40–49	1.191	78.884	< 0.001	3.289 (2.529–4.278)
50–59	1.570	136.02	< 0.001	4.808 (3.693–6.260)
60–69	1.886	163.29	< 0.001	6.590 (4.935–8.800)
70 and over	1.503	104.14	< 0.001	4.497 (3.369–6.002)
Type of settlements				
urban				1.000
rural	0.260	10.356	0.001	1.296 (1.107–1.519)
Marital status				
married				1.000
unmarried	-0.304	13.121	< 0.001	0.738 (0.626–0.870)
Education level		7.914	0.019	
primary school				1.000
secondary school	-0.079	0.700	0.403	0.924 (0.767–1.113)
college, University	-0.387	7.605	0.006	0.679 (0.515–0.894)
Household income		22.949	< 0.001	
first				1.000
second	0.234	4.253	0.039	1.264 (1.012–1.578)
third	0.434	12.267	< 0.001	1.544 (1.211–1.969)
fourth	0.450	12.432	0.001	1.569 (1.221–2.015)
the richest	0.649	18.730	< 0.001	1.913 (1.426–2.566)
Breakfast				
always				1.000
never/sometimes	0.095	1.334	0.248	1.100 (0.936–1.293)
Watching TV		12.052	0.002	
never				1.000
sometimes	0.526	10.108	0.001	1.692 (1.223–2.340)
always	0.566	11.998	0.001	1.760 (1.278–2.424)
constant	-1.805	66.576	< 0.001	

*Dependent variable: overweight and obesity (BMI ≥ 25 kg/m^2)

The results of logistic regression, which was used to evaluate factors that were associated with odds of being overweight or obese recognized by indication that increasing ageing influences increased incidence of overweight and obesity. Males had 50.9% greater odds for obesity regarding to females. Rural examinees had 29.6% greater odds for obesity regarding those from urban settlements. Marital status had a significant association with obesity, so single examinees (non-married, divorced, widowhood) had 26.2% less odds for obesity regarding to married examinees. Increased educational level influenced decreased odds for obesity, so examinees with secondary school had 7.6% less odds for obesity regarding those with lower educational level (without education, incomplete or finished elementary school), i.e. 32.1% less odds for obesity had examinees with finished college or university. Improved income was followed by the increased odds for obesity. The richest examinees had nearly two times greater odds for obesity regarding the poorest population. Examinees that never/sometimes having breakfast had 10.0% greater odds for obesity regarding examinees have regular breakfasts. More frequent watching TV increased odds for obesity, so examinees who frequently watched TV had 76.0% greater odds for obesity as compared to those who did not. Sensitivity for the Logistic regression model (Table 3) for prediction obesity was 81.8% and specificity 45.8%. Overall rate of correct classification was 66.5%.

Discussion

National health survey of Serbia 2006 indicated that 54.5% of adult population of the Republic of Serbia was overweight, subdivided as 18.3% obese and 36.2% preobese. The highest percentage of obese people was found in population of Vojvodina (21.7%) and eastern Serbia (21.4%) [16].

The surveys carried out in the Province of Vojvodina (2000 and 2006 year) indicated that a higher proportion of men were in the overweight category than women, while

proportion of women were more present in the obese category. Compared to 2000 decrease of the prevalence of overweight occurred in 2006 among women aged 20–29 ($p = 0.027$) while obesity decreased in women aged 50–59 ($p = 0.001$) and 70 and over ($p = 0.040$). In 2000, higher prevalence of obesity was in women aged 50 years and over. In 2006, the prevalence of obesity was lower in young women than in young men, except the age of 30–39 when obesity prevalence was higher in men than in women ($p = 0.001$) while in the age 60 and over ($p < 0.001$) prevalence of obesity was higher in women.

The high prevalence of overweight and obesity in Vojvodina is still lower than the reported rate for 2003–2004 from the United States (66.3%), but is very similar to the reported data from an Australian study in 1999–2000 AusDiab (59.8%) and Canada (51.3%) [17–19]. Increasing levels of adult overweight and obesity can be found through Europe, although there are variations in prevalence. In parts of Europe the combination of overweight and obesity in men exceeds even 67% prevalence found in the United States most recent measured survey. Finland, Germany, Greece, Cyprus, the Czech Republic, Slovakia and Malta all have overweight rates which surpass that of the USA. Discussing on obesity alone, at least nine European countries have male obesity rates above 20%, including Greece and Cyprus reaching 27%. For women obesity levels vary from 10 to 26% in the Czech Republic. In at least seven countries one in five women is obese [20]. Population of Vojvodina, with 23.1% obese women and 20.2% obese men is one of severely affected European populations.

The results of our research indicate that there is a strong correlation between sex and age pattern of BMI. The prevalence of overweight and obesity are lower in women than in men and are increasing with ageing. Similar results were also found in some other research [18].

We found a consistent relationship between lower educational level and overweight and obesity. These findings are supported by other studies [21]. Strong association was found between BMI and marital status. We confirmed results from other studies [22]. Marriage was associated with a weight gain while unmarried status, divorce or widowhood with a weight loss. One of the examined factors was type of settlements. People from villages had a higher chance for overweight and obesity than those from towns. On the other hand, there was no difference in prevalence of overweight and obesity in rural and urban areas of ten European countries [23]. Increase in income was followed with a chance for overweight and obesity. The richest people showed two times higher odds for overweight and obesity compared with the poorest people. Similar results were obtained in other studies, too [24]. People who never/sometimes had breakfast had higher odds for overweight and obesity compared with those who had regular breakfast. This was found in many studies [25–27]. Regular television watching showed a significant correlation with overweight and obesity. Similar results are found in some other surveys [18].

Conclusion

The existing situation concerning a high prevalence of obesity in the Province of Vojvodina requires urgent public health action. It is essential to develop preventive public health strategies which would affect the whole society. Healthy lifestyle, combined with balanced nutrition with low energy intake and increased physical activity have be promoted, but it is not a responsibility of individuals only. Health services, community, food industry, mass media etc, have a crucial role in modification of environment in a way that it will be a less supportive for increase of body weight. Strategy of prevention and management of obesity should be in accordance with the existing public health policy and program for prevention of non-communicable diseases.

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L I T E R A T U R A

1. *Goodman C, Ayodola A.* What Is Known About the Effectiveness of Economic Instruments to Reduce Consumption of Foods High in Saturated Fats and Other Energy-Dense Foods for Preventing and Treating Obesity? Copenhagen:Health Evidence Network; World Health Organization 2006.
2. *World Health Organization.* Obesity. Preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: WHO; 1998.
3. *Popkin BM, Doak CM.* The obesity epidemic is a worldwide phenomenon. Nutr Rev 1998; 56(4 Pt 1): 106–14.
4. *James WPT, Jackson-Leach R, Mhurchu C.* Overweight and obesity (high body mass index). In: *Ezzati M, Lopez AD, Rodgers A, Murray CJL,* editors. Comparative quantification of health risks: the global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization; 2004. p. 497–596.
5. *World Health Organization.* Food and health in Europe: a new basis for action. Copenhagen: WHO; 2002.
6. *Poobalan AS, Aucott LS, Smith WC, Avenell A, Jung R, Broom J.* Long-term weight loss effects on all cause mortality in overweight/obese populations. Obes Rev 2007; 8(6): 503–13.
7. *Manson JE, Stampfer MJ, Hennekens CH, Willett WC.* Body weight and longevity. A reassessment. JAMA 1987; 257(3): 353–8.
8. *Torrance GM, Hooper MD, Reeder BA.* Trends in overweight and obesity among adults in Canada (1970-1992): evidence from national surveys using measured height and weight. Int J Obes Relat Metab Disord 2002; 26(6): 797–804.
9. *Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM.* Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006; 295(13): 1549–55.

10. *Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL*. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord 1998; 22(1): 39–47.
11. *Mirilov M, Svirčević A, Jakovljević Đ, Trifunović S, Stanulović D, Popović B.* Importance of the nutrition in overall protection of the cardiovascular diseases. Hrana i ishrana 1979; 9(12): 241–6. (Serbian)
12. *Grujić V*. Health status, health needs and utilization of the health sevices among the population of Serbia. Glasnik Instituta za zaštitu zdravlja Srbije; 2002; 1(2): 26–147. (Serbian)
13. *Republic Professional Committee for Creating and Implamentation Guides in Clinical Practice*. Obesity – National guide for physicians in primary health care. The Ministry of Health of the Republic of Serbia, 2004. (Serbian)
14. *World Health Organization*. Physical Status: The use and interpretation of. Anthropometry. Geneva: Report of a WHO Expert Committee; 1995.
15. *Katzmarzyk PT*, *Mason C*. Prevalence of class I, II and III obesity in Canada. CMAJ *2006*; 174(2): 156–7.
16. *Ministry of Health of the Republic of Serbia*. National Health Survey Serbia, 2006. Beograd: Key findings; 2007. p. 249–60.
17. *Cameron AJ, Welborn TA, Zimmet PZ, Dunstan DW, Owen N, Salmon J,* et al. Overweight and obesity in Australia: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Med J Aust 2003; 178(9): 427–32.
18. *Tjepkema M*. Adult obesity in Canada: measured heigh and weight. Ottawa: Statistics Canada; 2005.
19. *Lobstein T*, *Rigby N*, *Leach R*. UE Platform on diet, physical activity and health. Brussel: International Obesity Task Force Eu Platform Briefing Paper in collaboration with the European association for the study of obesity; 2005; 15: 1–8.
20. *Panagiotakos DB, Pitsavos C, Chrysohoou C, Risvas G, Kontogianni MD, Zampelas A,* et al. Epidemiology of overweight and obesity in a Greek adult population: the ATTICA Study. Obes Res 2004; 12(12): 1914–20.
21. *Cameron AJ, Welborn TA, Zimmet PZ, Dunstan DW, Owen N, Salmon J,* et al. Overweight and Obesity in Adults. Australia, Canberra: Australian Bureau of Statistics. 2004-05.
22. *Peytremann-Bridevaux I, Faeh D, Santos-Eggimann B*. Prevalence of overweight and obesity in rural and urban settings of 10 European countries. Prev Med 2007; 44(5): 442–6.
23. *Pickett KE, Kelly S, Brunner E, Lobstein T, Wilkinson RG*. Wider income gaps, wider waistbands? An ecological study of obesity and income inequality. J Epidemiol Community Health 2005; 59(8): 670–4.
24. *Haines PS, Guilkey DK, Popkin BM*. Trends in breakfast consumption of US adults between 1965 and 1991. J Am Diet Assoc 1996; 96(5): 464-70.
25. Adams M. Missing breakfast may lead to obesity, new study findings. [serial outline]. 2005 February 14. Avalailble from: http://www.naturalnews .com./004603.html/.
26. *Cho S, Dietrich M, Brown CJ, Clark CA, Block G*. The effect of breakfast type on total daily energy intake and body mass index: results from the Third National Health and Nutrition Examination Survey (NHANES III). J Am Coll Nutr 2003; 22(4): 296–302.

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Presence of anatomical variations of the circle of Willis in patients undergoing surgical treatment for ruptured intracranial aneurysms

Prisustvo anatomskih varijacija Willis-ovog prstena kod operativno lečenih bolesnika nakon rupture intrakranijalnih aneurizmi

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Abstract

Bacground/Aim. The presence of aneurysmal changes on the brain blood vessels has been subject to numerous research. This study investigated the relation between ruptured aneurysms and anatomical configuration of the Circle of Willis, with the purpose to obtain an insight into their mutual connection. **Methods.** The analysis included 114 patients suffering from ruptured intracranial aneurysms. Preoperative cerebral angiography was performed and compared with the intraoperative findings in order to attain a precise insight into morphological changes occurring on the circle of Willis. **Results.** The prevalence of asymmetrical Willis in the whole group of patients was 64%. Within the group of patients suffering from multiple aneurysms, the presence of asymmetrical Willis' circle was 75.7%. The highest incidence of the asymmetrical Circle of Willis was found among patients with aneurysmal rupture detected at the anterior comunicative artery (ACoA) site (72.7% among cases with solitary and 100% among those with multiple aneurysms). Morphological changes on the A1 segment of ACoA were observed in 50 (44%) cases, with higher incidence found on the right side (60%). When comparing location of ruptured aneurysms between genders, a statistically significant prevalence of the ruptured aneurisms on ACoA was present in men, whereas women showed higher incidence of ruptured aneurysms on interior cartid artery (ICA) site ($p < 0.01$). The linkage between aneurysms with hypoplasia of the A1 segment of ACA and decreasing of the angle at which segments A1 and A2 join suggests the relationship between their onset, corresponding configuration type of Willis and subsequent hemodynamic changes. **Conclusion.** High incidence of asymmetry of Willis circle in the group of patients with ruptured aneurysms imply association of asymmetrical configuration and disorder in haemodynamic relations with forming and rupture of intracranial aneurysms.

Key words:
anatomy; central nervous system vascular malformations; circle of willis; intracranial aneurysm; aneurysm, ruptured.

Apstrakt

Uvod/Cilj. Prisustvo aneurizmatskih promena na krvnim sudovima mozga predmet je mnogih istraživanja. U ovom radu ispitivan je odnos rupturisanih aneurizmi sa anatomskom konfiguracijom vilisovog prstena u cilju sagledavanja njihove međusobne povezanosti. **Metode.** Analizi je bilo podvrgnuto 114 bolesnika sa rupturisanim intrakranijalnim aneurizmama. Analiziran je preoperativni angiografski nalaz i upoređivan sa intraoperativnim nalazom. Precizirane su morfološke promene na Wilis-ovom prstenu koje su bile predmet posmatranja. **Rezultati.** Zastupljenost asimetričnog Willis-ovog prstena u celokupnoj grupi bolesnika bila je 64%. U grupi bolesnika sa multiplim aneurizmama asimetričnost Willis-ovog prstena bila je zastupljena 75,7%. Najveća zastupljenost asimetrije Willis-onovog prstena bila je u grupi bolesnika sa rupturom aneurizme na prednjoj komunikativnoj arteriji (AcoA) – 72,7% u grupi solitarnih i 100% u grupi multiplih. Morfološke promene na A1 segmentu ACoA nađene su kod 50 (44%) ispitanika, pri čemu je veća zastupljenost promena bila na desnoj strani (60%). Upoređujući lokalizaciju rupturisanih aneurizmi između polova, utvrđena je statistički značajna zastupljenost rupture aneurizmi na AcoA kod muškaraca i rupture aneurizmi na unutrašnjoj karotidnoj arteriji (*Inferior Carotid Artery* - ICA) kod žena ($p < 0,01$). Povezanost aneurizmi sa hipoplazijom A1 segmenta ACoA i sa smanjenjem ugla spajanja A1 i A2 segmenta, jasno je ukazala na povezanost njihovog nastajanja sa odgovarajućim tipom konfiguracije Willlis-ovog prstena i posledičnih hemodinamskih promena. **Zaključak.** Visoka zastupljenost asimetrije Willis-ovog prstena u grupi bolesnika sa rupturisanim aneurizmama ukazuje na povezanost asimetrične konfiguracije i poremećenih hemodinamskih odnosa sa formiranjem i rupturom intrakranijalnih aneurizmi.

Ključne reči:
anatomija; anomalije; vilisov arterijski prsten; aneurizma, intrakranijalna; aneurizma, ruptura.

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Introduction

The presence of hypoplastic segments in certain parts of Willis' circle was established in a number of autopsies [1–6]. A significant incidence of such variations of the circle of Willis in the overall population points to an inability to define them as pathological changes, that is, anatomical variations of Willis, but rather as its types. Anatomical anomalies can be defined as rare changes appearing on the brain blood vessels which can hardly be related to the normal brain perfusion. On the other hand, redistribution of flow and involvement of the respective adaptive mechanisms of Willis, were not found to contribute to disorders in the brain perfusion needs [7–11].

Disturbed flow in certain anatomical variations of Willis' circle might, partialy, cause changes in the blood hitwave which, accompanied with the existing weakness of the blood vessels at these sites, could represent a factor responsible for aneursysmal formation [12–18]. The linkage between aneurysms and variations of Willis was investigated in a number of studies [19–21].

The aim of this study was to check relevant facts delienating the linkage between aneurysms and anatomical variations of the Circle of Willis.

Methods

In the period between 2006 and 2007, an investigation was made on a series of 114 patients surgically treated for ruptured intracranial aneurysms. The patients were observed with regard to gender, age, number of aneurysms, time of rupture, location, size and the presence or absence of morphological changes in the brain blood vessels and anterior segment of the circle of Willis. Rupture had been diagnosed by means of clinical manifestation, computerized tomography finding and cerebral angiography of the brain blood vessels. A detailed analysis of cerebral angiography was performed prior to surgery to determine the relation to Willis' elements, as well as its size and relation to the mother and surrounding blood vessels. The aneurysmal site was viewed in relation to the anterior communicative artery (AcoA), Medial carotid artery (MCA), interior carotid artery (ICA) and pericalose artery (PerA). The presence or absence of morphological changes on blood vessels were determined by means of diameter analysis, whereby symmetry/asymmetry of these changes was also considered. A diameter of a respective blood vessel was now compared with a diameter of the symmetrical blood vessel opposite it. Narrowing of the blood vessel diameter by one third or two thirds, as compared to the opposite blood vessel diameter, was denoted as 'hypoplasia', whereas such narrowing by less than 1/3 was marked as 'extreme hypoplasia'. The presence of ICA angulation after PcoA separated from its supraclinoid part by less than 120°, was marked as "extreme ICA angulation". The MCA bifurcation angle over 90° was marked as "atypical branching". The presence or absence of these elements on one side pointed to the symmetrical of asymmetrical configuration of the Willis. The connection was monitored between the site or aneurysmal change and changes present on Willis' circle, and the obtained findings were examined and corrected after getting an intraoperative insight. Apart from monitoring the overall group for changes on Willis' circle, two separate groups were examined for ruptured solitary and multiple aneurysms, aimed at measuring the incidence of respective changes and possible interrelation between these and multiplicity. The results were displayed as absolute numbers and percentage. Comparing the obtained findings was completed within the respective groups with regard to the position of the aneurysm and incidence of morphological changes found on Willis' circle. To determine the statistical significance, *t* test or non-parameter Mann-Witney rank-sum test was used. Numerical parameters were presented as a mean value (X) ± standard deviation (SD).

Results

Of 114 patients, 68 (59.7%) were women and 46 (40.3%) men. Solitary aneurysms were found in 81 (71%) cases, whereas 33 (29%) subjects had multiple aneurisms. Aneurismal rupture occurred on the average at the age of 52 ± 10.58 years, with earlier presence recorded in men (48 ± 9.74 years).

In terms of location, in the group of solitary aneurysms, ruptures were present in 40.7% of the patients at ACoA site, on the carotid artery in 27.2% (sum location of PCoA 14.8% and ICA 12.4%; in the branching of the MCA in 24.7%). In our series, aneurysms of Oer A (4.9%) and a. basilaris (2.5%) were present only in the female patients. Rupture of solitary aneurysm most often found in men was localized on ACoA (58.8%), on MCA (23.5%) and ICA (aneurysms on PCoA included) in 17.6%. In women, distribution of ruptured aneurysms greatly differed: ruptures on ACoA was present in 27.7%, on MCA in 25.5% and on ICA (aneurysms on PCoA included) in 34%. By comparing the location of ruptured aneurisms across genders, we were able to determine statistically significant prevalence of aneurysms on ACoA site in men, and aneurysmal rupture on ICA in women ($p < 0.01$). With regard to location and size, we found that aneurysms on ACoA site ruptured in 81.9% at the size of 3–10 mm, on MCA and ICA in 60%, whereas ruptures on PCoA occurred in 83.9%, which in total, concerning this size on ICA, was 72.7% (Table 1).

The data of patients with solitary aneurisms are shown in Table 2.

Of the total of 33 aneurysms found on ACoA segment 75.7% of morphological changes were present on A1 segment and ACoA (45.5% of various degree hypoplasias of the right A1, 27.2% of the left A1 and 3% of ACoA fenestrations) (Figure 1).

Of the total of 20 aneurysms localized on MCA 35% were found with morphologically atypical Willis' circle (20% atypical MCA branching and 15% hypoplasia of A1 segment).

In 60% of the total of 10 aneurysms localized on ICA the presence of morphological changes on the anterior seg-

Table 1

Size of ruptured solitary aneurysms and locations

Locations of aneurysms	Size of aneurysms (mm)					Total (%)
	< 3	3–6	7–10	11–25	> 25	
ACoA	/	10	17	5	1	33 (40.7)
MCA	2	5	7	2	4	20 (24.7)
ICA	/	2	4	2	2	10 (12.4)
PCoA	1	5	5	1	/	12 (14.8)
PerA	/	1	2	/	1	4 (4.9)
VB	/	/	2	/	/	2 (2.5)
Total (%)	3 (3.7)	23 (28.4)	37 (45.7)	10 (12.4)	8 (9.8)	81 (100.0)

ACoA – Anterior Communicative Artery; MCA – Medial Cerebral Artery; ICA – Interior Carotid Artery;
PCoA – Posterior Communicative Artery; PerA – Pericalosis Artery; VB – Vertebrobasilar Artery

Table 2

Morphological changes of cerebral vessels in patients with solitary aneurysms

Locations of aneurysms	With no morphological changes	With morphological changes				Total
		Type of changes	left	right	left + right	
ACoA	6	hypoplasia A1	9	15	24	33
		Fenestration AcoA	1	2	3	
		a. mediana cor. call.				
MCA	13	hypoplasia A1	1	2	7	20
		atypical branching of MCA	2	2		
ICA	4	hypoplasia A1	2	/	6	10
		fetal type PCoA	1	/		
		hypoplasia PCoA	1	/		
		prominent angulation of ICA	2	/		
PcoA	4	fetal type PcoA-hypoplasia A1	1	1	8	12
		hipoplasia PCoA	1	2		
		prominent angulation of ICA	1	2		
PerA	1	hypoplasia A1	/	2	3	4
		hypoplasia *a. pericalosis*	1	/		
VB	2			/		2
Total	30				51	81

ACoA – Anterior Communicative Artery; MCA – Medial Cerebral Artery; ICA – Interior Carotid Artery;
PCoA – Posterior Communicative Artery; PerA – Pericalosis Artery; VB – Vertebrobasilar Artery

ment of Willis' circle was detected, right-side presentation in 65% (Figure 2).

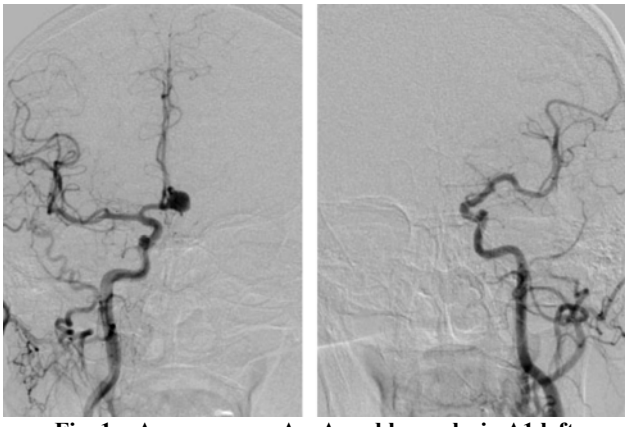

Fig. 1 – Aneurysm on AcoA and hypoplasia A1 left

Of the total of 12 aneurysms found on the postrior communicative artery (PCoA) morphologically atypical Willis' circle was present in 66.7%. Their right-side presentation was recorded in the same percentage (Figure 3).

A 70% of the total of four aneurysms localized on a. pericalosys (APer) was present with the morphologically atypical Willis' circle.

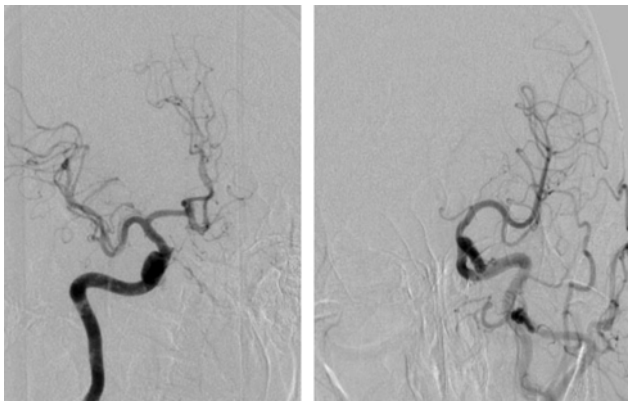

Fig. 2 – Aneurysm on ICA left and hypoplasia A1 left

The data on patients with multiple aneurisms viewed in relation to the site of ruptured aneurism are shown in Table 3.

Of 81 patients with solitary aneurysm, in 48 (59.2%) cases, certain morphological changes were found on the anterior segment of Willis' circle. In 33 (40.7%) patients changes were registered on the A1 segment of ACoA, with more changes found on the right side.

In the group of 33 patients with multiple aneurysms, 25 (59.2%) were found with morphological changes on the anterior segment of Willis' circle. In 17 (51.5%) changes on A1

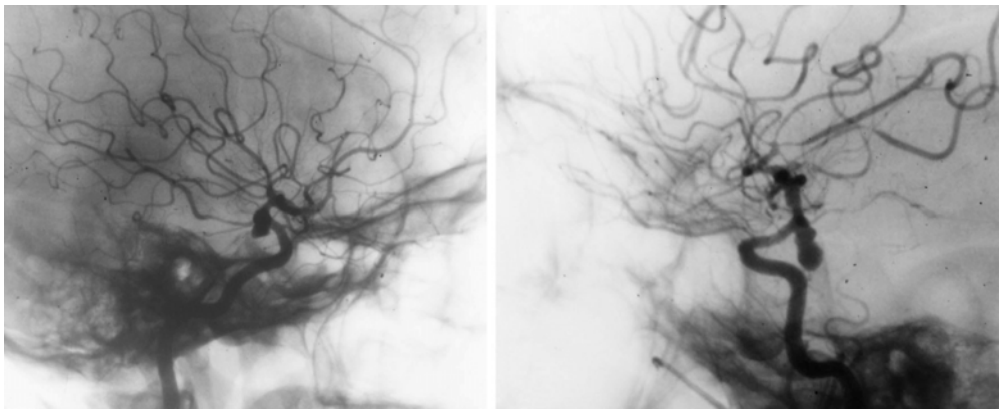

Fig. 3 – Prominent angulation of ICA with aneurysms on PcoA bill.

Table 3

Morphological changes of cerebral vessels in patients with multiple aneurysms

Locations of aneurysms	With no morphological changes	With morphological changes				Total
		Type of changes	left	right	left+ right	
ACoA	/	hypoplasia A1 prominent hypoplasia A1	3 /	7 2	12	12
MCA	4	atypical branching of MCA fetal type PCoA	2 2	2 /	6	10
ICA	2	hypopasia A1sin-hypoplasia PCoA fetal type PCoA prominent angulation of ICA bill	2 / /	/ 1 1	4	6
PCoA	2	hypoplasia A1/fetal type PCoA dex(1) and hypoplasia PCoA dex(2)/	2	1	3	5
Total	8				25	33

ACoA – Anterior Communicative Artery; MCA – Medial Cerebral Artery; ICA – Interior Carotid Artery; PCoA – Posterior Communicative Artery.

segment of ACoA were registered. The entire group of patients had 73 (64%) cases with morphological changes on Willis' circle which caused certain types of its asymmetry, the higher percent of asymmetry being present in multiple aneurysms. Morphological changes on the A1 segment of ACoA were found in 50 (44%) cases, with the prevalence of changes on the right side (60%).

Discussion

A total number of aneurysms with left-side or right-side presentation or dominant flow did not show any difference. However, higher number of aneurysms was noticed on ACoA with dominant left-side flow (46.3%) as compared to their presence on ACoA with the dominant right-side flow

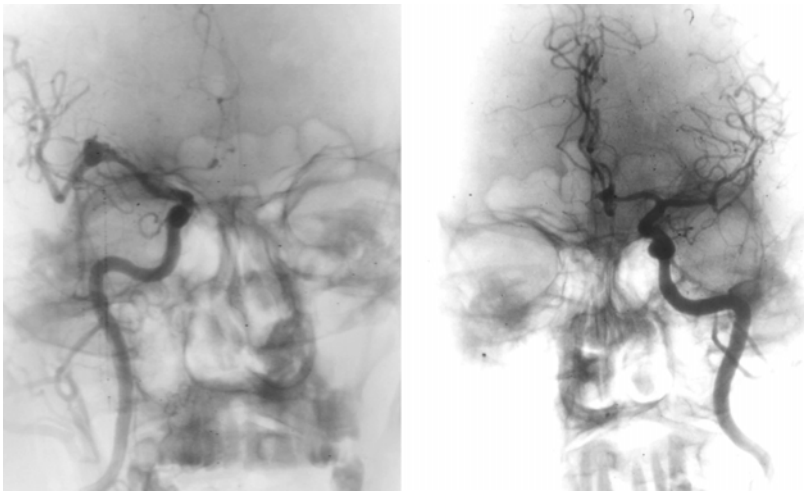

Fig. 4 – Aneurysms on MCA right and on AcoA with hypoplasia A1 right

(31%). Such presentation on ACoA is associated with higher incidence of hypoplasia of the right A1 segment, which was in our series present 60%. Some series indicated a three times more common hypoplasia of the A1 segment on the right side than on the left one. A higher incidence of aneurysms on the right MCA (31%) and right PCoA (21.8%) compared to the left MCA (24%) and left PCoA (9.3%), could be ascribed to a higher blood flow from the carotid artery towards the MCA due to a decreased flow through the hypoplastic A1 segment [8, 22–24].

Also, right-side hypoplasias of the A1 segment were present in two thirds of the cases, thus being correlated with other studies [20–22].

The linkage between A1 segment hypoplasias and aneurysmal formations on AcoA was found to be directly dependent on the hemodynamic adaptation of the AcoA to regulate the collateral flow and ensure adequate perfusion. Arterial tolerance to collateral circulation through ACoA is a diameter 0.4–0.6 mm [12, 13]. An increase in diameter by 0.4–1.6 mm in the physiological conditions of a limited flow through some of the A1 segments, will supply normal flow in the distal segments [24]. However, in the circumstances of hypoplasia or aplasia of some of the A1 segments, the ACoA diameter increases and shunt flow establishes [13]. It is noteworthy that this process stands in direct correlation with the perfusion needs of the corresponding irrigation areas, and as such it starts immediately after embryogenesis. Once formed, shunt flow can meet perfusion needs without further ultrastructural degradation on a blood vessels joint elements. Remodelling of blood vessels to provide adequate perfusion, can be stopped at the moment of establishing suitable collateral circulation [25].

If compared with the rest of intracranial arteries, the efficacy of ACoA vasodilatation will be limited as it is the only cerebral artery developing from the plexiform blood vessel complex [26]. In cases of further increase beyond the limit through the ACoA, blood flow becomes more turbulent and laminar movement ceases to exist. The ACoA-A2 joint begins to function as a stagnation point of a hemodynamic strike [13]. The flow itself through norm-plastic A1 segment and enlarged ACoA increases by 50% and more (from 214 mL/min to 303 mL/min) [8]. The effect of hemodynamic strike on blood vessels wall is directly dependent on the flow way and direction of the hit wave. The latter depends on the angle of A1–A2 joining, which in aneurysms on ACoA was significantly smaller and ranged between 103 and 116 degrees, whereas in norm-plastic segments it was approximately 143 degrees [13].

An increased flow through the collateral ACoA system, accompanied by diversion from the optimal bifurcation angle at the A1–A2 link, can greatly influence the increase of stress on blood vessel's wall, thus being directly responsible, along with turbulent flow, for the forming of degenerative lesions of the intimae and endothelium. The stress on the wall in the region of stationary points can under such conditions become 5–10 times higher than the normal intra-arterial stress which naturally ranges between 1.0–2.0 Pa [4, 25–29, 32, 36].

A linkage between aneurysm and hypoplasia of the A1 segment and decreasing of the A1–A2 joining angle, points clearly to the connection between their forming, corresponding configuration type of Willis and consequential hemodynamic changes.

When we investigated the location of aneurysms on ICA, separated from the aneurysms on PCoA, we noticed that 70% of them had left presentation. In 60% of the cases, morphological specificities were observed on Willis' circle in terms of extreme angulations of the carotid artery after separation of the PCoA, and the presence of hypoplasia on the A1 segment and changes on PCoA (hypoplasia and phoetal type). Smaller ruptures on ICA (ICA – 12%, PCoA – 14%) compared to their incidence (40%), suggest a significantly lower level of stress in the region of supraclinoid part of the carotid artery, unlike the PCoA complex, or higher adaptability of the carotid artery to destructive changes in its walls and their remodeling [29]. The data supporting this finding were of the 55% incidence rupture on ICA 8 mm, while the incidence of those on ACoA was 60% not bigger than 3 mm [30]. The most common location on ICA is supraclinoid up to the point of PCoA separation. They belong to lateral aneurysms whose growth and rupture are contingent on the flow and radius formed by blood vessel. These are characterized by a stable intra-aneurysmal flow [31, 32], explaining the lower incidence of ruptures on ICA in relation to aneurysmal incidence. More often left-side presentation of the ruptured solitary aneurysms on ICA may be connected to a higher blood flow through the left carotid artery directly going out of the aortal arch and therefore being more prone to excessive cardiovascular mechanisms. Another assumption is that greater perfusion needs of the left brain hemisphere may influence increasing of the blood flow through the carotid artery. These assumptions call for further investigation of the blood flow of magistral blood vessels and their relationship with the cerebral perfusion.

Rupture of ICA aneurisms within multiple aneurysms is characterized by the right-side position. This finding might be in collision with the more common left-side rupture of solitary aneurysms on ICA; however, aneurysmal ruptures on the right ICA were combined with the hypoplasia of the A1 segment and aneurysms on the bifurcation of the left MCA. There is a clear indication that distribution of blood flow through the right A1 segment has direct impact on intensifying the blood flow through the right carotid artery [8], which, depending on the curve of the blood vessel, may influence aneurysmal growth and rupture.

Solitary aneurysms on PCoA ruptured more often on the right side (in nearly 67%). Morphological changes were present in the same percent in the form of hypoplasia or fetal PCoA type, and sharp angulations above the PCoA separation point. Higher right-side incidence of PCoA aneurysms correlates with more frequent changes on PCoA on the right side. The right-side incidence of changes on PCoA becomes more prominent in ruptures on PCoA within the multiple group. Aneurysms localized on PCoA belong to the group of bifurcation aneurysms, their growth and rupture being clearly connected with the distribution of blood vessels and size of

the bifurcation angle. They are characterized by circular intra-aneurysmal flow accountable for high circumferential stress, causing thus a fusiform growth of aneurysm along the length of PCoA [21, 24, 33].

The rupture of solitary aneurysms localized on MCA was not associated with more frequent morphological changes on the Circle of Willis. A bigger bifurcation angle on the media and the hypoplasia of the A1 segment were present in 35%, suggesting another form of hemodynamic and morphological changes was responsible for the forming and growth of aneurysms on the MCA branching.

Aneurysms localized on MCA bifurcations show certain specificities in comparison to other locations. The medial cerebral artery is formed at the earliest stage of embryogenesis from the primitive capillary plexus, and turns laterally as the embryo grows, forming a fan of blood vessels. Morphologically, it is not part of Willis' circle, but in a hemodynamic sense it is directly linked to the distribution of blood within the circle. The end part of the MCA functions as a terminal type bifurcation with the tendency of forming optimal bifurcation geometry, intended at providing minimal apical stress [8, 25, 27]. Maintenance of the static equilibrium of the bifurcation region depends on the ratio between the flow through the afferent and its efferent vessels, and the present bifurcation angle. The tendency of optimal bifurcation geometry is for the larger branches to have smaller angles in relation to the parent vessel, while the ratio between the flow in the branches and that in the parent vessel tends to be smaller or equal to 1.0 m and the angle of branching about 90° [34]. Optimal bifurcation would retain its angle in the circumstances of a more intense blood flow resulting from higher blood pressure or some other hemodynamic disorders [21]. This clearly suggests that inadequate bifurcation geometry was basically responsible for aneurismal formation. Due to inadequate equilibrium between the flow in the afferent and efferent vessels, pulse opening of the bifurcation angle maintains a constant ratio between the transmural pressure in the afferent vessel and its branches. A long-term adapting to pulse bifurcation may lead to degenerative and ultrastructural changes in the vessel's wall [17, 35]. With aging, as a result of dystrophic changes on the brain vessels, their elasticity decreases, and may disable compensatory pulse adaptability of the bifurcation thus impairing redistribution of the transmural pressure due to stress increase in the region of stationary point [36–42].

Conclusion

In the general population, the incidence and distribution of asymmetric configurations of the Circle of willis ranges between 15 and 22%. The asymmetry of Willis in as much as 64% of the cases in this group, indicates a clear linkage between morphological changes occurring as a result of asymmetrical configuration, and disorder of hemodynamic relationships while the brain is supplied with adequate perfusion. Not only due to configuration of Willis with no visible asymmetrical morphological changes, hemodynamic load may occur within elongated and perfusion-loaded joint angles of the asymmetry of Willis. A significantly higher incidence of asymmetry in relation to aneurysmal changes on the brain blood vessels, suggest that the blood flow in the brain is adaptable to higher perfusion needs. Disorder and disturbance of dynamic stability may lead to ultrastructural changes in the walls of blood vessels as a result of higher intra-arterial flow, and possibly trigger off a cascade of mechanisms for pathological adaptation of the wall before it finally causes the forming of aneurismal changes. The notion of significantly smaller aneurysmal ruptures as compared to their incidence in the overall population, make us to speculate on whether the development of aneurysmal changes on the brain blood vessels might be an attempt of a respective brain flow variations at adapting themselves to the higher perfusion needs of certain parts of the brain.

R E F E R E N C E S

1. *Eftekhar B, Dadmehr M, Ansari S, Ghodsi M, Nazparvar B, Ketabchi E.* Are the distributions of variations of circle of Willis different in different populations? - Results of an anatomical study and review of literature. BMC Neurol 2006; 6: 22.
2. *Ardakani SK, Dadmehr M, Nejat F, Ansari S, Eftekhar B, Tajik P,* et al. The cerebral arterial circle (circulus arteriosus cerebri): an anatomical study in fetus and infant samples. Pediatr Neurosurg 2008; 44(5): 388–92.
3. *Kapoor K, Singh B, Dewan LI.* Variations in the configuration of the circle of Willis. Anat Sci Int 2008; 83(2): 96–106.
4. *Inagawa T, Hirano A.* Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol 1990; 34(6): 361–5.
5. *Mackenzie JM.* The anatomy of aneurysm-bearing circles of Willis. Clin Neuropathol 1991; 10(4): 187–9.
6. *Orlandini GE, Ruggiero C, Orlandini SZ, Gulisano M.* Blood vessel size of circulus arteriosus cerebri (circle of Willis): a statistical research on 100 human subjects. Acta Anat (Basel) 1985; 123(1): 72–6.
7. *Lee RM.* Morphology of cerebral arteries. Pharmacol Ther 1995; 66(1): 149–73.
8. *Hendrikse J, van Raamt AF, van der Graaf Y, Mali WP, van der Grond J.* Distribution of cerebral blood flow in the circle of Willis. Radiology 2005; 235(1): 184–9.
9. *Yamaguchi K, Uchino A, Sawada A, Takase Y, Kuroda Y, Kudo S.* Bilateral anterior cerebral artery territory infarction associated with unilateral hypoplasia of the A1 segment: report of two cases. Radiat Med 2004; 22(6): 422–5.
10. *Baumgartner RW, Baumgartner I, Mattle HP, Schroth G.* Transcranial color-coded duplex sonography in the evaluation of collateral flow through the circle of Willis. AJNR Am J Neuroradiol 1997; 18(1): 127–33.
11. *Ferrández A, David T, Bamford J, Scott J, Guthrie A.* Computational models of blood flow in the circle of Willis. Comput Methods Biomech Biomed Engin 2000; 4(1): 1–26.
12. *Burleson AC, Strother CM, Turitto VT.* Computer modeling of intracranial saccular and lateral aneurysms for the study of their hemodynamics. Neurosurgery 1995; 37(4): 774–82;

13. *Ujiie H, Liepsch DW, Goetz M, Yamaguchi R, Yonetani H, Takakura K.* Hemodynamic study of the anterior communicating artery. Stroke 1996; 27(11): 2086–93.
14. *Kayembe KN, Sasahara M, Hazama F.* Cerebral aneurysms and variations in the circle of Willis. Stroke. 1984; 15(5): 846–50.
15. *Ersin E, Apler B, Onder O, Zusuf I, Erdener T.* Haemodinamic effect on the growth of experimentally indiced saccular aneurysms in rats. Anals of Neurosurgery 2002; 2(4): 1–6.
16. *Hashimoto N, Handa H, Nagata I, Hazama F.* Experimentally induced cerebral aneurysms in rats: Part V. Relation of hemodynamics in the circle of Willis to formation of aneurysms. Surg Neurol 1980; 13(1): 41–5.
17. *Hashimoto N, Handa H, Nagata I, Hazama F.* Animal model of cerebral aneurysms: pathology and pathogenesis of induced cerebral aneurysms in rats. Neurol Res 1984; 6(1-2): 33–40.
18. Krex D, Schackert HK, Schackert G. Genesis of cerebral aneurysms--an update. Acta Neurochir (Wien). 2001;143(5):429-48; discussion 448–9.
19. Kayembe KN, Sasahara M, Hazama F. Cerebral aneurysms and variations in the circle of Willis. Stroke. 1984 Sep-Oct;15(5):846–50.
20. Kasuya H, Shimizu T, Nakaya K, Sasahara A, Hori T, Takakura K. Angeles between A1 and A2 segments of the anterior cerebral artery visualized by three-dimensional computed tomographic angiography and association of anterior communicating artery aneurysms. Neurosurg. 1999; 45(1): 89–93; discussion 93–4.
21. *Liou TM, Chang TW, Chang WC. Effects of the bifurcation* angle on the steady flow structure in model saccular aneurysms. Experiments in Fluids 1993; 14(5): 289–95.
22. Kwak R, Niizuma H, Suzuki J. Hemodynamics in the anterior part of the circle of Willis in patients with intracranial aneurysms: a study of cerebral angiography. Tohoku J Exp Med 1980;132(1):69–73.
23. *Hoksbergen AW, Fülesdi B, Legemate DA, Csiba L.* Collateral configuration of the circle of Willis: transcranial color-coded duplex ultrasonography and comparison with postmortem anatomy. Stroke 2000; 31(6): 1346–51.
24. *Cassot F, Vergeur V, Bossuet P, Hillen B, Zagzoule M, Marc-Vergnes JP.* Effects of anterior communicating artery diameter on cerebral hemodynamics in internal carotid artery disease. A model study. Circulation 1995; 92(10): 3122–31.
25. *Liou TM, Chang WC, Liao CC.* Experimental study of steady and pulsatile flows in cerebral aneurysm model of various sizes at branching site. J Biomech Eng 1997; 119(3): 325–32.
26. *Marinković S, Milisavljević M, Kovacević M.* Anatomical bases for surgical approach to the initial segment of the anterior cerebral artery. Microanatomy of Heubner's artery and perforating branches of the anterior cerebral artery. Surg Radiol Anat 1986; 8(1): 7–18.
27. *Ingebrigtsen T, Morgan MK, Faulder K, Ingebrigtsen L, Sparr T, Schirmer H.* Bifurcation geometry and the presence of cerebral artery aneurysms. J Neurosurg 2004; 101(1): 108–13.
28. *Fry DL.* Acute vascular endothelial changes associated with increased blood velocity gradients. Circ Res 1968; 22(2): 165–97.
29. *Kalimo H, Kaste M, Haltia M.* Vascular disease. In: *Graham DI, Lantos PL,*
30. *Okuyama T, Sasamori Y, Takahashi H, Fukuyama K, Saito K.* Study of multiple cerebral aneurysms comprised of both ruptured and unruptured aneurysm-an analysis of incidence rate with respect to site and size. No Shinkei Geka 2004; 32(2): 121–5. (Japanese)
31. *Steiger HJ, Poll A, Liepsch D, Reulen HJ.* Haemodynamic stress in lateral saccular aneurysms. An experimental study. Acta Neurochir (Wien) 1987; 86(3–4): 98–105.
32. *Löw M, Perktold K, Raunig R.* Hemodynamics in rigid and distensible saccular aneurysms: a numerical study of pulsatile flow characteristics. Biorheology 1993; 30(3–4): 287–98.
33. *Baker CJ, Fiore A, Connolly ES Jr, Baker KZ, Solomon RA.* Serum elastase and alpha-1-antitrypsin levels in patients with ruptured and unruptured cerebral aneurysms. Neurosurg 1995; 37(1): 56–61.
34. *Brown N.* A mathematical model for the formation of cerebral aneurysms. Stroke 1999; 22(5): 619–25.
35. *Fukuda S, Hashimoto N, Naritomi H, Nagata I, Nozaki K, Kondo S,* et al. Prevention of rat cerebral aneurysm formation by inhibition of nitric oxide synthase. Circulation 2000; 101(21): 2532–8.
36. *Chopard RP, Gerhard R.* Histomorphometrical study of the elastic fiber system in the anterior cerebral artery of man. Arq Neuropsiquiatr 2000; 58(4): 1040–6.
37. *Fujimoto K, Tanaka O.* Morphological examination of the circulus arteriosus cerebri humani (circle of Willis). I. Anterior and posterior communicating arteries. Kaibogaku Zasshi 1989; 64(5): 481–9.
38. *Andrews RJ, Spiegel PK.* Intracranial aneurysms. Age, sex, blood pressure, and multiplicity in an unselected series of patients. J Neurosurg 1979; 51(1): 27–32.
39. *Milenković Z, Vucetić R, Puzić M.* Asymmetry and anomalies of the circle of Willis in fetal brain. Microsurgical study and functional remarks. Surg Neurol 1985; 24(5): 563–70.
40. *Yong-Zhong G, van Alphen HA.* Pathogenesis and histopathology of saccular aneurysms: review of the literature. Neurol Res 1990; 12(4): 249–55.
41. *Chason JL, Hindman WM.* Berry aneurysms of the circle of Willis; results of a planned autopsy study. Neurology 1958; 8(1): 41–4.
42. *de la Monte SM, Moore GW, Monk MA, Hutchins GM.* Risk factors for the development and rupture of intracranial berry aneurysms. Am J Med 1985; 78(6 Pt 1): 957–64.

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Preoperative echocardiographic parameters influencing quality of life five years after coronary artery bypass graft surgery

Uticaj preoperativnih ehokardiografskih parametara na kvalitet života bolesnika pet godina posle hirurške revaskularizacije miokarda

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Abstract

Background/Aim. Factors associated with mortality and morbidity following coronary artery bypass graft surgery have been well defined and the Parsonnet score is widely used in mortality prediction. The evaluation of quality of life has not been still implemented in everyday work and preoperative echocardiographic factors affecting the quality of life in patients undergoing coronary artery bypass graft surgery have been poorly documented. The aim of this study was to evaluate echocardiographic parameters influencing quality of life following coronary artery bypass graft surgery and its correlation with widely used Parsonnet score. **Methods.** A total of 449 consecutive patients with myocardial revascularization, operated during 1999 and 2000 were enrolled in this retrospective-prospective study. The patients with comorbidities were excluded as well as those with in complete myocardial revascularization. A group of 180 patients who accepted to participate in quality of life evaluation was followed for 60 months. The quality of life was evaluated using a questionnaire SF-36. **Results.** The mean patients' age was 57.8 ± 7.8 years, 79.4% were males. A 5-year survival was 84.2%. The mean number of risk factors was 3.4 ± 1.0. Most of the patients were in New York Heart Associatiation (NYHA) II class (104 of them or 59.4%), 61 of them (34.9%) in NYHA III class and only 10 patients or 5.7% of them were in NYHA IV class. The mean End-Diastolic Diameter (EDD) was 55.3 ± 5.6 mm, mean End-Systolic Diameter (ESD) 38.7 ± 5.6 mm and mean ejection fraction (EF) 51.7 ± 9.6%. Left atrium dilatation ($p < 0.001$), as well as left ventricle dilatation ($p < 0.001$), low left ventricle ejection fraction ($p < 0.001$), multisegmental disorders of contractility ($p < 0.001$), and severe mitral regurgitation ($p < 0.001$) were in negative correlation with almost all dimensions of quality of life. ROC analysis showed that left ventricle EDD of 54.5 mm can be used as good cut-off value for prediction of optimal quality of life, with sensitivity of 57% and specificity of 70% (RR = 1.386), left ventricle ESD of 37.5 mm with sensitivity of 65% and specificity of 57% (RR = 0.855) and left ventricle EF of 50% with sensitivity of 61% and specificity of 70% (RR = 0.916). **Conclusion.** Echocardiographic parameters, that can easily be obtained preoperatively, have strong predictive value not only in postoperative survival, but also in determination of the quality of life of the patients five years after coronary artery bypass graft surgery.

Key words:
myocardial revascularization; preoperative care; echocardiography; quality of life; postoperative period; comorbidity.

Apstrakt

Uvod/Cilj. Upotreba *Parsonnet* skora u proceni postoperativnog trenda mortaliteta bolesnika nakon hirurške revaskularizacije miokarda već je standardno dobro poznat model predikcije koji je našao svoje mesto u svim svetskim kardiohirurškim centrima. Cilj našeg rada bio je da se proceni njihov uticaj na kvalitet života bolesnika pet godina nakon hirurške revaskularizacije miokarda, kao i da se ispita prediktivna vrednost skora kvaliteta života u poređenju sa već široko korišćenim *Paronnet* skorom predikcije mortaliteta. **Metode.** Studija je obuhvatila 449 bolesnika, kod kojih je u toku 1999. i 2000. godine izvršena hirurška revaskularizacija miokarda. Izuzeti su bolesnici kod kojih je istovremeno izvršena i operacija zaliska, bolesnici sa komorbiditetima ili bez kompletne revaskularizacije miokarda. Šezdeset meseci posle operacije izvršena je analiza kvaliteta života korišćenjem upitnika SF-36. Analizirano je sedam aspekata kvaliteta života, kao i ehokardiografski parametri i njihova korelacija sa aspektima kvaliteta života. **Rezultati.** Petogodišnje preživljavanje iznosilo je 84,2%. Prosečni enddijastolni dijametar (EDD) je 55,3 ± 5,6 mm, endsistolni dijametar (ESD) 38,7 ± 5,6 mm, ejekciona frakcija (EF) 51,7 ± 9,6%. Dilatacija leve pretkomore, leve komore, ejekciona frakcija, multisegmentni ispadi u kontraktilnosti i umereno teška mitralna regurgitacija bili su u negativnoj korelaciji sa svim aspektima kvaliteta života ($p < 0,001$). Kritične eokardiografske vrednosti za optimalni kvalitet života bili su EDD > 54,5 mm (senzitivnost 57%, specifičnost 70%, RR = 1,386), ESD > 37,5 mm (senzitivnost 65%, specifičnost 57% RR = 0,855), a EF < 50% ima najjaču prediktivnu vrednost (senzitivnost 61%, specifičnost 70%, RR = 0,916). **Zaključak.** Predperativni ehokardiogarfski parametri imaju vrlo visoku prediktivnu vrednost ne samo za postoperativno preživljavanje već i za kvalitet života bolesnika posle hirurške revaskularizacije miokarda.

Ključne reči:
miokard, revaskularizacija; preoperativna priprema; ehokardiografija; kvalitet života; postoperativni period; komorbiditet.

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Introduction

Coronary artery disease (CAD) is a major cause of mortality and morbidity in developed countries and coronary artery bypass graft (CABG) surgery is a primary treatment option when intervention cannot be done, usually in cases of multivessel coronary artery disease. Coronary artery disease is also a leading cause of mortality and morbidity in Serbia. The number of CABG procedures performed each year in the United States has risen from approximately 150 000 in 1979 to 598 000 in 1996, that is a 425% increase [1]. In our aging patient population improvement of quality of life (QoL) becomes more and more primary indication [2, 3]. Several studies have been undertaken to evaluate patients assessment of their general health status following CABG, mostly reporting an improvement [2–7]. Although a great number of studies analyzed perioperative mortality, survival and prediction of patients recovery after CABG, only few of them concerned quality of life long term after CABG. Parsonnet score is a widely used mortality predictive model after coronary revascularization and echocardiographic parameters are only a small part of this model. However, the predictors of QoL after myocardial revascularization are not completely recognized and the echocardiographic parameters have not been discussed enough yet, although they can easily be obtained preoperatively.

The aim of this study was to assess the preoperative echocardiographic parameters influencing QoL five years after primary isolated CABG.

Methods

The study enrolled 449 consecutive patients with primary isolated CABG done in the years 1999 and 2000 at the Clinic for Cardiac Surgery (Second Surgery Clinic), at the Clinical Center of Serbia. Comorbidities that could influence QoL, reported in previous studies as statistical bias, (renal failure serum, diabetes mellitus, liver cirrhosis, previous cerebral insult, malignancy) were exclusive criteria. Only 258 patients fulfilled inclusion and exclusion criteria and thus enrolled in the further investigation. Written informed consent was provided for all patients included in the study and Ethical Committee approved study methodology.

A follow-up period was 60 months for all the patients. A total 180 of the patients accepted to participate in the study and gave back a completely fulfilled questionnaire with a written informed consent. The answer rate was 69.8%.

Quality of life and echocardiographic parameters assessment

Quality of life was assessed 60 months after CABG using a questionnaire SF-36, that was sent to the patients by mail. A sample size of approximately 175 patients was calculated to be sufficient to give 90% power to detect an increase of 10% in the mean score in any subscale of the SF-36 at the 5% significance level.

The questionnaire SF-36 (UK standard version – Serbian translation) was sent with a stamped, addressed envelope to the patients, to fill them in and send them back by post. The SF -36 is a validated questionnaire widely used in medical practice and research, especially with cardiac surgery patients. It consists of 36 items measuring seven domains of QoL: physical functioning, physical role, body pain, general health, vitality, social functioning, emotional role and mental health. Scores range from 0–100 points; higher scores indicate better health. Internal consistency (Cronbachs alpha) for this subscale has been reported at 0.84, that is regarded as a high value comparing to other questionnaires used in the similar type of studies. All the participants were asked to complete questionnaires within two weeks.

An optimal quality of life score was regarded to be an overall questionnaire score ≥ 70% of maximum SF-36 score.

The parsonnet score was also calculated for all patients using the original Parsonnet formula and correlation of SF-36 score and Parsonnet score was analyzed.

All the patients had (ABG) surgery using the standard cardiopulmonary bypass technique and standard cardioplegia. None of them was operated 'off-pump'.

Standard echocardiography was performed using commercially available equipment with 2.0–4.0 MHz transducer. The M-mode echocardiographic study of the left ventricle was performed under 2-D control. Left ventricle end diastolic (EDD) and end systolic (ESD) diameters, left ventricular posterior wall thickness and interventricular septal thickness were measured. Left ventricle ejection fraction (EF) was estimated by visual method. Echocardiographic parameters were measured according to the American Society of Echocardiography. Values of each parameter were obtained by the same examiner.

Echocardiographic parameters EDD, ESD, EF segmental disorders of contractility, existence of dilatative ischemic cardiomyopathy and severity of mitral regurgitation were analyzed.

The data are expressed as mean values with standard deviations for continuous variables or as absolute numbers with percentages for categorical data. Correlation coefficients with related *p* values were also reported. Univariante and Multivariante Logistic Regression Analysis were used to assess the relationship between QoL and several preoperative variables. Sensitivity and specificity of these preoperative variables of patients with CABG for the prediction of optimal quality of life score > 70% were determined by the ROC (Receiver Operating Characteristics) curve method, and "cut-off" level was determined. Sensitivity was defined as a number of optimal quality of life score patients with Ejection Fraction (EF) above "cut-off" or End diastolic diameter/End Systolic Diameter (EDD/ESD) levels below "cut-off" (test positive) / number of all patients with optimal quality of life score. Specificity was defined as a number of patients with suboptimal quality of life score patients and EF levels below "cut-off" or EDD/EDS levels above "cut-off" (test negative) / number of all patients with suboptimal quality of life score. An area under the curve (AUC) was calculated representing a quantitative measure of predictive value of EF and EDD/EDS for optimal quality of life score in the patients with CABG. In all tests, p value < 0.05 was considered sta-

tistically significant and p value < 0.01 highly statistically significant.

Results

The mean age of the patients was 57.8 ± 7.8 years. Most of them (139 patients or 77.2%) were males.

A five-year survival after coronary artery by-pass surgery was 84.2 %.

The mean number of risk factors was 3.4 ± 1.0. Most of the patients were smokers (148 patients or 82.2%), with positive family history for cardiovascular diseases (139 patients or 77.2%), with hyperlipoproteinemia (146 patients or 81.1%) and hypertension (121 patients or 67.2%). Obesity was present in 48 patients (26.6%).

Even 92 patients (51.1% patients) had prior myocardial infarction in history of disease, and nine patients (5.0%) had also prior myocardial reinfarction.

Most of the patients were in New York Hear Association (NYHA) II class (104 of them or 57.8%), 61 of them (33.9%) in NYHA III class and only 15 patients or 8.3% of them were in NYHA IV class (Table 1).

patients (13.9%) and 127 patients (70.5%) had mild mitral regurgitation (1+) (Table 1).

A total of 133 patients (73.9%) achieved optimal quality of life (> 70% of total score in all dimensions) after surgical revascularization, while 47 of them (26.1%) did not and thus regarded to have suboptimal QoL.

Patients with bigger left ventricle EDD had worse QoL in all aspects ($p < 0.001$). Left ventricle ESD was also in strong negative correlation with all aspects of quality of life ($p < 0.01$). The correlation with emotional role of quality of life and left ventricle ESD had important statistical significance ($p < 0.05$), although correlation was not as strong as with other QoL aspects ($p < 0.01$).

Posterior and interventricular septum wall thicknes was in correlation with none of QoL dimensions five years after coronary artery bypass surgery ($p > 0.05$).

Left ventricle EF was very important prognostic factor for QoL five years after coronary artery bypass surgery. There was positive correlation between left ventricle EF and all QoL aspects. Higher preoperative left ventricle EF was a strong predictor of better 5-year postoperative QoL.

Table 1

Clinical and echocardiographic characteristics of the patients

Patients' characteristics	n	%
male	139	77.2
smokers	148	82.2
positive family history	139	77.2
hyperlipoproteinemia	146	81.1
hypertension	121	67.2
obesity	48	26.6
prior myocardial infarction	92	51.1
prior myocardial reinfarction	9	5.0
II	104	57.8
NYHA class III	61	33.9
IV	15	8.3
left ventricle dilatation	31	17.2
left ventricle hypertrophy	78	43.3
left atrium dilatation	39	21.6
moderate mitral regurgitation (2± , 3+)	25	13.9
Echocardiographic variables	Mean ± SD	
end diastolic diameter (EDD) (mm)	55.3 ± 5.6	
end systolic diameter (ESD) (mm)	38.7 ± 5.8	
ejection fraction (EF) (%)	51.7 ± 9.6	

The mean time of extracorporal circulation (ECC time) was 89 ± 15 min (range 22–127 min), and the mean duration of aortic cross-clamping (AoX-time) was 56 ± 13 min (range 18–79 min). There was a mean of three grafts (range 1–5), and a mean of four (range 1–7) distal anastomoses.

Only 81 of the patients (44.6%) received arterial graft.

Left ventricle dilatation was present in 31 of the patients (17.2%). Left ventricle hypertrophy was present in 78 patients (43.3%), but with higher frequency in female (59.1% in women and 27.8 % in men, $p < 0.05$).

The mean EDD was 55.3 ± 5.6 mm, mean EDS 38.7 ± 5.6 mm and mean EF was 51.7 ± 9.6 %. More than fifth of the patients (21.6%) had left atrial dilatation (more than 40 mm transversal diameter in M mode).

Moderate mitral regurgitation (2+ and 3+ measured by color doppler semiquantitative method) was present in 25

A level of left ventricle systolic dysfunction (mild, moderate and severe) was also in very strong correlation with all QoL aspects ($p < 0.001$). There was an exception in emotional role wich was not affected by the level of left ventricle systolic dysfunction.

Left atrium dilatation was in negative correlation with all QoL dimensions.

Severity of mitral regurgitation was in a very strong correlation with almost all QoL aspects, exceptemotional role, wich was again not affected by severity of mitral regurgitation.

The presence of segmental disorders of myocardial contractility, as well as multisegmental disorders in myocardial contractility were in strong correlation with all QoL aspects five years after coronary artery the bypass surgery ($p < 0.001$) (Table 2).

Table 2

Correlation of QoL dimensions left to ventricle end diastolic diameter (EDDLV), end systolic diameter (ESDLV) and ejection fraction (EF)

QoL dimensions	EDDLV			ESDLV			Left ventricle EF		
	r	*p*	corr	*r*	*p*	corr	*r*	*p*	corr
Physical functioning	0.378	< 0.001	negative	0.403	< 0.001	negative	0.534	< 0.001	positive
Physical role	0.353	< 0.001	negative	0.379	< 0.001	negative	0.533	< 0.001	positive
Body pain	0.239	< 0.001	negative	0.272	< 0.001	negative	0.394	< 0.001	positive
General health	0.406	< 0.001	negative	0.457	< 0.001	negative	0.613	< 0.001	positive
Vitality	0.369	< 0.001	negative	0.389	< 0.001	negative	0.543	< 0.001	positive
Social functioning	0.413	< 0.001	negative	0.438	< 0.001	negative	0.564	< 0.001	positive
Emotional role	0.210	< 0.01	negative	0.168	< 0.05	negative	0.267	< 0.001	positive
Mental health	0.276	< 0.001	negative	0.316	< 0.001	negative	0.461	< 0.001	positive
Parsonnet score	0.538	< 0.001	positive	0.495	< 0.001	positive	0.486	< 0.001	negative

ROC analysis showed that left ventricle EDD of 54.5 mm can be used as a good cut-off value for an optimal quality of life, with sensitivity of 57% and specificity of 70%, left ventricle ESD of 37.5 mm with sensitivity of 65% and specificity of 57% and left ventricle EF of 50% with sensitivity of 61% and specificity of 70%. (Table 3). These echocardiographic parameters can be also used with high sensitivity and specificity in Parsonnet score calculation. Multivariante analysis revealed that preoperative left ventricle EF had the strongest predictive value in distinguishing future optimal quality of life five years following CABG (Table 3).

Table 3

ROC analysis of sensitivity and specificity regarding echocardiographic parameters, quality of life (QoL) and Parsonnet score

Variable	Area	*p*	Cut-off value	Sn (%)	Sp (%)
Quality of life analysis					
end diastolic diameter – EDD (mm)	0.657	0.002	54.5	57	70
end systolic diameter – ESD (mm)	0.685	< 0.001	37.5	65	57
ejection fraction – EF (%)	0.717	< 0.001	50	61	70
Parsonnet score analysis					
end diastolic diameter – EDD (mm)	0.692	< 0.001	54.5	65.5	57
end systolic diameter – ESD(mm)	0.682	< 0.001	37.5	69	45
ejection fraction – EF (%)	0.684	< 0.001	50	71	55

Table 4

Comparation of relative risk and confidence interval of 95 % for cut-off values of left ventricle parameters with quality of life score (less than 70% of maximal score) and Parsonnet score (≥ 20)

Variable	*p*	RR	95% CI for RR
Quality of life analysis			
end diastolic diameter (EDD > 54.5 mm)	0.627	1.386	0.372–5.165
end systolic diameter (ESD > 37.5 mm)	0.839	0.855	0.189–3.866
ejection fraction (EF < 50%)	0.006	0.916	0.861–0.975
Parsonnet score analysis			
end diastolic diameter (EDD > 54.5 mm)	0.050	3.694	1.002–13.613
end systolic diameter (ESD > 37.5 mm)	0.800	0.830	0.196–3.512
ejection fraction (EF < 50%)	0.264	0.968	0.915–1.024

A low Parsonnet score (< 20) was present in 124 patients (68.9%), with 56 patients (31.1%) had high Parsonnet score (≥ 20).

Left ventricle echocardiographic characteristics (EDD, ESD and EF) also had high sensitivity and specificity in prediction of Parsonnet score.

The Parsonnet score was in positive correlation with left ventricle EDD ($r = 0.538$, $p < 0.001$) and ESD ($r = 0.495$, $p < 0.001$), and in negative correlation with left ventricle EF ($r = 0.461$, $p < 0.001$), with high level of statistical significance in all cases (Table 3).

Analyzing relationship between the Parsonnet and SF-36 QoL score, we revealed very strong negative correlation: patients with a high Parsonnet score had low QoL score ($r = 0.351$, $p < 0.001$).

Relative risk and confidence intervals for echocardiographic parameters and the Parsonnet score were analyzed in Table 4.

Discussion

The main goal of CABG is relief of symptoms of angina pectoris and prolongation of life expectancy [1]. An improvement of QoL is also another very important endpoint [2–6]. In Serbia, considering economic and war crisis, during the last years of 1990, an average waiting time for coronarography and following CABG operation was 12 months and in

the time of operation a great number of patients had progression of ischemic heart disease. This article deals with the problem of preoperative echocardiographic parameters influence on quality of life 5 years after CABG and proper identification of risk group of patients.

Since previous studies showed that comorbidities (diabetes mellitus, renal failure, liver failure and malignancies) are very important factors of poor postoperative quality of life, this study was designed to exclude these patients in order to avoid comorbidity bias and to evaluate in the best way narrow field of echocardiographic parameters and its relationship with postoperative QoL [4–6]. This on the other hand, resulted in a smaller, but more homogenous group of patients, that can be seen in some similar studies [4, 5].

The mean patients age in our study was 57.8 ± 7.8 years and most of them were males, which is similar to results of other investigators [3–9]. They had a great mean number of risk factors; most of them were smokers with hyperlipoproteinemia and hypertension, with positive family history for cardiovascular diseases. But only third of them had obesity, although it is well known risk factor for coronary artery disease. More than a half of the patients had prior myocardial infarction (that is a higher proportion than in other studies) and 5% of the patients had prior myocardial reinfarction. This information had to be regarded in analysis of primary and secondary coronary artery disease prevention and used as a good measure of a delay in myocardial revascularization [7, 10].

Most of the patients were in NYHA II class and only 5.7% of patients in NYHA IV, which could be considered as a good marker of mostly slightly impaired left ventricular function in the time of surgery.

The mean values of left ventricle echocardiographic parameters showed that in the time of surgery in most cases left ventricle systolic function was not significantly impaired. Small proportion of patients with moderate mitral regurgitation could also be used as a good marker of mostly preserved left ventricle function in the group of patients. The patients with heavy mitral regurgitation were elected not only for surgical myocardial revascularization but also for concomitant mitral valve surgery, which was not the objective of this study.

A the significantly smaller ratio of patients who received arterial graft compared to other world cardiac surgery centers could be explained by the fact that our study analyzed patients operated 10 years ago, in 1999 and 2000 when this technique was not so frequently implemented as nowadays in our country.

Several new studies addressed QoL 12 and 18 months after bypass surgery but none of them analyzed preoperative echocardiographic parameters influencing QoL after CABG [9, 10]. Evaluation of QoL is difficult because it is not independent of subjective perception and static measurements cannot define it [11]. Besides questionnaire SF-36, which was used in our study, there are several other questionnaires used for evaluation of QoL (Physical activity score, Nottingham Health Profile and Psychological General Well-being Index), but SF-36 is highly validated. In this study a very strong correlation was found between all SF-36 aspects and echocardiographic parameters, as in several other studies [11–13].

Poor preoperative EF, as a measure of poor systolic function, had a very important negative influence at all aspects of QoL in our study. The results of other studies are not uniform. Herlitz and al. [15, 16] have shown in a group of 1904 patients that preoperative left ventricle EF had a huge impact on 5-year mortality but no influence on physical activity, symptoms of chest pain, neither dyspnea nor any indices of QoL after CABG. Evaluation of the quality of life in this study was done by different questionnaires, not used in our study: Physical Activity Score, Nottingham Health Profile and Psychological General Well-Being Index and the difference is a product of using different tools for QoL measurement.

Our results are in correlation with results of Rumsfeld and al. [17] who used the same method for evaluation of QoL as we did: SF-36 questionnaire. Their results showed in a group of 1973 patients that preoperative left ventricle EF indeed is very important predictor of postoperative QoL dimensions. Analyzing a group of patients with advanced left ventricular dysfunction Trachiotis and al. [18] also suggested that there was a higher mortality in patients with sequentially decreased left ventricular function undergoing coronary artery bypass grafting, although more than 60% of patients with an EF less than 25% were alive and had good control of angina after five year. Our results are also in concordance with previously mentioned, since Parsonnet score was in a highly significant correlation with echocardiographic parameters.

Cut-off values of left ventricle EDD, ESD and EF can be used with good sensitivity and specificity for evaluation and prognosis of optimal postoperative quality of life, similarly as for Parsonnet score prediction. Specifity is even higher regarding quality of life analysis compared to widely conventionally used Parsonnet score analysis [13]. Multivariante analysis showed that although all tested echocardiographic parameters could be used with high statistical confidence, EF had the best balance of high sensitivity and specifity in prediction of both Parsonnet score and QoL score.

The patients with multisegmental disorders in contractility had poorer QoL in all dimensions. The presence and degree of mitral regurgitation were also very important factors for postoperative QoL. This could be explained by haemodynamical changes in left ventricle function, since functional mitral insuffitiency is a well-known parameter of elevated enddiastolic left ventricle pressure and poor systolic and diastolic function [18–20].

A strong correlation between Parsonnet and QoL score indicates that the patients with high Parsonnet score (and high risk of mortality after myocardial revascularization) are in the same time with a low QoL after myocardial revascularization. This group of patients is a group with high risk and should be properly preoperatively identified and more often controlled.

High relative risks (RR) suggest the importance of preoperative echocardiographic parameters and their influence

on quality of life (SF-36 score) as well as postoperative surviving (Parsonnet score).

Conclusion

Echocardiographic parameters are easily obtained preoperatively. They have a strong predictive value in prediction not only postoperative mortality, but also in prediction of quality of life after surgical myocardial revascularization. Postoperative quality of life can be improved by early echocardiographic screening in patients with coronary artery disease before CABG surgery. Considering the results of this study it could be concluded that in the patients with mild left ventricular dysfunction myocardial revascularization could be performed relatively safely with an optimal improvement in all aspects of the quality of life.

These predictors of health-related quality of life after coronary artery bypass surgery may be useful in preoperative risk assessment and counseling of patients with regard to the anticipated health status outcomes.

R E F E R E N C E S

1. *Eagle KA, Guyton RA, Davidoff R, Edwards FH, Eny GA, Gardner TJ,* et al. American College of Cardiology; American Heart Association. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004; 110(14): e340–437.
2. *Loponen P, Luther M, Wistbacka JO, Korpilahti K, Laurikka J, Sintonen H,* et al. Quality of life during 18 months after coronary artery bypass grafting. Eur J Cardiothorac Surg 2007; 32(1): 77–82.
3. *Järvinen O, Saarinen T, Julkunen J, Huhtala H, Tarkka MR.* Changes in health-related quality of life and functional capacity following coronary artery bypass graft surgery. Eur J Cardiothorac Surg 2003; 24(5): 750–6.
4. *Herlitz J, Wiklund I, Caidahl K, Karlson BW, Sjöland H, Hartford M,* et al. Determinants of an impaired quality of life five years after coronary artery bypass surgery. Heart 1999; 81(4): 342–6.
5. *Herlitz J, Caidahl K, Wiklund I, Sjöland H, Karlson BW, Karlsson T,* et al. Impact of a history of diabetes on the improvement of symptoms and quality of life during 5 years after coronary artery bypass grafting. J Diabetes Complications 2000; 14(6): 314–21.
6. *Järvinen O, Julkunen J, Saarinen T, Laurikka J, Tarkka MR.* Effect of diabetes on outcome and changes in quality of life after coronary artery bypass grafting. Ann Thorac Surg 2005; 79(3): 819–24.
7. *Abramov D, Tamariz MG, Fremes SE, Guru V, Borger MA, Christakis GT,* et al. Trends in coronary artery bypass surgery results: a recent, 9-year study. Ann Thorac Surg 2000; 70(1): 84–90.
8. *Mathisen L, Andersen MH, Veenstra M, Wahl AK, Hanestad BR, Fosse E.* Quality of life can both influence and be an outcome of general health perceptions after heart surgery. Health Qual Life Outcomes 2007; 5: 27.
9. *Lindsay GM, Hanlon P, Smith LN, Wheatley DJ.* Assessment of changes in general health status using the short-form 36 questionnaire 1 year following coronary artery bypass grafting. Eur J Cardiothorac Surg 2000; 18(5): 557–64.
10. *Hunt JO, Hendrata MV, Myles PS.* Quality of life 12 months after coronary artery bypass graft surgery. Heart Lung 2000; 29(6): 401–11.
11. *Dauphinee SW, Gauthier L, Gandek B, Magnan L, Pierre U.* Readying a US measure of health status, the SF-36, for use in Canada. Clin Invest Med 1997; 20(4): 224–38.
12. *Kiebzak GM, Pierson LM, Campbell M, Cook JW.* Use of the SF36 general health status survey to document health-related quality of life in patients with coronary artery disease: effect of disease and response to coronary artery bypass graft surgery. Heart Lung 2002; 31(3): 207–13.
13. *Parsonnet V, Dean D, Bernstein AD.* A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989; 79(6 Pt 2): I3–12.
14. *Ware JE, Snow KK,* Kosisnki M, Gandek B. SF-36 Health Survey Manual and. Interpretation Guide. Boston: Nimrod Pres; 1993.
15. *Herlitz J, Wiklund I, Sjöland H, Karlson BW, Karlsson T, Haglid M,* et. al. Relief of symptoms and improvement of quality of life five years after coronary artery bypass grafting in relation to preoperative ejection fraction. Qual Life Res 2000; 9(4): 467–76.
16. *Herlitz J, Haglid M, Wiklund I, Caidahl K, Karlson BW, Sjöland H,* et al. Improvement in quality of life during 5 years after coronary artery bypass grafting. Coron Artery Dis 1998; 9(8): 519–26.
17. *Rumsfeld JS, Ho PM, Magid DJ, McCarthy M Jr, Shroyer AL, MaWhinney S,* et al. Predictors of health-related quality of life after coronary artery bypass surgery. Ann Thorac Surg 2004; 77(5): 1508–13.
18. *Trachiotis GD, Weintraub WS, Johnston TS, Jones EL, Guyton RA, Craver JM.* Coronary artery bypass grafting in patients with advanced left ventricular dysfunction. Ann Thorac Surg 1998; 66(5): 1632–9.
19. *Welke KF, Stevens JP, Schults WC, Nelson EC, Beggs VL, Nugent WC.* Patient characteristics can predict improvement in functional health after elective coronary artery bypass grafting. Ann Thorac Surg 2003; 75(6): 1849–55.
20. *Al-Ruzzeh S, Athanasiou T, Mangoush O, Wray J, Modine T, George S,* et al. Predictors of poor mid-term health related quality of life after primary isolated coronary artery bypass grafting surgery. Heart 2005; 91(12): 1557–62.

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The Model for the End-Stage Liver Disease and Child-Pugh score in predicting prognosis in patients with liver cirrhosis and esophageal variceal bleeding

Model terminalnog stadijuma bolesti jetre i Child-Pugh skora u predviđanju prognoze bolesnika sa cirozom jetre i ezofagusnim varikoznim krvarenjima

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Abstract

Background/Aim. Esophageal variceal bleeding is one of the most frequent and gravest complications of liver cirrhosis, directly life-threatening. By monitoring certain clinical and laboratory hepatocellular insufficiency parameters (Child-Pugh score), it is possible to determine prognosis in patients who are bleeding and evaluate further therapy. Recently, the Model for the End-Stage Liver Disease (MELD) has been proposed as a tool to predict mortality risk in cirrhotic patients. The aim of the study was to evaluate survival prognosis of cirrhotic patients by the MELD and Child-Pugh scores and to analyze the MELD score prognostic value in patients with both liver cirrhosis and variceal bleeding. **Methods.** We retrospectively evaluated the survival rate of a group of 100 cirrhotic patients of a median age of 57 years. The Child-Pugh score was calculated and the MELD score was computed according to the original formula for each patient. We also analysed clinical and laboratory hepatocellular insufficiency parameters in order to examine their connection with a 15-month survival. The MELD values were correlated with the Child-Pugh scores. The Student's *t*-test was used for statistical analysis. **Results.** Twenty-two patients died within 15-months follow-up. Age and gender did not affect survival rate. The Child-Pugh and MELD scores, as well as ascites and encephalopathy significantly differed between the patients who survived and those who died ($p < 0.0001$). The International Normalized Ratio (INR) values, serum creatinine and bilirubin were significantly higher, and albumin significantly lower in the patients who died ($p < 0.0001$). The MELD score was significantly higher in the group of patients who died due to esophageal variceal bleeding ($p < 0.0001$). **Conclusion.** In cirrhotic patients the MELD score is an excellent survival predictor at least as well as the Child-Pugh score. Increase in the MELD score is associated with decrease in residual liver function. In the group of patients with liver cirrhosis and esophageal variceal bleeding, the MELD score identifies those with a higher intrahospital mortality risk.

Key words:
liver diseases; liver cirrhosis; esophageal and gastric varices; questionnaires; prognosis.

Apstrakt

Uvod/Cilj. Krvarenje iz varikoziteta najčešća je i najteža komplikacija ciroze jetre i direktno ugrožava život bolesnika. Praćenjem kliničkih i laboratorijskih parametara hepatocelularne insuficijencije (*Child-Pugh* skor) moguće je odrediti prognozu bolesnika koji krvare. Model terminalnog stadijuma bolesti jetre (MELD) od nedavno preporučuje se u predikciji mortaliteta kod bolasnika sa cirozom jetre. Cilj rada bio je praćenje prognoze preživljavanja bolesnika sa cirozom jetre MELD i *Child Pugh* skorom i analiza prognostičke vrednosti MELD skora kod bolesnika sa varikoznim krvarenjem. **Metode.** Retrospektivno je analizirano preživljavanje grupe od 100 bolesnika sa cirozom jetre prosečne starosti 57 godina. Za svakog bolesnika izračunavani su *Child-Pugh* i MELD skor. Analizirana je povezanost kliničkih i laboratorijskih parametara hepatocelularne insuficijencije sa petnaestomesečnim preživljavanjem. Korelisane su vrednosti MELD i *Child-Pugh* skora. Statistička obrada podataka vršena je Studentovim *t*-testom. **Rezultati.** U toku petnaestomesečnog praćenja umrlo je 22 bolesnika. Pol i starost bolesnika nisu uticali na stepen preživljavanja. *Child-Pugh* i MELD skor signifikantno su se razlikovali između grupa bolesnika koji su preživeli i onih koji su umrli ($p < 0,0001$). Takođe, nađena je signifikantno značajna razlika prisustva ascitesa i encefalopatije između grupa preživelih i umrlih bolesnika ($p < 0,0001$). Vrednosti INR (International Normalized Ratio), kao i nivoa kreatinina i bilirubina u serumu

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bile su signifikantno veće, a albumina signifikantno manje kod bolesnika koji su umrli ($p < 0,0001$). MELD skor bio je signifikantno veći u grupi bolesnika koji su umrli zbog ezofagusnog varikoznog krvarenja ($p < 0,0001$). **Zaključak.** MELD skor je pouzdan u prognozi preživljavanja bolesnika sa cirozom jetre kao i *Child-Pugh* skor. Porast MELD skora udružen je sa smanjenjem rezidualne funkcije jetre. MELD skorom može da se proceni rizik od intrahospitalnog mortaliteta u grupi bolesnika sa cirozom jetre i ezofagusnim varikoznim krvarenjem.

Ključne reči:
jetra, bolesti; jetra, ciroza; jednjak i želudac, variksi; upitnici; prognoza.

Introduction

Over the years, many clinical and biochemical parameters have been suggested in order to predict more accurately the prognosis of cirrhotic patients and correctly assess their survival rate. They are important because of application of adequate therapy and prioritization of transplantation lists, particularly because of the fact that there is an increasing discrepancy between the number of cirrhotic patients on waiting lists for orthotopic liver transplantation (OLT) and the number of available liver donors [1].

The Child-Pugh score is still considered the cornerstone in prognostic evaluation of cirrhotic patients although it was formulated more than 30 years ago. Nevertheless, it has some drawbacks such as the subjectivity of clinical parameters and a limited discriminatory ability [2, 3]. The Child-Pugh Class A patients usually show a good median survival term without OLT unless other events (such as hepatocellular carcinoma, uncontrolled bleeding due to portal hypertension, etc) occur [1, 4]. The Child-Pugh Class C patients are considered the conventional candidates for the procedure. The Child-Pugh Class B patients can be considered a heterogeneous group, as their clinical condition may remain stable for more than a year or rapidly deteriorate [5].

Recently, the Model for the End-stage Liver Disease (MELD) was introduced as a tool for predicting mortality risk and to assess the severity of the disease in patients with liver cirrhosis, as well as to determine organ allocation priorities [6–12].

Although the MELD score takes into consideration objective parameters (serum creatinine, the International Normalised Ratio – INR, bilirubin levels) and is computed with statistically derived coefficients on a continuous scale with no upper or lower limits, thus avoiding many drawbacks of the Child-Pugh score, it is not being used yet in everyday practice [13, 14].

The aim of the study was to evaluate the survival prognosis of cirrhotic patients and patients with complications by means of the MELD score compared to the Child-Pugh one. We also analysed the prognostic value of the MELD score in patients with both liver cirrhosis and variceal bleeding.

Methods

This retrospective study included cirrhotic patients (76 males, 24 females; median age 57 years, ranging from 32–79) hospitalised due to complications of the disease. Patients with the hepatorenal syndrome, spontaneous bacterial peritonitis and hepatocellular carcinoma were excluded from the study. Liver cirrhosis was diagnosed on the basis of histological, clinical and biochemical results, as well as by echosonographic and endoscopic examination. The etiology of liver disease was hepatitis C virus (HCV) in 4% of the patients, hepatitis B virus (HBV) in 7%, alcohol abuse in 88%, and autoimmunity in 1%. We calculated the Child-Pugh score using an original formula (Table 1) [15].

Table 1

Child-Pugh score parameters

Parameters	1 point	2 points	3 points
Serum bilirubin total (mg/dL)	< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin (mg/dL)	> 35	28–35	< 28
INR	< 1.7	1.71–2.20	> 2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

INR- International Normalized Ratio

The patients were classified as follows: Class A – 28, class B – 37 and class C – 35 patients. The MELD score was calculated according to the original formula proposed by the Mayo Clinic group: 10 {0.957 Ln [creatinine (mg/dL)] + 0.378 Ln [bilirubin (mg/dL)] + 1.12 Ln INR + 0.643}

Statistical analysis was first performed on the whole group of 100 patients and then on the subgroup of 48 patients with liver cirrhosis and esophageal variceal bleeding, evaluating survival and intrahospital mortality. For statistics we used the Student's *t*-test.

The results were expressed as median (range). Receiver operating characteristic (ROC) curves were used to determine the cut-off values of the Child-Pugh and MELD scores, with the best sensitivity (SS) and specificity (SP) in discriminating between patients who survived and those who

died. The validity of the models was measured by means of concordance (*c*) statistics (equivalent to the area under the ROC curve)[12]. A *c* value of 0.8–0.9 indicated an excellent diagnostic accuracy; a model with a c value > 0.7 was considered useful. For all analyses a *p* value < 0.05 was considered statistically significant. The data were analysed using XL Stat, Microsoft Office Excel, Statistics 6.

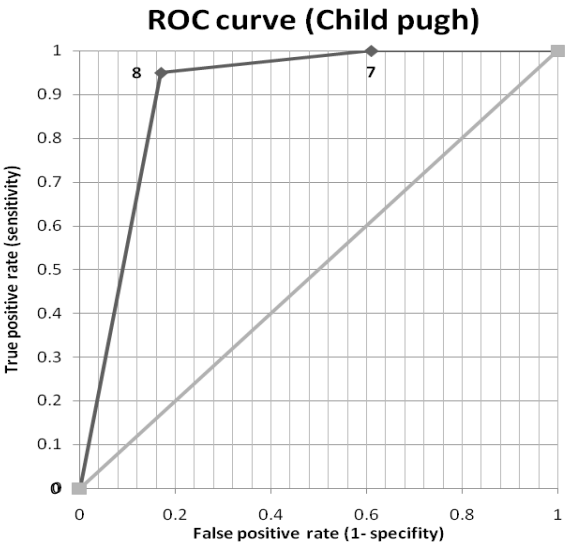

Fig. 1 – ROC curve (the Child-Pugh score)

Results

During a 15-month follow up, 22 patients died, out of whom none from the Child-Pugh Class A (0%), 1 from Class B (3%), and 21 from Class C (58%). The causes of death were all related to liver disease. Seventyeight patients survived more than 15 months: 28 were Child-Pugh Class A (100%), 36 Class B (97%), and 14 Class C (42%).

Clinical and biochemical parameters, the MELD and Child-Pugh scores were presented in Table 2. Age and gender did not affect survival. The Child-Pugh and MELD scores significantly differed in patients who survived from those who died ($p < 0.01$). Ascites and encephalopathy were significantly different in patients who survived as compared to those who died ($p < 0.01$). The values of INR, serum creatinine and bilirubin were significantly higher and albumin significantly lower in patients who died ($p < 0.01$).

Table 2

Clinical and biochemical characteristics, MELD and Child-Pugh scores

Parameters	Surviving patients	Deceased patients	*t*	*p*
Sex (M/F)	59/19	17/5		
Average age (years)	60	55		
Encephalopaty (Yes/No)	12/66	19/3	-8.28	< 0.0001
Ascites (Yes/No)	47/31	18/4	-6.50	< 0.0001
INR	1.445	2.13	-4.52	< 0.0001
Serum albumin (mg/dL)	31.15	26.35	4.56	< 0.0001
Serum bilirubin (mg/dL)	0.401	0.765	-4.93	< 0.0001
Serum creatinine (mg/dL)	0.867	1.225	-5.94	< 0.0001
Variceal bleeding MELD (Yes/No)	39/49	9/13	-5.43	< 0.0001
Child-Pugh score	7	12	-10.90	< 0.0001
MELD score	5.457	18.42	-7.33	< 0.0001

INR - International Normalized Ratio; Child-Pugh score – see Table 1;
MELD - Model for the End-stage Liver Disease = 10 {0.957 Ln [creatinine (mg/dL)] + 0.378 Ln [bilirubin (mg/dL)] + 1.12 Ln INR + 0.643}

A calculated sensitivity and specificity of the MELD and Child-Pugh score showed that both methods are highly sensitive, but the MELD score had a lower specificity for predicting survival prognosis (Figures 1 and 2). The cut-off values with the best SS and SP, the Child-Pugh and MELD scores were calculated using ROC curves. We also calculated the *c* value using ROC curve. The *c* values were 0.89 for Child-Pugh score and 0.84 for MELD score (Table 3.)

In the group of 48 patients with esophageal variceal bleeding, 9 (19%) died and 39 (81%) survived. The MELD score in patients who died was significantly higher than the MELD score in patients who survived. The *c* value was 0.71. Most of the patients died within five days after the admission.

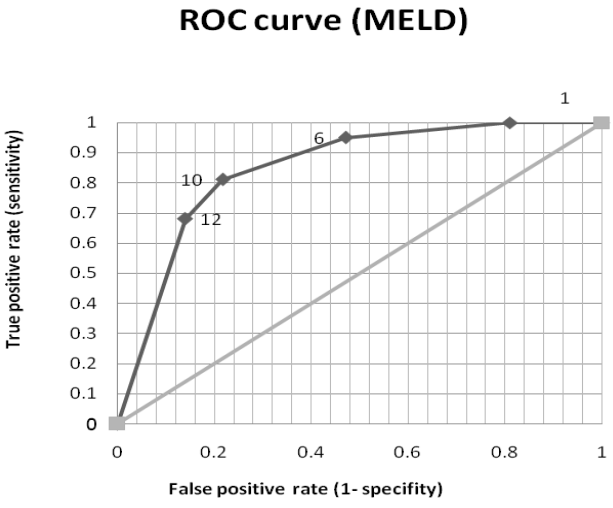

Fig 2 – ROC curve (the MELD score)

Table 3

Sensitivity, specificity, c-value of MELD and Child-Pugh scores

Score	Cut-off	Sensitivity (%)	Specificity (%)	*c* – value
Child-Pugh	8	95.45	82.05	0.89
MELD	6	95.45	53.84	0.84

MELD- Model for the End-stage Liver Disease

Discussion

Prognostic evaluation of patients with liver cirrhosis is an important topic often challenging clinicians. Correct timing of liver transplantation can reduce the mortality of patients on waiting lists and improve post-transplant survival [16-19]. Predicting prognosis is important for further plan of treatment, especially in patients with esophageal variceal bleeding. The Child-Pugh score is an important component of the prognostic evaluation of cirrhotic patients, although this traditional score has several shortcomings such as subjectivity of some parameters and a limited discriminatory ability. In order to overcome the limits of the Child-Pugh score, previous studies have evaluated a "combined score" with quantitative liver function tests, or have applied the scores that were originally formulated to evaluate multiorgan insufficiency in critically ill patients to cirrhotic patients [20–22].

Recently, a study group at the Mayo Clinic introduced a new scoring system, called MELD, to evaluate the prognosis in patients with liver cirrhosis. Two independent studies performed in North American cirrhotic patients showed that the MELD score performed at least as well as the Child-Pugh score in predicting patient outcome following acute variceal bleeding and mortality in patients referred for liver transplantation [23, 24]. In this study our objective was to evaluate survival prognosis in patients with liver cirrhosis by comparison of the two groups of patients: patients with liver cirrhosis who died, and those who survived for 15 months. We compared the MELD and Child-Pugh scores and each parameter separately between these two groups in order to assess their significance. Finally, we compared the MELD scores in patients who survived esophageal bleeding with those who died. By comparison of the MELD and Child-Pugh scores of the surviving patients to those who died we found a statistically significant difference. A multivariate analysis showed that signs of liver decompensation, such as the presence of ascites, higher values of INR, serum bilirubin and creatinine levels and encephalopathy, were independently associated with a 15-month mortality; our analyses showed a statistically significant difference between the two groups. Age and gender did not affect survival. We calculated sensitivity and specificity of the MELD and Child-Pugh scores and showed that both methods are highly sensitive, but that the MELD has lower specificity in predicting the survival prognosis. The *c* values were 0.89 for the Child-Pugh score and 0.84 for the MELD score implying an excellent diagnostic assessment. Finally, we analysed the group of patients with variceal bleeding and computed the MELD score for each patient. The MELD score was statistically significantly higher in patients who died due to variceal bleeding. Using the ROC curve we found the cut-off value of the MELD score to be 16, and the *c* value 0.71, which showed good prognostic accuracy.

Conclusion

The MELD and Child-Pugh scores are highly sensitive methods in predicting survival prognosis in patients with both liver cirrhosis and variceal bleeding.

Increase in the MELD score is associated with decrease in the residual liver function. In cirrhotic patients with esophageal variceal bleeding the MELD score identifies a group of patients with a higher risk of in-hospital mortality.

R E F E R E N C E S

1. *Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keefe EB,* et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Transplantation 1998; 66(7): 956–62.
2. *Oellerich M, Burdelski M, Lautz HU, Rodeck B, Duewel J, Schulz M,* et al. Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation 1991; 51(4): 801–6.
3. *Testa R, Valente U, Risso D, Caglieris S, Giannini E, Fasoli A,* et al. Can the MEGX test and serum bile acids improve the prognostic ability of Child-Pugh's score in liver cirrhosis? Eur J Gastroenterol Hepatol 1999; 11(5): 559–63.
4. *Keeffe EB.* Summary of guidelines on organ allocation and patient listing for liver transplantation. Liver Transpl Surg 1998; 4(5 Suppl 1): S108–14.
5. *Oellerich M, Burdelski M, Lautz HU, Binder L, Pichlmayr R.* Predictors of one-year pretransplant survival in patients with cirrhosis. Hepatology 1991; 14(6): 1029–34.
6. *Samuel D.* MELD-Na as a prognostic score for cirrhotic patients: Hyponatremia and ascites are back in the game. J Hepatol 2009; 50(4): 836–8.
7. *Hofmann WP, Rädle J, Moench C, Bechstein W, Zeuzem S.* Prediction of perioperative mortality in patients with advanced liver disease and abdominal surgery by the use of different scoring systems and tests. Z Gastroenterol 2008; 46(11): 1283–9. (German)
8. *Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK.* Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005; 22(11–12): 1079–89.
9. *Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC.* A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000; 31(4): 864–71.
10. *Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P, Uriz J, Quintó L, Ventura PJ,* et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001; 34(1): 46–52.

11. *Yousfi MM, Douglas DD, Harrison E.* Model for end-stage liver disease (MELD). Dynamic changes in MELD score is important in predicting mortality for patients awaiting liver transplantation (LTX). Hepatology 2001; 34: 254A.
12. *Samada Suarez M, Hernández Perera JC, Ramos Robaina L, Barroso Márquez L, González Rapado L, Cepero Valdés M,* et al. Factors that predict survival in patients with cirrhosis considered for liver transplantation. Transplant Proc 2008; 40(9): 2965–7.
13. *McCaughan GW, Strasser SI.* To MELD or not to MELD? Hepatology 2001; 34(1): 215–6.
14. *Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK,* et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001; 7(7): 567–80.
15. *Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.* Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60(8): 646–9.
16. *Hanley JA, McNeil BJ.* The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1): 29–36.
17. *Carithers RL Jr.* Liver transplantation. American Association for the Study of Liver Diseases. Liver Transpl 2000; 6(1): 122–35.
18. *Freeman RB Jr, Edwards EB.* Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transpl 2000; 6(5): 543–52.
19. *Rufat P, Fourquet F, Conti F, Le Gales C, Houssin D, Coste J.* Costs and outcomes of liver transplantation in adults: a prospective, 1-year, follow-up study. GRETHECO study group. Transplantation 1999; 68(1): 76–83.
20. *Singh N, Gayowski T, Wagener MM, Marino IR.* Outcome of patients with cirrhosis requiring intensive care unit support: prospective assessment of predictors of mortality. J Gastroenterol 1998; 33(1): 73–9.
21. *Muto P, Freeman RB, Haug CE, Lu A, Rohrer RJ.* Liver transplant candidate stratification systems. Implications for third-party payors and organ allocation. Transplantation 1994; 57(2): 306–8.
22. *Zauner C, Schneeweiss B, Schneider B, Madl C, Klos H, Kranz A,* et al. Short-term prognosis in critically ill patients with liver cirrhosis: an evaluation of a new scoring system. Eur J Gastroenterol Hepatol 2000; 12(5): 517–22.
23. *Chalasani N, Kahi CJ, Francois F.* Mayo clinic end-stage liver disease model (MELD) for predicting patient outcomes following acute variceal bleeding. Hepatology 2001; 34: 345A.
24. *Abouassi SG, Mihas AA, Williams LM.* MELD and CTP scores are equivalent predictors of mortality in cirrhotic veterans referred for orthotopic liver transplantation (OLT). Hepatology 2001; 34: 207A.

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Juvenile diabetes eye complications and treatment

Očne komplikacije i njihovo lečenje kod obolelih od juvenilnog dijabetes melitusa

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Abstract

Background/Aim. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. The aim of this study was to explore the prognosis of patients with juvenile DM regarding diabetic eye complications, as well as the course of the diabetic eye disease related to the treatment undertaken. **Methods.** The study series involved 33 patients with juvenile DM during the period 1992–2007. The influence of the following factors on the course of the disease was estimated: age, the age of the disease onset, time when eye complications appeared, treatment modalities. **Results.** Of the total of 33 diabetics 15 patients were followed for 10 or more years and 18 from 5 to 9 years. At the time of their first visit the mean age was 23.12 ± 6.39 and the mean duration of DM was 17.42 ± 7.42 years. On their first visit, 7 eyes were without any complication. Most of the patients already developed clinical signs of proliferative diabetic retinopathy (41.39%), the signs of nonproliferative diabetic retinopathy (13.13%) and macula involvement (10.10%). Diabetic cataract was found in 8.8% as well as tractional retinal detachment. Eleven out of 66 eyes were with vitreous hemorrhage. Two patients (5.5%) suffered neovascular glaucoma. There was 1 (2.2%) patient with developed rubeosis iridis and simplex glaucoma. Panretinal photocoagulation was performed in 65% of patients, focal photocoagulation in 15%, 12% patients underwent pars plana vitrectomy and 4% had cataract surgery with intraocular lens implantation and peripheral retinal kryopexy. **Conclusion.** Total vision loss due to eye complications of juvenile DM may be prevented if timely diagnosed with regular check ups and early treatment.

Key words:
diabetes mellitus, type I; diabetic retinopathy; therapeutics; laser coagulation; treatment outcome.

Apstrakt

Uvod/Cilj. Dijabetes melitus (DM) je metabolički poremećaj koji karakteriše hiperglikemija. Cilj studije bio je da se ispita prognoza vida bolesnika sa insulin-zavisnim juvenilnim DM, kao i efekta lečenja komplikacija dijabetičke bolesti oka. **Metode.** U studiju su bila uključena 33 bolesnika sa juvenilnim DM u periodu 1992–2007. Razmatran je uticaj sledećih faktora na tok bolesti: životno doba bolesnika, vreme početka bolesti, vreme pojave komplikacija, vrsta lečenja. **Rezultati.** Od ukupnog broja bolesnika, 15 su praćeni u periodu od 10 i više godina, a 18 od pet do devet godina. U vreme prvog oftalmološkog pregleda, srednje životno doba obolelih bilo je 23,12 ± 6,39, a srednje vreme trajanja bolesti je 17,42 ± 7,42 godine. Na prvom pregledu sedam očiju bilo je bez dijabetičkih promena. Većina drugih bolesnika imala je komplikacije u vidu proliferativne dijabetičke retinopatije (41,39% očiju), neproliferativne dijabetičke retinopatije (13,13% očiju), dok je makula bila zahvaćena kod 10,10% očiju. Dijabetička katarakta bila je prisutna kod 8,8%, kao i trakciona ablacija retine. Jedanaest od 66 očiju imalo je vitreusne hemoragije. Dva bolesnika (5,5% očiju) bolovalo je od neovaskularnog glaukoma. Jedan bolesnik (2,2% očiju) imao je rubeozu dužice i simpleks glaukom. Urađena je panretinalna fotokoagulacija 65% očiju, fokalna fotokoagulacija 15%, pars plana vitrektomija 12%, dok je 4% operisano zbog katarakte uz ugradnju intraokularnog sočiva i perifernom kriopeksijom retine. **Zaključak.** Potpuni gubitak vida kao posledica komplikacija juvenilne dijabetičke bolesti oka može se prevenirati pravovremeno postavljenom dijagnozom, urednim kontrolama i adekvatnom terapijom.

Ključne reči:
dijabetes melitus, insulin-zavisni; dijabetesna retinopatija; lečenje; koagulacija laserom; lečenje, ishod.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. In the Western World, approximately 1% of the population is diabetic, and at least another 1% is with undiagnosed high levels of serum glucose. Juvenile onset insulin-dependent DM (IDDM) accounts for approximately 10–15% of DM, the remainder being maturity onset or non insulin-dependent diabetics. Aside from acute glucose serum level abnormalities, the main risks to health are the characteristic long-term complications. These include cardiovascular diseases, chronic renal failure, retinal and nerve damages [1].

Retinal damage is presented with diabetic retinopathy (DR) which is the most frequent complication of diabetes and a leading cause of impaired vision in the Western World. It is well-known that the age of onset and the duration of diabetes are the strongest risk factors for development and progression of retinopathy [2, 3], which can be presented in the form of nonproliferative (NPDR), preproliferative or proliferative form (PDR), depending on the presence of the new blood vessels on the surface of retina or optic disc. For juvenile onset IDDM, PDR is the most frequent finding [3].

The essence of eye complications are the mechanisms through which microvascular occlusion transforms DR into an ischemic retinopathy**,** with neovascularisation [4, 5]. The first pathologic sign seen in the retina are retinal capillary microaneurysms. They cause the development of excessive vascular permeability and therefore leakage. Further, microvascular occlusion occurs followed by the proliferation of new blood vessels and accompanying fibrous tissue on the surface of the retina and optic disk which contracts together with the vitreous. Further, bleeding that occurs from new blood vessels and contraction of the fibrous tissue compromises visual acuity (VA) through hemophthalmos or tractional retinal detachment. If the process spreads to the anterior part of the eye, neovascular glaucoma develops with painful eye and total vision loss. Aside from these severe complications, VA is more often compromised through macular edema, due to disruption and increased permeability of perifoveolar capillary network, in a form of clinically significant macular edema.

In attempt to avoid diabetic eye complications and total visual loss, laser photocoagulation (LFK) of retina is indicated. It may be performed in a form of focal or panretinal LFK (PRP). The aim of these procedures is to decrease retinal ischemia through direct destruction of the retinal tissue and reduction of angiogenic factors indirectly. There are also opinions that pigment epithelial proliferation after photocoagulation has some antiangiogenic effect [6].

New vessel proliferation is a consequence of the effect of angiogenic factors, delivered from the ischemic retinal tissue. Researchers learn more about how angiogenic agents such as vascular endothelial growth factor, as well as the isoenzyme protein kinase C beta conspire to disrupt endothelial cell function, leading to increased retinal vascular permeability. In that sense, modern investigations are trying to find an answer to the question whether pharmacological treatments might someday supplement LFK as a preferable early intervention for diabetic eye disease [7–10]. But, until new therapeutic possibilities are available, we have to perform PRP in order to save patient's vision, although there are some undesirable effects of it, such as compromised VA, visual field constriction, color vision perception disturbances, reduced contrast sensitivity and night vision.

Therefore, in order to gain a better understanding of this serious disease, the authors performed a 15-year follow up based on young patients with IDDM–related eye complications and therapy performed in order to save VA. The base for this research is general agreement that early diagnosis and treatment of DR can slow its progression and help to prevent blindness [1, 11].

Methods

A retrospective study was based on records of 33 patients (66 eyes) diagnosed with juvenile onset DM at the Department of Ophthalmology, University Hospital "Zvezdara", Belgrade, Serbia, between 1992 and 2007. All the patients came with the diagnosis of juvenile-onset IDDM.

All the patients were examined by the same ophthalmologists (authors) for at least five times and the examination included the same procedure. An incorrected best VA and best corrected VA were taken, intraocular pressure measurments with Goldmann applanational tonometry, examination on the slit lamp and finally, after pupil dilatation, optic disc and retina were evaluated. Fundoscopy was performed by direct and indirect ophthalmoscopy (included biomicroscopy).

The diagnosis of DR was established based on its characteristic presentation, either as a NPDR or PDR form. Fluorescein angiography was obtained for the small number of patients. It was done in cases in which clinical presentation was not sufficient for classification of retinopathy. It was performed also in cases with maculopathy to ease focal photocoagulation. Slit lamp presentation of rubeosis iridis, neovascular glaucoma or cataract formation were recorded, too. During the treatment, ophthalmologic evaluation was performed to determine new retinal lesions, enlargement of pre-existing lesions, and changes in their appearance.

As a complication of DR we posed a diagnosis of rubeosis iridis, neovascular glaucoma, cataract, partial or total hemophthalmos and tractional retinal detachment.

The treatment was initiated as soon as the diagnosis was confirmed. Depending on the type of changes, we performed focal LFK or PRP, cataract surgery with intraocular lens implantation, glaucoma medications, pars plana vitrectomy or peripheral retinal kryopexy.

All analyses were performed using an electronic database organized in the SPSS (version 11.5) statistical package. Descriptive methods were used for mean values of the onset of DM, age of patients, gender, etc. The effects of treatment to VA, and VA on the first and the last examination were compared by the one-way ANOVA, with the level of significans of 0.05. The Kaplan-Meier survival method was used to determine the median time complications appearing.

Results

We reviewed the charts of 33 patients with juvenile IDDM, out of which 39.39% males and 60.60% females. The youngest patient at the first visit was 12-year old and the oldest one was 37, with the mean age of 23.12±6.39 years. The minimum duration of DM was 7 years and the maximum 33 years with the mean 17.42±7.42 years. The age at which the diagnosis of DM was first established was as little as 2 and as big as 19, with the mean age of 8.61±4.27 years.

For 15 patients we reviewed the charts for more than 10 years of a regular follow-up and for 18 patients from 5 to 9 years of a regular follow-up.

In 13 eyes the first eye complication developed 6 to 10 years from the beggining of the diesease. In 30 eyes DM lasted betwen 11 and 20 and in 16 eyes over 21 years before the first signs of ophthalmological complications were noticed. After 20 years of duration there were no patients (eyes) without complications. Using the Kaplan Meier test of probability, we can see that after 10 years of duration 50% of patients would have some complications, but after 20 years of DM, almost 90% of patients would have it, and this difference is significant.

On their first visit, a diagnosis of PDR was established in 41.39% of the patients, NPDR at 13.13%, macula was involved in 10.10% of the patients. Cataract was found in 8.8% as well as tractional retinal detachment. Seven of 66 eyes were without any changes at the first visit. Eleven of 66 (16.66%) eyes had vitreous gel hemorrhage. Neovascular glaucoma suffered 5.5% of the patients. There were 2.2% with rubeosis iridis and simplex glaucoma.

Panretinal laser photocoagulation was performed in 65% of the patients, focal treatment in 15%, 12% had pars plana vitrectomy and 4% had cataract surgery and peripheral retinal kryopexy. We compared best corrected VA at the first visit with best corrected VA at the last visit according to the therapy performed, and found statistical significance (p = 0.037 and p = 0.045).

Visual acuity at the time of first visit was as follow: none of the patients were blind, light perception had 7 eyes, 14 eyes had VA less than 0.7 and 45 eyes had VA of 0.8 or better. At the last visit 7 of the eyes were blind, two had light perception, 14 eyes had VA less than 0.7 and VA of 0.8 and better had 43 eyes. The VA at the first and last visit differed significantly (p = 0.00).

Discussion

Diabetic retinopathy is the most frequent complication of diabetes and a leading cause of impaired vision in most countries. Its asymptomatic nature and its etiopathogenesis, which is still unclear due to its multifactorial complexity makes DR-related blindness a growing social problem in many countries [12]. This refers especially to the cases of juvenile-onset DM.

Physicians are aware of the fact that with the age of onset and the duration of juvenile diabetes, the development and progression of retinopathy rises [1, 11, 13]. Still, it remains unknown which is the best time to start with controls of young diabetics, having in mind that there are still some subjects who develop mild changes in spite of a long duration of disease.

Burger et al. [3] point out that compared with ophthalmoscopy, as performed by an experienced ophthalmologist, fluorescein angiography allows detection of retinal changes about 4 years earlier.

Some authors confirm that preschool-age children at the onset of diabetes stay free from even minimal retinal complications longer than adolescents. Furthermore, the "onset" of retinopathy over 15 years of age in the great majority of subjects suggests some influence of sexual maturation during puberty [3, 14]. Based on up to date studies, yearly exams are not necessarily required for juvenile-onset diabetics within the first decade of life, but should be performed after 5 years of diabetes in younger children and after 2 years in adolescents [15].

On the other hand, proliferative changes may develop in previosly "normal" fundus from one examination to another within only two years in young diabetics [3].

Most of our patients had complications on their first visit. There were no patients with DM lasting less than 7 years. The mean age of duration of DM was 17.42 ± 7.42 and the mean age at their first visit was 23.12 ± 6.39 years.

In our series, the risk of severe eye complications rose with the duration of diabetes, so that after 10 years of duration almost half of the patients had some complications, while after 20 years, none of the patients was without complication ($p < 0.05$).

In the series of Krolewsky et al.[16], the risk of development of severe eye complications was almost nonexistent during the first 10 years of diabetes, but rose abruptly to its maximum level, and remained at that level for the next 25 years. Other authors report that the median risk age for the development of retinopathy 17.5 years, which is consistent with our findings [5, 16, 17].

In our serie the most common DM-related complication on the first visit was PDR (41.39%). Some authors mention different percents (21.6%; 55.2%) [13, 16–18].

To avoid blindness, nowadays methods include medical management (control of blood sugar, blood pressure, and serum lipids) and ocular management (LFK and pars plana vitrectomy). Adjunctive pharmacologic therapies (intravitreal triamcinolone acetonide and antivascular endothelial growth factor agents) have shown early promise in the treatment of both diabetic macular edema and PDR [15]. Meanwhile, laser treatment is still the gold standard of treatment for focal and diffuse diabetic macular edema and PDR, although its associations with some decline in visual functions are expected [2, 15, 19– 22]. When properly treated, PRP reduces the risk of moderate and severe visual loss by 50–90% in patients with severe NPDR and PDR, and the risk of visual loss from macular edema by 50–70% [22–25]. Some other treatment possibilities are recommended in cases in which PRP is not enough, like pars plana vitrectomy, cataract surgery and peripheral retinal kryopexy [26–29].

The goal of these treatments is to obtain good VA. Yet, VA in our patients was worse at the end of the study. This is because most of the patients came when severe complica-

tions already developed, so the therapy had no beneficial effect. These values for VA were statisticaly significant ($p = 0.00$). On the other hand, patients who came with PDR and less macular involvement, kept their VA for a long period of time. In the series of some authors, VA was guarded through the study (0.5 and better) and at the end of their treatment, although they did not find any significance in a VA before and after the therapy [30].

Visual stability after PRP indicated the need for this kind of treatment in an early phase of PDR in order to preserve visual function.

Conclusion

According to our results, we would like to confirm and support the opinion that if a patient with DM refers to ophthalmologist on time, VA could be saved for a long period of time. In that sence, the most important are early detection of the disease, intensive metabolic control, patient education about asymptomatic nature of DR and the use of screening programs for the youngsters from the age of 10 years. In case of present complications the treatment should be considered as soon as possible.

R E F E R E N C E S

1. *Rubio Cabezas O, Argente Oliver J.* Diabetes mellitus in children and adolescents: chronic complications and associated diseases. An Pediatr 2007; 66(3): 282–9. (Spanish)
2. *Mohamed Q, Gillies MC, Wong TY.* Management of diabetic retinopathy: a systematic review. JAMA 2007; 298(8): 902–16.
3. *Burger W, Hövener G, Düsterhus R, Hartmann R, Weber B.* Prevalence and development of retinopathy in children and adolescents with type 1 (insulin-dependent) diabetes mellitus. A longitudinal study. Diabetologia 1986; 29(1): 17–22.
4. *Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS,* et al; JDRF Diabetic Retinopathy Center Group. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes 2006; 55(9): 2401–11.
5. *Hykin PG.* Diabetic Retinopathy: Clinical Features and Management. J Comm Eye Health 1996; 9: 58–62.
6. *Glaser BM, Campochiaro PA, Davis JL Jr, Jerdan JA.* Retinal pigment epithelial cells release inhibitors of neovascularization. Ophthalmology 1987; 94(7): 780–4.
7. *Ryan GJ.* New pharmacologic approaches to treating diabetic retinopathy. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S15–21.
8. *Das Evcimen N, King GL.* The role of protein kinase C activation and the vascular complications of diabetes. Pharmacol Res 2007; 55(6): 498–510.
9. *Dieudonné SC, La Heij EC, Diederen RM, Kessels AG, Liem AT, Kijlstra A,* et al. Balance of vascular endothelial growth factor and pigment epithelial growth factor prior to development of proliferative vitreoretinopathy. Ophthalmic Res 2007; 39(3): 148–54.
10. *Damico FM.* Angiogenesis and retinal diseases. Arq Bras Oftalmol 2007; 70(3): 547–53. (Portuguese)
11. *Massin P, Erginay A, Mercat-Caudal I, Vol S, Robert N, Reach G,* et al. Prevalence of diabetic retinopathy in children and adolescents with type-1 diabetes attending summer camps in France. Diabetes Metab 2007; 33(4): 284–9.
12. *Morello CM.* Etiology and natural history of diabetic retinopathy: an overview. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S3–7.
13. *Chetthakul T, Likitmaskul S, Plengvidhya N, Suwanwalaikorn S, Kosachunhanun N, Deerochanawong C,* et al. Thailand diabetes registry project: prevalence of diabetic retinopathy and associated factors in type 1 diabetes mellitus. J Med Assoc Thai 2006; 89(Suppl 1): S17–26.
14. *Frank RN, Hoffman WH, Podgor MJ, Joondeph HC, Lewis RA, Margherio RR,* et al. Retinopathy in juvenile-onset type I diabetes of short duration. Diabetes 1982; 31(10): 874–82.
15. *Bloomgarden ZT.* Screening for and managing diabetic retinopathy: current approaches. Am J Health Syst Pharm 2007; 64(17 Suppl 12): S8–14.
16. *Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR.* Risk of proliferative diabetic retinopathy in juvenile-onset type I diabetes: a 40-yr follow-up study. Diabetes Care 1986; 9(5): 443–52.
17. *Palmberg P, Smith M, Waltman S, Krupin T, Singer P, Burgess D,* et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. Ophthalmology 1981; 88(7): 613–8.
18. *Maia OO Jr, Takahashi WY, Bonanomi MT, Marback RF, Kara-José N.* Visual stability in diabetic retinopathy treated by panretinal laser photocoagulation. Arq Bras Endocrinol Metabol 2007; 1(4): 75–80.
19. *Fong DS, Girach A, Boney A.* Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: a literature review. Retina 2007; 7(7): 16–24.
20. *Sánchez MC, Luna JD, Barcelona PF, Gramajo AL, Juarez PC, Riera CM,* et al. Effect of retinal laser photocoagulation on the activity of metalloproteinases and the alpha(2)-macroglobulin proteolytic state in the vitreous of eyes with proliferative diabetic retinopathy. Exp Eye Res 2007; 85(5): 644–50.
21. *Schwartz SG, Flynn HW Jr.* Pharmacotherapies for diabetic retinopathy: present and future. Exp Diabetes Res 2007; 2007: 524–87.
22. *Lang GE.* Laser treatment of diabetic retinopathy. Dev Ophthalmol 2007; 39: 48–68.
23. *Mohamed Q, Gillies MC, Wong TY.* Management of diabetic retinopathy: a systematic review. JAMA 2007; 298(8): 902–16.
24. *Boyer DS, Ron P.* Gallemore, Changing Approaches to Diabetic Retinopathy Despite a variety of treatments, diabetic retinopathy is a common couse of blindness in adults. Review of Ophthalmology 2007; 14(3): ID 13269.
25. *Giusti C.* Retinopathy in juvenile diabetes: a 10-year (1990–2000) review. Pediatr Diabetes 2001; 2(2): 83–93.
26. *Korda V.* Surgical treatment of diabetic retinopathy. Vnitr Lek 2007; 53(5): 509–11.
27. *Kleinmann G, Hauser D, Schechtman E, Landa G, Bukelman A, Pollack A.* Vitreous hemorrhage in diabetic eyes previously treated with panretinal photocoagulation. Int Ophthalmol 2008; 28(1): 29–34.
28. *Meyer CH.* Current treatment approaches in diabetic macular edema. Ophthalmologica 2007; 221(2): 118–31.
29. *Wilson ME Jr, Levin AV, Trivedi RH, Kruger SJ, Elliott LA, Ainsworth JR,* et al. Cataract associated with type-1 diabetes mellitus in the pediatric population. J AAPOS 2007; 11(2): 162–5.
30. *Hitani K, Yamamoto T, Sato Y.* Long-term results of grid pattern photocoagulation for diffuse diabetic macular edema. Nippon Ganka Gakkai Zasshi 2007; 111(5): 401–6.

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Udruženost unilateralne multicistične displazije bubrega fetusa sa drugim anomalijama urinarnog sistema

Association of fetal unilateral multicystic kidney disease with other urinary tract anomalies

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Apstrakt

Uvod/Cilj. Multicistični displastični bubreg je poremećaj u razvoju ploda koji se može ispoljiti pre ili posle rođenja, a zbog rizika od dodatnih anomalija, neophodan je poseban oprez kod takve dece. Cilj ovog rada bio je da se utvrdi incidencija i tip udruženih anomalija urinarnog sistema kod dece sa prenatalno dijagnostikovanom unilateralnom multicističnom displazijom bubrega i da se ukaže na potrebu postnatalnih dijagnostičkih procedura u cilju evaluacije urinarnog sistema. **Metode.** Studijom je bilo obuhvaćeno 38 trudnica sa prenatalno dijagnostikovanom unilateralnom multicističnom displazijom bubrega fetusa prezentovanih Konzilijumu za fetalne anomalije Instituta za ginekologiju i akušerstvo Kliničkog centra Srbije i Univerzitetske dečje klinike u periodu od tri godine. Podaci o postojanju udruženih anomalija dobijeni su obdukcijom ploda nakon prekida trudnoće, odnosno na osnovu kliničkih i operativnih nalaza rođene dece kada je trudnoća nastavljana. **Rezultati.** Kod svih fetusa nakon prekinutih trudnoća ili letalnog ishoda deteta po rođenju, obdukcijom je otkriveno više udruženih renalnih ili ekstrarenalnih anomalija. Od 32 preživele dece (84,3%) postnatalnim ispitivanjem otkriveno je da 31,4% dece ima anomaliju kontralateralnog bubrega, 26,3% dodatnu anomaliju ipsilateralnog bubrega, 13,2% anomaliju nižih partija urinarnog sistema i isti procenat dece neku od udruženih ekstrarenalnih anomalija. Operisano je 73,6% dece, pri čemu je više od polovine operacija podrazumevalo rešavanje udruženih anomalija urinarnog sistema. Kod 17% dece postoperativnim praćenjem zapaženo je pogoršanje bubrežne funkcije. **Zaključak.** Deca sa unilateralnom multicističnom displazijom bubrega imaju veliki rizik od postojanja anomalije kontralateralnog bubrega i urinarnog sistema uopšte tako da moraju biti precizno pregledana i prenatalno i postnatalno. Predlažemo primenu obaveznih serijskih ekspertskih prenatalnih ultrazvučnih pregleda a zatim, postnatalno, ultrazvučnih pregleda, izotopskog skena. Izuzetno je značajno izvođenje mikcione cistoreterografije, s obzirom na visoki procenat postojanja vezikoureteralnog refluksa kontralateralnog bubrega. Kada se planira nefrektomija treba uraditi cistoskopiju i kolposkopiju radi otkrivanja mogućih skrivenih anomalija urogenitalnog sistema.

Ključne reči:
bubreg, multicistični, displastični; dijagnostika, prenatalna; fetus; urogenitalni poremećaji; rizik, procena; vezikoureteralni refluks.

Abstract

Background/Aim. Multicystic dysplastic kidney represents a disorder in the fetus development presented prenatally of postnatally, this deserving special attention due to a risk of additional anomalies in children with this disorder. The aim of this study was to determine the incidence and type of common anomalies of the urinary system in the prenatal diagnosis of unilateral multicystic dysplastic kidney, and point out the necessity of postnatal diagnostic procedures in order to evaluate the state of the urinary system. **Methods.** This retrospective-prospective study encompassed 38 cases of prenatally diagnosed unilateral fetal multicystic dysplastic kidney, presented to the Council for Fetal Anomalies from the Institute for Gynecology and Obstetrics of the Clinical Centre of Serbia and the University Children's Clinic within a three-year period. Associated anomalies were revealed by autopsy findings when pregnancy was terminated, *ie* resumed with clinical and operative findings of born children. **Results.** In every case of terminated pregnancy and death after birth the autopsy revealed additional renal or exstrarenal anomaly which were not prenataly detected. Postnatal evaluation of survived children with unilateral multicistic disease revealed that 31,4% of them have an anomaly of the contralateral kidney, 26,3% anomaly of the ipsilateral side, 13,2% anomaly of the lower portions of the urinary system and the same percent an additional extrarenal anomaly. The surgery was performed in 73,6% of children, more than half of the interventions were related to extrarenal anomaly. In 17% of children the kidney function was deteriorated after surgery. **Conclusion.** Children suffering from unilateral multicystic dysplastic kidney have a greater chance of exhibiting an anomaly of the contralateral kidney and the urinary system in general. Therefore, they require thorough examination, both prenatally and postnatally. We propose obligatory serial professional prenatal ultrasound examinations, followed by postnatal ultrasound, isotope scan, and we especially emphasize the need for performing urinary cystouretherography, bearing in mind the high incidence of the vesicoureteral reflux of the contralateral kidney. In addition to nephrectomy, cytoscopy and colposcopy also need to be performed for the purpose of discovering possible hidden anomalies of the urogenital system.

Key words:
multicystic dysplastic kidney; prenatal diagnosis; fetus; urogenital abnormalities; risk assessment; vesicoureteral reflux.

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Uvod

Kongenitalna anomalija je poremećaj u razvoju ploda koji može nastati u bilo kojem trenutku trudnoće i može se ispoljiti u toku intrauterinog razvoja, perinatalnom periodu ili kasnije u toku života [1]. Po podacima iz literature nešto manje od jedne četvrtine svih anomalija otkrivenih antenatalno čine anomalije urinarnog sistema a blizu 30% tih anomalija ovog sistema čini unilateralna multicistična displazija bubrega [2].

Multicistični displastični bubreg nastaje kao posledica aberantnog razvoja bubrega, tj. kao posledica opstruktivne uropatije koja se javlja veoma rano (8–10 nedelja nakon koncepcije), pri čemu od početka ne dolazi do razvoja normalnog bubrežnog parenhima, već on kompletno biva zamenjen cistama različite veličine. Bolest može biti segmentna, unilateralna ili bilateralna [3].

Multicistični displastični bubreg retko predstavlja dijagnostički problem i lako se otkriva prenatalno rutinskim sonografskim pregledom. Tipična sonografska slika je postojanje brojnih cisti, koje međusobno ne komuniciraju, koje su različite veličine, promera 1–9 cm, i između kojih je prisutan bubrežni parenhim. Zbog postojanja cisti i sam bubreg je znatno uvećan i predstavlja najčešći uzrok sonografskog nalaza cistične mase u abdomenu fetusa. Jedina anomalija koja prenatalno diferencijalno-dijagnostički dolazi u obzir jeste teška opstrukcija pijeloureteralnog spoja koja i sama dovodi do displazije, tako da se dijagnoza postavlja isključivo histološkim pregledom [4, 5].

Funkcija multicističnog bubrega je niža od 10% ili je takav bubreg potpuno nefunkcionalan, stoga je bilateralna multicistična displazija inkompatibilna sa životom. Prognoza unilateralne multicistične displazije bubrega je povoljna i zavisi prvenstveno od stanja kontralateralnog bubrega i njegove funkcije, a zatim i od postojanja dodatnih anomalija urinarnog sistema [6].

Cilj ove studije bio je utvrđivanje incidencije i tipa udruženih anomalija urinarnog sistema kod dece sa prenatalno dijagnostikovanom unilateralnom multicističnom displazijom bubrega, kao i ukazivanje na potrebu postnatalnih dijagnostičkih procedura u cilju evaluacije urinarnog sistema.

Metode

Ovom retrospektivno-prospektivnom studijom obuhvaćene su trudnice sa multicističnom displazijom bubrega fetusa prezentovane Konzilijumu za fetalne anomalije Instituta za ginekologiju i akušerstvo Kliničkog centra Srbije i Univerzitetske dečje klinike u periodu od 01.01.2005. do 31.12.2007. godine. Nakon prenatalne evaluacije urinarnog sistema fetusa koja je podrazumevala ekspertski ultrazvučni pregled trudnice fetalnom ehokardiografijom, magnetnu rezonanciju i amniocentezu sa kariotipizacijom, dalji postupak bio je uslovljen procenjenom bubrežnom funkcijom fetusa: očuvana bubrežna funkcija fetusa, praćenje trudnoće od strane ordinirajućeg ginekologa i dovršavanje trudnoće po akušerskim indikacijama, evaluacija urinarnog sistema novorođenčeta u Univerzitetskoj dečijoj klinici (ultrasonografski pregled, mikciona cistoureterografija i radioizitopske metode pregleda, markaptracetil triglicin (MAG-3), dimerkaptosukcinska kiselina (DMSA), dietiltriazmin pentarcetična kiselina (DTPA); narušena bubrežna funkcija fetusa, preterminsko dovršavanje trudnoće ispitivanje novorođenčeta (prematurusa) u Univerzitetskoj dečijoj klinici i operacija ukoliko postoji indikacija; postojanje anomalije fetusa inkompatibilne sa životom, prekid trudnoće nakon dobijanja saglasnosti Etičkog odbora, kliničko-patološka obdukcija pobačenog ploda.

Podaci korišćeni u radu dobijeni su na osnovu prenatalno postavljenih dijagnoza, obdukcionih nalaza (u slučaju letalnih ishoda) i kliničkih operativnih nalaza rođene dece.

Rezultati

U periodu od tri godine od 101 trudnice upućene na konzilijum za fetalne anomalije sa suspektnom anomalijom urinarnog sistema fetusa kod 38 (37,62%) trudnica postavljena je dijagnoza multicistične displazije bubrega fetusa. Prosečno vreme u trudnoći kada je anomalija bubrega fetusa otkrivena bilo je 29. nedelja gestacije, a muški pol je bio češće zastupljen (1,8 : 1). Multicistična displazija češće je zahvatala jedan nego oba bubrega fetusa (18 : 1). Displazija je bila bilateralna kod dva fetusa, a unilateralna displazija nešto češće bila je prisutna na levom bubregu (1,2 : 1).

Kod četiri trudnice (10,5%), zbog postojanja anomalije fetusa inkompatibilne sa životom, trudnoće su prekinute nakon dobijene saglasnosti Etičkog odbora, a kod dvoje dece (5,2%) smrt je nastupila nakon rođenja. Ukoliko isključimo dva fetusa sa bilateralnom multicističnom displazijom bubrega koja je potvrđena obdukcionim nalazom, kod fetusa prenatalno dijagnostikovanom unilateralnom multicističnom displazijom obdukcija je pokazala udružene anomalije urinarnog sistema (tabela 1).

Tabela 1

Obdukcioni nalaz fetusa (udružene renalne i ekstrarenalne anomalije) kod četiri prekinute trudnoće

Prenatalna dijagnoza	Obdukcioni nalaz	
	Udružene anomalije urinarnog sistema	Ekstrarenalne anomalije
Multicističan levi bubreg i anomalija desnog bubrega	agenezija uretre i desnog bubrega	atrezija anusa i vagine
Multicističan desni bubreg i anamnion	hipoplazija levog bubrega i bešike	hipoplazija penisa
Multicističan levi bubreg i anamnion	agenezija desnog bubrega	rascep mekog nepca
Multicističan levi bubreg i policističan desni bubreg	displazija desnog bubrega	hipoplazija spoljnih genitalija

Postnatalnim ispitivanjem urinarnog sistema od 32 preživele dece kod 27 (84,3%) otkrivena je jedna ili više dodatnih anomalija urinarnog sistema. Dvanaestoro dece (31,4%)

imalo je anomaliju kontralateralnog bubrega sa vezikoureteralnim refluksom kao najčešćim nalazom, osmoro dece (29,6%), desetoro dece (26,3%) anomaliju ipsilateralnog bubrega, a petoro dece (13,2%) imalo je anomaliju nižih partija urinarnog sistema (tabela 2).

Cistoskopijom koja je prethodila nefrektomiji postavljena je dijagnoza ektopičnog uretera, ureteralne stenoze i ureterocele.

Kolposkopiju su prihvatili roditelji samo četvoro dece ženskog pola, te je postavljena dijagnoza neperforisanog himena i ektopičnog uretera sa otvorom u vagini.

Tabela 2

Anomalije kontralateralnog i ipsilateralnog bubrega kao i nižih partija urinarnog sistema kod trideset dvoje preživele dece sa prenatalnom dijagnostikovanom unilateralnom multicističnom displazijom bubrega

Tip anomalije	Kontralateralni bubreg (broj anomalija)	Ipsilateralni bubreg (broj anomalija)	Niže partije urinarnog sistema (broj anomalija)
Hidronefroza	3		
Pijelektazija	4		
Megaureter	1	2	
Ektopični ureter	2	2	
Ureterocela	2	1	
Posteriorna uretralna valvula			4
Stenoza uretre			1
Vezikoureteralni refluks	8	2	
Ukupno	20	5	5

Petoro dece (13,2%) imalo je i neku od udruženih ekstrarenalnih anomalija.

Strukturnu anomaliju imalo je troje dece, od kojih je jedno dete muškog pola imalo atreziju anusa, a drugo hipoplaziju spoljnih genitalija i rascep mekog nepca, dok je dete ženskog pola imalo neperforisani lumen. Funkcijsku anomaliju imalo je dvoje dece muškog pola – jedno panhipopituitarizam a drugo tešku hipertenziju, pored mentalne i motorne retardacije.

U odnosu na prenatalno dijagnostikovanu multicističnu displaziju bubrega anomaliju kontralateralnog bubrega imalo je 31,4% dece, anomaliju ipsilateralnog bubrega 26,31%, a po 13,2% dece anomaliju nižih delova urinarnog sistema i neku ekstrarenalnu anomaliju.

Operisano je 28 dece (73,6%). Kod trinaestoro dece (46,5%) izvršena je nefrektomija ili seminefrektomija, a kod ostalih 15 (53,5%) bilo je neophodno ukupno 28 intervencija za rešavanje udruženih anomalija urinarnog sistema. Kod sedmoro dece (17%) u postoperativnom toku došlo je do pogoršanja bubrežne funkcije (tabela 3). Intervencije kod ostale dece nisu bile potrebne i na redovnim su kontrolama.

Diskusija

Deca sa unilateralnom multicističnom bolešću bubrega imaju povećani rizik od anomalija kontralateralnog bubrega i nižih partija urinarnog sistema [7, 8]. Prenatalni nalaz unilateralne multicistične bolesti bubrega stoga zahteva kompletnu evaluaciju urinarnog sistema kako prenatalno, tako i postnatalno, najpre u cillju potvrđivanja dijagnoze, zatim i procene bubrežne funkcije i na kraju radi isključivanja ili potvrde postojanja dodatnih anomalija koje bi, eventualno, zahtevale dodatni urološki tretman [9]. Naročito treba obratiti pažnju na ehogenost kontralateralnog bubrega pri ehosonografskom pregledu, s obzirom na rezultate autopsije kod umrle dece sa unilateralnom multicističnom bolešću bubrega koji su u najvećem broju slučajeva pokazali displaziju kontralateralnog bubrega [10, 11].

U literaturi ne postoji opšteprihvaćeno mišljenje o potrebi za nefrektomijom kod unilateralne multicistične displazije bubrega. Većina autora ističe da su indikacije za ekstirpaciju multicistično izmenjenog bubrega velika masa koja kompromituje respiraciju ili uzimanje hrane, bolna masa ili

Tabela 3

Intervencije kod dece sa prenatalno dijagnostikovanom unilateralnom multicističnom displazijom bubrega, broj intervencija i broj dece sa pogoršanjem renalne funkcije nakon intervencije (patološki porast kreatinina)

Operacija	Intervencija (broj)	Operisana deca sa pogoršanjem bubrežne funkcije (broj)
Nefrektomija	11	
Seminefrektomija	2	
Postavljanje stome	11	4
Pijeloplastika	8	2
Reimplantacija uretera	4	
Resekcija posteriorne uretralne valvule	3	1
Ekscizija ureterocele	2	
Ukupno	41	7

masa koja se uvećava [12, 13]. Pojedini autori navode potrebu za ultrazvučnim kontrolama na svakih 3–6 meseci zbog povećanog rizika od maligne degeneracije, dok se drugi ne slažu sa ovim [14, 15]. Postoje neslaganja i oko potrebe za čestim kontrolama krvnog pritiska i renalne funkcije, naročito kod dečaka, zbog pretpostavljenog povećanog rizika od hipertenzije. Mišljenja su oprečna i oko razloga za izvođenje nefrektomije. Dok Webb i sar. [16] predlažu nefrektomiju zbog povećanog rizika od hipertenzije i maligne alteracije, Ranke i sar. [17] kao razlog za nefrektomiju navode izbegavanje doživotnog praćenja dece.

Dansko udruženje pedijatrijskih urologa smatra da multicistični bubreg treba odstraniti veoma rano, već u šestom mesecu života, s obzirom na to da je poprečnoprugasta muskulatura još uvek nerazvijena i da većina dece u ovom periodu još uvek ne sedi. Na ovaj način izbegava se doživotno praćenje deteta koje inače u slučaju ostavljenog bubrega vremenom postaje sve ređe, i otklanja strah kod roditelja kada se dete požali na bol u stomaku [18]. Dečji hirurzi Univerzitetske dečje klinike u Beogradu, smatraju da nakon kompletne evaluacije urinarnog sistema treba sačekati eventualno spontano povlačenje cisti i ne insistirati na nefrektomiji pre treće godine života zbog mogućih komplikacija anestezije. Ukoliko je u pitanju velika masa koja narušava respiraciju i gutanje ili se progresivno uvećava treba odmah uraditi nefrektomiju. Velike randomizirane studije koje su nedavno rađene govore u prilog ekspektativnog postupka i uzdržavanja od nefrektomije (osim u navedenim slučajevima kada je ona neophodna), i takođe ističu da je rizik od maligne alteracije praktično zanemarljiv [19, 20].

Uprkos suprostavljenim mišljenjima primeni cistoskopije i kolposkopije pre nefrektomije, u ovoj seriji dece cistoskopijom je otkriven ektopični ureter kod 10% dece, a kolposkopijom kod jedne devojčice neperforisani himen i ektopični ureter sa otvorom u vagini [21]. Iako neki autori ističu da je u odnosu na ukupan broj dece ovaj procenat nizak, dečji hirurzi koji su pratili ovu seriju dece smatraju da su ovo minorne intervencije, jer su deca već bila u anesteziji zbog nefrektomije koja je sledila, a svaka otkrivena anomalija od velikog je značaja kako za roditelje tako i za samo dete, naročito kod devojčica kod kojih sama anomalija ne bi bila otkrivena pre puberteta.

Upoređujući rezultate naše studije sa drugima kada je u pitanju anomalija kontralateralnog bubrega dolazimo do sličnih procenata. Blizu 32% dece od ukupnog broja prenatalno dijagnostikovane multicistične diplazije bubrega fetusa imalo je anomaliju kontralateralnog bubrega, dok je u najvećem broju studija ovaj procenat nešto viši (35%). Kod 7,9% dece radilo se o hidronefrozi u poređenju sa 8–12% kao rezultatom drugih studija [22]. Procenat ageneze kontralateralnog bubrega je 2,7% što odgovara rezultatima koje su izneli Dimmick i sar. [23] (2,3%), ali je znatno niži u poređenju sa 9% koje navode Lazebnik i sar. [22]. Kod 22% dece postavljena je dijagnoza vezikoureteralnog refluksa, što je znatno više procenat u odnosu na rezultate koje su naveli Eijk i sar. [24] (8%), ali i znatno niži od 43% koje navode Wacksman i sar. [15]. S obzirom na visok procenat postojanja vezikoureteralnog refluksa kod unilateralne multicistične bolesti bubrega, dečji hirurzi Univerzitetske dečje klinike smatraju da nakon ultrazvučnog pregleda deteta posle rođenja, bez obzira na to da li je nalaz normalan ili ne, treba predložiti mikcionu cistouretrografiju. Razlog za to je što čak i kod ozbiljnog vezikoureteralnog refluksa ehosonografski nalaz može biti sasvim normalan. Međutim, s obzirom na činjenicu da vezikoureteralni refluks predisponira infekciju urinarnog sistema i može voditi ka ožiljavanju bubrežnog parenhima i hroničnoj bubrežnoj insuficijenciji, oni smatraju da svu decu sa prenatalno dijagnostikovanom unilateralnom displazijom bubrega treba lečiti malim dozama antibiotika do trećeg meseca života.

Što se tiče anomalija ipsilateralne strane, rezultati se razlikuju u odnosu na druge studije. U našoj studiji kao najčešća anomalija javljaju se megaureter, ektopični ureter i vezikoureteralni refluks, dok se u većini drugih studija kao najčešći uzroci navode stenoza pijeloureteralnog spoja i vezikoureteralni refluks [25]. Ureterocela je bila prisutna kod 2,7% dece što je nešto više od rezultata koje navode Lazebnik i sar. [22] po kojima je ona sporadični uzrok, kod svega 0,5% dece [22]. Vezikoureteralni refluks ipsilateralne strane bio je prisutan kod 5,4% dece što je znatno niži procenat u odnosu na rezultate koje su u svojoj studiji izneli Eijk i sar. [24] (14%) i čak 43% koje navode drugi autori [15].

Anomalije nižih partija bile su prisutne kod 13,2% dece što je znatno više od 6% koje navode Atiyeh i sar. [7]. Pri tome, u našoj studiji najčešća anomalija bila je posteriorna ureteralna valvula dok se u većini drugih studija kao najčešća anomalija navodi intravezikalna opstrukcija.

Procenat udruženih ekstrarenalnih anomalija od 13,2% niži je od onih koje navode Aubertin i sar. [11] (16%) i Lazebnik i sar. [22] (35%). S obzirom na to da je bilo samo petoro dece sa udruženim ekstrarenalnim anomalijama i da je kod svih bilo reči o drugoj anomaliji, nije moguće zaključiti koja ekstrarenalna anomalija se najčešće udružuje sa unilateralnom multicističnom bolešću bubrega. Kurjak i sar. [1] navode da su to najčešće anomalije kardiovaskularnog i genitalnog sistema.

Podaci o polnoj distribuciji u saglasnosti su sa podacima iz drugih studija o ukupno većoj učestalosti anomalija kod muških fetusa, što se uglavnom objašnjava specifičnostima embrionalnog razvoja urinarnog sistema, u prvom redu muške uretre [26, 27].

Kao i u drugim studijama, anomalija je bila češća sa leve strane. Za ovu „pravilnost“ ne postoji jasnije objašnjene izuzev činjenice da su specifični anatomski odnosi (položaj renalnih krvnih sudova, utok testikularnih/ovarijalnih vena, pelvični deo puta uretera), razlog za češću sinistroponiranost anomalije [26, 27]. U literaturi postoji podatak o češćoj zastupljenosti megauretera sa leve strane, pri čemu ne nalazimo jasnije objašnjenje za ovu statističku pravilnost [28].

Zaključak

Deca sa unilateralnom multicističnom displazijom bubrega imaju veliki rizik od postojanja anomalije i kontralateralnog bubrega i urinarnog sistema uopšte, tako da moraju biti precizno pregledana kako prenatalno tako i postnatalno. Predlažemo obavezne serijske ekspertske prenatalne ultraz-

vučne preglede, a zatim postnatalno ultrazvuk, izotopski sken i posebno izvođenje mikcione cistureterografije, s obzirom na visoki procenat postojanja vezikoureteralnog refluksa kontralateralnog bubrega. Kada se planira nefrektomija traba uraditi cistoskopiju i kolposkopiju radi otkrivanja mogućih skrivenih anomalija urogenitalnog sistema.

L I T E R A T U R A

1. *Kurjak A. Mirić D.* Prenatal detection of congenital fetal malformation. In: *Kurjak A,* editor. Gynecology and perinatology. Varaždinske Toplice; Golden Time; 1995. p. 101–19. (Serbian)
2. *Rudnik-Schöneborn S, John U, Deget F, Ehrich JH, Misselwitz J, Zerres K.* Clinical features of unilateral multicystic renal dysplasia in children. Eur J Pediatr 1998; 157(8): 666–72.
3. *Coplen DE, Ortenberg J. Early* Development of the Genitourinary Tract. In: *Gillenwater JY, Grayhack JT, Howards Ss, Mitchell ME,* editors. Adult and pediatric urology. Philadelphia:Lippincott Williams and Wilkins; 2002. p. 2027–40.
4. *Prats P, Maiz N, Rodriguez MA, Pedrero C,. Torrents M, Astudillo F, Carrera JM.* Ultrasound diagnosis of urinary tract anomalies. In: *Kurjak A,* editor. Perinatal medicine. London: Taylor & Francis; 2006. p. 451–81.
5. *Pinto V, Wankelmuth M, D'Addario V.* General aspects on ultrasound screening of congenital anomalies. In: *Kurjak A, Chervenak FA,* editors. Donald scholl textbook of ultrasound in obstetrics and gynecology. 1th ed. New Delhi: Yaypee brothers medical publishers; 2004; p. 365–72.
6. *Weiner JS.* Multicystic dysplastic kidney. In: *Belman AB, King LR, Kramer SA,* editors. Clinical Pediatric Urology. 4th ed. London: Taylor & Francis; 2002; p. 633–45.
7. *Atiyeh B, Husmann D, Baum M.* Contralateral renal abnormalities in multicystic-dysplastic kidney disease. J Pediatr 1992; 121(1): 65–7.
8. *Nicolaides KH, Cheng HH, Abbas A, Snijders RJ, Gosden C.* Fetal renal defects: associated malformations and chromosomal defects. Fetal Diagn Ther 1992; 7(1): 1–11.
9. *al-Khaldi N, Watson AR, Zuccollo J, Twining P, Rose DH.* Outcome of antenatally detected cystic dysplastic kidney disease. Arch Dis Child 1994; 70(6): 520–2.
10. *Aslam M, Watson AR; Trent & Anglia MCDK Study Group.* Unilateral multicystic dysplastic kidney: long term outcomes. Arch Dis Child 2006; 91(10): 820–3.
11. *Aubertin G, Cripps S, Coleman G, McGillivray B, Yong SL, Van Allen M,* et al. Prenatal diagnosis of apparently isolated unilateral multicystic kidney: implications for counselling and management. Prenat Diagn 2002; 22(5): 388–94.
12. *Elder JS, Hladky D, Selzman AA.* Outpatient nephrectomy for nonfunctioning kidneys. J Urol 1995; 154(2 Pt 2): 712–4.
13. *Maloney ME.* Multicystic Dysplastic Kidney. E:edicine; February 14, 2004; Avalable from: URL: http://www.emedicine.com/radio/topic458.htm
14. *LaSalle MD, Stock JA, Hanna MK.* Insurability of children with congenital urological anomalies. J Urol 1997; 158(3 Pt 2): 1312–5.
15. *Wacksman J, Phipps L.* Report of the Multicystic Kidney Registry: preliminary findings. J Urol 1993; 150(6): 1870–2.
16. *Webb NJ, Lewis MA, Bruce J, Gough DC, Ladusans EJ, Thomson AP,* et al. Unilateral multicystic dysplastic kidney: the case for nephrectomy. Arch Dis Child 1997; 76(1): 31–4.
17. *Ranke A, Schmitt M, Didier F, Droulle P.* Antenatal diagnosis of Multicystic Renal Dysplasia. Eur J Pediatr Surg 2001; 11(4): 246–54.
18. *Lippert MC*: Renal cystic disease. In *Gillenwater JY, Grayhack JT, Howards SS, Duckett JW* editors. Adult and Pediatric Urology. 3th ed. Philadelphia: Lippincott Williams and Wilkins; 2002; p. 829.
19. *Rabelo EA, Oliveira EA, Diniz JS, Silva JM, Filgueiras MT, Pezzuti IL,* et al. Natural history of multicystic kidney conservatively managed: a prospective study. Pediatr Nephrol 2004; 19(10): 1102–7.
20. *Rabelo EA, Oliveira EA, Silva GS, Pezzuti IL, Tatsuo ES.* Predictive factors of ultrasonographic involution of prenatally detected multicystic dysplastic kidney. BJU Int 2005; 95(6): 868–71.
21. *Cooper CS, Snyder HM.* Ureteral anomalies. In *Gillenwater JY, Grayhack JT, Howards SS, Duckett JW* editors. Adult and Pediatric Urology. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2002; p. 2156–86.
22. *Lazebnik N, Bellinger MF, Ferguson JE 2nd, Hogge JS, Hogge WA.* Insights into the pathogenesis and natural history of fetuses with multicystic dysplastic kidney disease. Prenat Diagn 1999; 19(5): 418–23.
23. *Dimmick JE, Johnson HW, Coleman GU, Carter M.* Wilms tumorlet, nodular renal blastema and multicystic renal dysplasia. J Urol 1989; 142(2 Pt 2): 484–5.
24. *van Eijk L, Cohen-Overbeek TE, den Hollander NS, Nijman JM, Wladimiroff JW.* Unilateral multicystic dysplastic kidney: a combined pre- and postnatal assessment. Ultrasound Obstet Gynecol 2002; 19(2): 180–3.
25. *Husmann D*, Baum M. Contralateral renal abnormalities in multicystic-dysplastic kidney disease. J Pediatr 1992; 12(1): 65–7.
26. *Bukowski R, Smith GC.* Faster growth of male fetuses in first trimester of pregnancy. Am J Obstetrics Gynecol 2006; 195(6): S134.
27. *Favorito LA, Cardinot TM, Morais AR, Sampaio FJ.* Urogenital anomalies in human male fetuses. Early Hum Dev 2004; 79(1): 41–7.
28. *Shokeir AA, Nijman RJ.* Primary megaureter: current trends in diagnosis and treatment. BJU Int 2000; 86(7): 861–8.

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Poor outcome in patients with diffuse large B-cell lymphoma is associated with high percentage of bcl-2 and Ki 67-positive tumor cells

Visok procenat bcl-2 i Ki-67 pozitivnih tumorskih ćelija udružen je sa lošijom prognozom kod bolesnika sa difuznim krupnoćelijskim B- limfomom

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Abstract

Background/Aim. Newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL) tretaed with immunochemotherapy have durable remission and improved overall survival. It is important to identify high risk patients who may benefit from even more effective therapies. **Methods.** In a group of 50 newly diagnosed patients with DLBCL, treated with CHOP/R-CHOP (cyclophosphemide doxorubicine, vincristine, prednisone with or without rituximab) regimen, we analyzed the prognostic value of the expression of Ki67 and bcl-2 at diagnosis as well as other standard clinical parameters: International Prognostic Index (IPI), bulky disease, extranodal distribution and lactat dehydrogenase (LDH). Significance was tested according to response rate and overall survival. **Results.** Univariate survival analysis showed that high IPI had a statistically significant negative influence on overall and event free survival time (log rank, $p < 0.01$). The log rank test analysis signified that patients with a high proliferative fraction (Ki-67 > 60%) had a worse overall survival rate (OS5y) of 40% compared to those with low proliferation (Ki-67 < 60%) with OS5y of 80% ($p < 0.01$). There was a clear difference between bcl-2 positivity (treshold 50%) and the achievement of complete remission (66% *vs* 86% in patients with bcl-2 high and low levels respectively, $p < 0.05$). In survival analysis, patients with low bcl-2 expression had significantly higher OS5y - 68% compared to those with high bcl-2+ with OS5y 37% ($p < 0.05$). Multivariate analysis performed by Cox model revealed that IPI > 3, high Ki-67+, bcl-2 positivity had a significant independent prognostic value concerning overall survival ($p < 0.05$). **Conclusion.** An initial high IPI score associated with high Ki-67+ and bcl2+ could represent possible predictive factors of poor prognosis, which would help to identify a high risk subgroup of newly diagnosed DLBCL.

Key words:
lymphoma, b-cell; genes, bcl-2; ki-67 antigen; prognosis; antineoplastic combined chemotherapy protocols.

Apstrakt

Uvod/Cilj. Novodijagnostikovani bolesnici sa difuznim krupnoćelijskim B-limfomom (DBKL) lečeni imunohemioterapijom imaju duge remisije i bolje ukupno preživljavanje. Važno je otkriti bolesnike sa visokim rizikom kojima primena efikasnijeg terapijskog pristupa može pomoći. **Metode.** U grupi od 50 novodijagnostikovanih bolesnika sa DBKL lečenih protokolom CHOP/R-CHOP (ciklofosfamid, doksorubicin, vinkristin, prednizon sa ili bez rituksimaba), analizirali smo prognostičku vrednost ekspresije Ki-67 i bcl-2 u trenutku postavljanja dijagnoze, uključujući i kliničke parametre: internacionalni prognozni indeks (IPI), voluminoznu tumorsku masu, ekstranodalnu lokalizaciju bolesti, nivo laktat-dehidrogenaze. Njihova značajnost testirana je u odnosu na terapijski odgovor i ukupno preživljavanje. **Rezultati.** Univarijantna analiza preživljavanja pokazala je da visok IPI ima statistički značajan negativan uticaj na *event-free survival* i ukupno preživljavanje (*logrank* test, $p < 0,01$). Analiza *logrank* testom pokazala je da bolesnici sa DBKL koji ima visok proliferativni indeks (Ki-67 > 60%) imaju lošije ukupno preživljavanje u odnosu na one sa niskom proliferacijom (Ki-67 < 60%) (40% : 80%, $p < 0,01$). Postoji jasna razlika između bcl-2 pozitivnosti (granična vrednost 50%) i postizanja potpune remisije (66% : 86% između bcl-2 pozitivnih i negativnih bolesnika, $p < 0,05$). U analizi preživljavanja bcl-2 negativni bolesnici imaju značajno bolje preživljvanje u odnosu na bcl-2 pozitivne bolesnike (68% prema 37%, $p < 0,05$). Multivarijantna analiza izvedena prema Koksovom modelu pokazala je da IPI > 3, visoka Ki-67 i bcl-2 pozitivnost imaju značaj nezavisne prognostičke varijable u pogledu ukupnog preživljavanja. ($p < 0,05$). **Zaključak**. Visoka vrednost IPI u trenutku postavljanja dijagnoze udružena sa visokim vrednostima Ki-67 i bcl-2+ potencijalno mogu predstavljati faktore lošije prognoze koji mogu pomoći u otkrivanju visokorizičnih bolesnika sa DBKL dijagnozom.

Ključne reči:
limfom, b-ćelije; geni, bcl-2; antigen, Ki-67; prognoza; lečenje kombinovanjem antineoplastika, protokoli.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of Non-Hodgkin lymphoma (NHL) accounting for 30% of all newly diagnosed cases [1, 2]. The CHOP (cyclophosphamide, doxorubicine, vincristine, prednisone) regimen alone or with rituximab (CHOP/R) is standard therapeutic approach for the most patients who have DLBCL. Even with current treatment approaches, a substantial minority of patients (about 30%) are not cured [3, 4]. The International Prognostic Index (IPI) is the most important tool for predicting response to treatment for DLBCL [5]. A substantial variability in outcome has been observed despite IPI subgroups [6]. Thus, identifying new prognostic parameters might contribute towards better prediction of outcome and the development of effective risk-adaptive strategies [7].

In all clinical models, including the IPI index, there was marked residual heterogenity in outcome, as reflected by the considerably variable survival of patients with identical prognostic scores [6]. The latter was attributed to the marked genetic and molecular heterogeneity that underlies disease aggressiveness and tumor progression, and led to the evaluation of molecular and genetic markers associated with patients survival [6]. The hallmark features of the tumor cell phenotype, which contribute to aggressive tumor behaviour are: its capacity for sustained proliferation, evasion of apoptosis, disregard of signals to stop proliferation and differentiation and the capacity to invade and promote angiogenesis [8].

Ki-67 is a nuclear antigen expressed by dividing cells. The percentage of Ki-67 expressing cells reflects the proportion of the tumor cells that are actively cycling and dividing [6].

Bcl-2 is an anti-apoptotic protein that is important in normal B-cell development and differentiation [4]. The role of bcl-2 as a predictor of survival in DLBCL is controversial [9]. Overexpression of bcl-2 protein in NHL cells has been blamed for their resistance to chemotherapy both *in vitro* and *in vivo* [10–13]. Bcl-2 overexpression has been reported in approximately 40-60% of patients with DLBCL and has been associated with inferior survival [4]. Rituximab can mitigate the negative prognostic effect of bcl-2 expression in DLBCL [3].

Herein, we evaluate the prognostic significance of initial bcl-2 and Ki-67 positivity in tumor cells. Furthermore we correlate these parameters with IPI and bulky disease and their significance was evaluated according to treatment response and overall survival.

Methods

Retrospective analysis was performed on 50 randomly selected patients diagnosed at the Institute of Hematology from 2001 to 2003. Patients included in the study had an initial diagnosis of DLBCL according to the World Health Organization (WHO) classification [14]. Clinical and laboratory data from the time of initial diagnosis as well as follow up information were available. The follow-up period was up to 6 years, with median follow-up time for all patients of 40 months from the date of starting the treatment up to the last follow-up or death.

The cases with histologic transformation of indolent lymphoma into DLBCL were not included.

This study was performed on samples taken during regular clinical work-up procedures and staging after approval by the Institutional Review Board of the Institute of Hematology, Clinical Center of Serbia, according to the Helsinki Declaration and good clinical practice policy.

In all patients standard clinical and laboratory data were collected: age, gender, Ann Arbor stage, extranodal sites, bulky disease, clinical stage, B symptoms (LDH) [15]. Bulky disease was defined as a mediastinal mass larger than one third of the maximum thoracic diameter and/or any node over 5 cm. The IPI was calculated according to the five high risk features: age > 60 years, performance status > 2 (PS), Ann Arbor tumor stage 3 or 4, LDH > 460 IU/μL, and number of extranodal sites >1 while patients were divided into a low risk group (0 – 2 factors) and a high-risk group (3 or 4 factors) [5].

This retrospective analysis was performed on 50 patients randomly selected from a large group of patients diagnosed and treated with CHOP/R-CHOP regimen with or without adjuvant radiotherapy and/or surgery over a five-year period. The response rate was determined according to standard Cheson criteria [16].

The 4 μm thick tissue sections were dehydrated and deparafinized according to standard procedures and stained with haematoxylin and eosin, Giemsa and reticulin (Gordon Sweet), and examined by light microscopy.

For immunohistochemical analysis, pretreatment antgen retrieval by microwave heating in 10 mM citrate buffer pH 8 was performed according to the manufacturer directions and current laboratory protocol. Incubation was performed using the following primary antibodies: bcl-2 (clone 124, Dako, Denmark) and Ki 67 (clone MIB 1, Dako, Denmark), together with standard diagnostic panel for DLBC NHL.

Immunoreaction with a standard indirect immunoperoxidase technique was developed applying an avidin-biotin complex method (ABC, LSAB2 kit peroxidase, Dako, Denmark) using AEC as chromogen. Sections were counterstained with Mayer hematoxylin.

Two hematopathologists reviewed and evaluated all slides at the time of immunohistochemical analysis. They confirmed the diagnosis of DLBCL according to criteria outlined by the WHO classification. The percentage of tumor cells with Ki-67+ nuclear staining on 10 different high power microscopy fields (HPF, 400×) was determined. The intensity of this staining were graded as weak (0-30% Ki-67+), moderate (31–60% Ki-67+ cells), and strong (>60% Ki-67+ cells). Tumors were considered positive when at least 50% of tumor cells expressed bcl-2 protein.

The response rates were analyzed according to widely accepted international Cheson criteria. For the purpose of statistical analysis, partial remission, non response and progressive disease were considered as treatment failures. Event free survival (EFS) was measured from the start of treatment to the date of primary treatment failure, relapse, or the date

of last follow-up. Overall survival (OS) was measured from the beginning of treatment to the time of last follow-up (censored patients) or time of death.

For univariate analysis, the χ^2 and Fischer exact tests were used to assess the association between molecular and clinical and laboratory variables. Survival analysis was performed by the Kaplan-Meier method. The statistical significance of differences in EFS and OS between groups of patients was estimated by the logrank test. Statistical significance of prognostic variables was also evaluated by multivariate analysis using Cox proportional hazard model. For nonparametric variables and analysis of factors influencing outcome of treatment, nonparametric tests Mann-Whitney U test and Kruskall-Wallis test were applied.

All tests were two-sided at the threshold of p values = 0.05. Values $p < 0.05$ were considered statistically significant. All statistical analysis were performed by licensed Statistical Analysis Software (Stat Soft, Inc. Tulsa USA, 2005. STATISTICA data analysis software system, version 7.1; www.statsoft.com) [16].

Results

Laboratory and clinical features of 50 patients (30 male/20 female) with DLBCL are listed in Table 1. The patients age ranged from 17–87 years, with the mean age of 50 ± 18.16 years. On presentation, 64% of patients were classified as being in stage III and stage IV. High IPI was present in 36% of patients. Initial bulky disease was confirmed in 24%, extranodal distribution in 68%, B symptoms in 76% and LDH > 460 IU/μL in 62% of patients.

After the first line therapy, complete remission (CR) was achieved in 39 patients (78%), while treatment of 11 patients failed. After a 5-year follow-up, 28 (56%) patients were still in CR, while 22 (44%) patients died.

Statistical analysis of certain clinical variables revealed that patients with bulky form of the disease had significantly higher LDH levels (*t*-test and χ^2 $p < 0.05$), but there was no association between bulky disease and other clinical variables.

Concerning remission rates, we were unable to show that bulky or extranodal disease, constitutional symptoms or LDH level bored any relation to CR rates (χ^2 $p > 0.05$).

According to IPI, the distribution of patients was as follows: IPI ≤ 1 in 11, IPI 2 in 21 and IPI ≥ 3 in 18 patients, meaning that low IPI score was present in 32 and high IPI score in 18 patients. Concerning IPI score values we found no correlations between low and high IPI and bulky disease. Univariate survival analysis showed that high IPI had statistically significant negative influence on OS, and also on EFS (logrank, $p < 0.01$). Patients with IPI ≥ 3 had significantly more progressive disease and shorter overall survival (OS5y not reached, median OS 7 months compared to OS5y of 87% in patients with low IPI).

Univariate analysis showed that extra nodal disease, bulky form, and the existence of B symptoms had certain influence on OS and EFS but these differences were not statistically significant (log rank, $p > 0.05$), whereas increased LDH level did have a significant effect on overall survival.

Table 1

Clinical data on analyzed patients (n = 50)

Patients' characteristics	n	%
Gender		
male	30	60
female	20	40
Constitutional symptoms		
yes	38	76
no	12	24
Clinical stage		
I, II	18	36
III, IV	32	64
International Prognostic Index (IPI) score		
low risk	32	64
high risk	18	36
Bulky disease		
yes	12	24
no	38	76
Extranodal disease		
yes	34	68
no	16	32
Lactate dexydrogenase (IU/μL)		
> 460	31	62
< 460	19	38

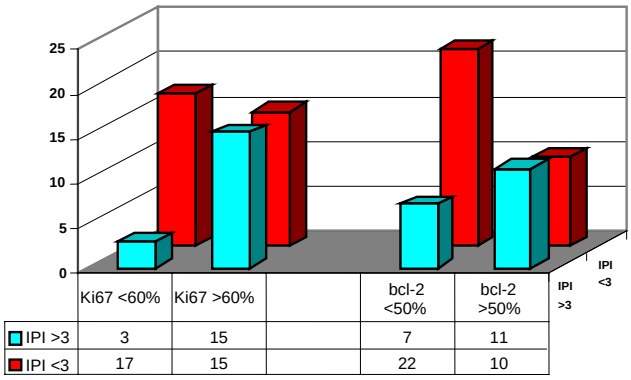
Multivariate analysis revealed that IPI > 3 had an independent prognostic impact on survival ($p < 0.01$) together with extranodal distribution and LDH levels ($p < 0.05$) as a part of IPI score.

The cell proliferation marker Ki-67 was observed as nuclear staining in tumor cells and in lymphocytes within the tumor tissues in all 50 cases. The staining intensity and number of tumor cells positive to Ki-67 varied from case to case, ranging from 30% to 95%. None of the patients had more than 95% Ki-67 positive tumor cells.

Statistical analysis of clinical variables revealed that there was a correlation between high Ki-67+ and high LDH levels, but this was not statistically significant (*t*-test and χ^2 $p > 0.05$).

Values of Ki-67 positive tumor cells follows the values of IPI scores, meaning that patients with a high proliferation rate also had high IPI value (IPI > 3). We found statistically significant positive correlation between low and high Ki-67+ and IPI scores (χ^2, Mann Whitney U test and Spearman Rank correlation, $p < 0.05$)

Thirty of 50 patients (60%) had Ki 67+ in > 60% of tumor cells. In the group with fatal outcome 15 out of 22 patients had Ki 67+ in > 60% of tumor cells (Figure 1). The logrank test analysis signified that patients with a high proliferative fraction (Ki-67 > 60%) had a worse overall survival (OS5y) of 40% compared to those with low proliferation (Ki-67 < 60%) with OS5y of 80% ($p < 0.01$) (Figure 2). In multivariate analysis performed by Cox model we found that high Ki-67+ (at a threshold of 60% of positive cells) was marginally significant ($p = 0.057$).



	Ki67 <60%	Ki67 >60%	bcl-2 <50%	bcl-2 >50%
IPI >3	3	15	7	11
IPI <3	17	15	22	10

Fig. 1 – Frequency of Ki-67, bcl-2 and International Prognostic Index (IPI) values in diffuse large B cell lymphoma patients

Antiapoptotic protein bcl-2, was detected as a distinct cytoplasmic staining pattern of the tumor cells. Immunohistochemical analysis revealed that bcl-2+ was dominantly high (> 50%) in 21 patients (42% of analyzed cohort) (Figure 1).

Concerning bcl-2 positivity at a threshold level of 50% of positive labeled cells, we found the same pattern as was detected for Ki-67, meaning that patients with high percentage of bcl-2+ tumor cells also had high IPI value (IPI > 3) (Figure 1), and there was statistically significant positive correlation between low and high bcl-2 and IPI scores (χ^2 Mann Whitney U test and Spearman Rank correlation, $p < 0.05$). There was a negative correlation between bcl-2+ and achievement of CR (66% vs. 86% in patients with bcl-2 high and low levels respectively, $p < 0.05$). Patients with low bcl-2 expression (< 50% of tumor cells) survived significantly longer (OS5y median time rate 68%) compared to those with high bcl-2+ (OS5y 37%) (Figure 3).

Multivariate analysis by Cox regression model, revealed that bcl-2 positivity (threshold 50%) had a significant independent prognostic value concerning overall survival ($p < 0.05$). Statistical analysis showed that there was significant correlation between high bcl-2 and Ki-67 positivity. Furthermore these patients had significantly shorter OS ($p < 0.05$).

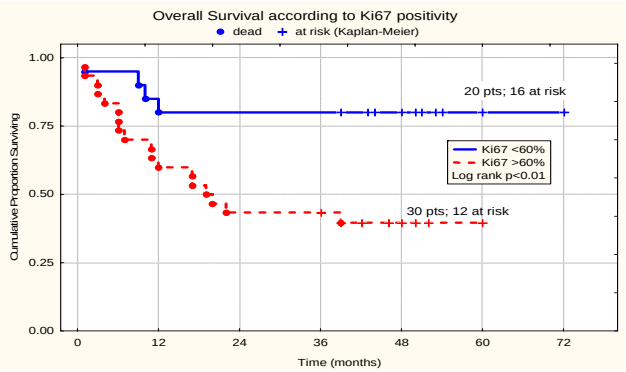


Fig. 2 – Survival curves of diffuse large B cell lymphoma patients according to Ki-67 values (Kaplan-Meier)

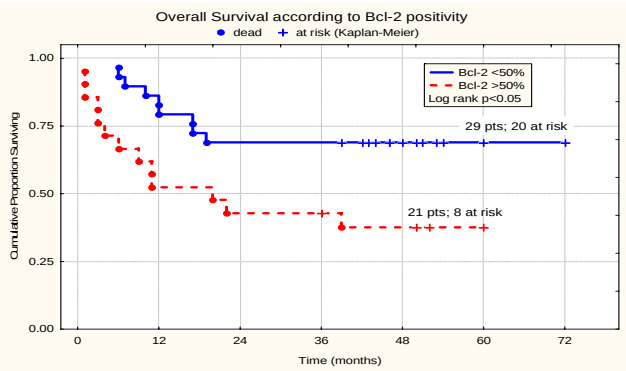


Fig. 3 – Survival curves of diffuse large B cell lymphoma patients according to bcl-2 values (Kaplan-Meier)

Discussion

Although studies of individual biomarkers have improved our understanding of the pathogenesis of DLBCL, many studies have yielded conflicting results. Reasons for these discrepancies include the retrospective nature of most studies, small patient sample size, lack of uniformity in technique and failure to control other simultaneous biologic processes that may confound outcomes. Importantly, these markers need to be revalidated in patients who have been treated with immunochemotherapy [4].

In the study of Hans et al [9] the IPI score predicted OS ($p < 0.001$) and EFS ($p < 0.001$) when comparing those with low (0-2) versus high (3-5) scores. In our study, univariate survival analysis showed that high IPI had a statistically significant negative influence on overall and also on event free survival time (logrank, $p < 0.01$). The patients with IPI ≥ 3 had significantly more progressive disease and shorter overall survival (OS5y not reached, median OS 7 months compared to OS5y of 87% in patients with low IPI). Multivariate analysis revealed that IPI > 3 had an independent prognostic impact on survival ($p < 0.01$) together with extranodal distribution and LDH levels ($p < 0.05$). In the study of Colomo et al. [17] the IPI

also had a high value for predicting OS (p<0.00001). Extranodal disease, bulky disease, and B symptoms had certain influence on OS and EFS, but these differences were not statistically significant (logrank, p>0.05). Increased LDH level had significant effect on overall survival.

Diffuse large B cell lymphoma is heterogenous, and the expression of bcl-2 is variable [18].

In most studies, bcl-2 protein expression alone or in combination with other factors (e.g. high IPI) is regarded as evidence of both t (14;18) and an aggressive clinical course, the OS and disease-free survival curves being significantly worse than in bcl-2- cases (19–22). In the study of Colomo et al. [17] bcl-2 expression was included in the Cox model along with the IPI (low risk *vs* low/intermediate-risk *vs* high/intermediate-risk *vs* high-risk). Bcl-2 maintained a trend of independent prognostic value, although the IPI remained most significant variable.

Concerning bcl-2 positivity at the threshold level of 50% of positive tumor cells, we have found that patients with high percentage of bcl-2+ tumor cells also had high IPI value (IPI > 3), and there was statistically significant positive correlation between low and high bcl-2 and IPI scores (χ^2, Mann Whitney U test and Spearman Rank correlation, $p < 0.05$). Furthermore, there was a clear difference between bcl-2+ and the achievement of CR (66% *vs* 86% in patients with bcl-2 high and low levels respectively, $p < 0.05$). Multivariate analysis by Cox regression model revealed that bcl-2 positivity (threshold 50%) had a significant independent prognostic value concerning OS ($p < 0.05$).

However, multiple studies have looked at the expression of bcl-2 using immunostains, and most have found no difference in OS (23–25).

A critical look at the various results during the last 10 years shows considerable variation. Although a predictive value for DFS is reported in most series, the predictive value of bcl-2 positivity for OS is not reliably consistent among those reports. Although some series may lack the statistical power to detect survival difference, variations in scoring and interpreting bcl-2 staining are likely to account for such discrepancies [26].

The prognostic significance of Ki-67 expression in DLBCL is controversial [6]. Tumors with low Ki-67 index may exibit resistance to chemotherapy, given that the majority of the malignant cells are in G0/G1 and thus are resistant to cycle specific cytotoxic chemotherapy. Furthermore, G0/G1 arrested cells have time to repair DNA damage induced by the chemotherapy and thus survive [6]. The proliferative fraction in DLBCL as detected by Ki-67 staining is usually high (> 40%) and may be greater than 90% in some cases [27].

Miller et al. [26] analyzed the prognostic significance of Ki-67 staining in 60 representative DLBCL patients from the Intergroup 0067 study that compared four different antracycline-based regimens, and found that the 3-year OS was significantly shorter in patients with Ki-67 nuclear expression in 80% or more malignant cells. In a subsequent study on 105 DLBCL patients, the same authors demonstrated that high proliferative activity, defined in this study as nuclear Ki-67 expression in greater than 60% of malignant cells, was a strong predictor of poor survival (logrank, $p = 0.003$,) [27]. The Nordic Lymphoma Group Study defined low expresion of Ki-67 as less than 60% of tumor cells, and found that expression of Ki-67 was not associated with significant differences in a 5-year OS [28].

We found that values of Ki-67 positive tumor cells follows the values of IPI scores, meaning that patients with high proliferation rate also had high IPI value (IPI > 3). There was a statistically significant positive correlation between low and high Ki-67+ and IPI scores (χ^2, Mann Whitney U test and Spearman Rank correlation, $p < 0.05$). The logrank test analysis signified that patients with a high proliferative fraction (Ki67 > 60%) had worse overall survival (OS5y) of 40% compared to those with low proliferation (Ki67 < 60%) with OS5y of 80% ($p < 0.01$) (Figure 2). In multivariate analysis performed by Cox model we found that high Ki-67+ (at a threshold of 60% of positive cells) was marginally significant ($p = 0.057$).

Conclusion

We found that a high percentage of bcl-2 and Ki-67 positive tumor cells was associated with worse prognosis. Furthermore there was positive correlation between these molecular parameters and high IPI score.

Taken together, biological factors in combination with clinical models such as IPI, might become an integral part of our daily practice in finding a way to a more individualized or patient-tailored practice in oncology.

R E F E R E N C E S

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997; 89(11): 3909–18.
2. *Coiffier B.* Diffuse large cell lymphoma. Curr Opin Oncol 2001; 13(5): 325–34.
3. *Mounier N, Briere J, Gisselbrecht C, Emile JF, Lederlin P, Sebban C,* et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2--associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003; 101(11): 4279–84.
4. *Sehn LH.* Optimal use of prognostic factors in non-Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program 2006: 295–302.
5. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329(14): 987–94.
6. *Lossos IS, Morgensztern D.* Prognostic biomarkers in diffuse large B-cell lymphoma. J Clin Oncol 2006; 24(6): 995–1007.
7. *Biasoli I, Morais JC, Scheliga A, Milito CB, Romano S, Land M,* et al. CD10 and Bcl-2 expression combined with the International Prognostic Index can identify subgroups of patients

with diffuse large-cell lymphoma with very good or very poor prognoses. Histopathology 2005; 46(3): 328–33.
8. *Hanahan D, Weinberg RA.* The hallmarks of cancer. Cell 2000; 100(1): 57–70.
9. *Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G,* et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004; 103(1): 275–82.
10. *Barrans SL, Carter I, Owen RG, Davies FE, Patmore RD, Haynes AP,* et al. Germinal center phenotype and bcl-2 expression combined with the International Prognostic Index improves patient risk stratification in diffuse large B-cell lymphoma. Blood 2002; 99(4): 1136–43.
11. *Hermine O, Haioun C, Lepage E, d'Agay MF, Briere J, Lavignac C,* et al. Prognostic significance of bcl-2 protein expression in aggressive non-Hodgkin's lymphoma. Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood 1996; 87(1): 265–72.
12. *Kramer MH, Hermans J, Wijburg E, Philippo K, Geelen E, van Krieken JH,* et al. Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. Blood 1998; 92(9): 3152–62.
13. *Hill ME, MacLennan KA, Cunningham DC, Vaughan Hudson B, Burke M, Clarke P,* et al. Prognostic significance of BCL-2 expression and bcl-2 major breakpoint region rearrangement in diffuse large cell non-Hodgkin's lymphoma: a British National Lymphoma Investigation Study. Blood 1996; 88(3): 1046–51.
14. *Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J,* et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17(12): 3835–49.
15. *Rosenberg SA.* Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep 1977; 61(6): 1023–7.
16. *Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM,* et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17(4): 1244.
17. *Colomo L, López-Guillermo A, Perales M, Rives S, Martínez A, Bosch F,* et al. Clinical impact of the differentiation profile assessed by immunophenotyping in patients with diffuse large B-cell lymphoma. Blood 2003; 101(1): 78–84.
18. *Gascoyne RD, Adomat SA, Krajewski S, Krajewska M, Horsman DE, Tolcher AW,* et al. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. Blood 1997; 90(1): 244–51.
19. *Rantanen S, Monni O, Joensuu H, Franssila K, Knuutila S.* Causes and consequences of BCL2 overexpression in diffuse large B-cell lymphoma. Leuk Lymphoma 2001; 42(5): 1089–98.
20. *Xu Y, McKenna RW, Molberg KH, Kroft SH.* Clinicopathologic analysis of CD10+ and CD10- diffuse large B-cell lymphoma. Identification of a high-risk subset with coexpression of CD10 and bcl-2. Am J Clin Pathol 2001; 116(2): 183–90.
21. *Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A,* et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J Clin Oncol 2006; 24(6): 961–8.
22. *Piris MA, Pezzella F, Martinez-Montero JC, Orradre JL, Villuendas R, Sanchez-Beato M,* et al. [corrected to Pezzella F, et al. p53 and bcl-2 expression in high-grade B-cell lymphomas: correlation with survival time. Br J Cancer 1994; 69(2): 337–41.
23. *Kramer MH, Hermans J, Parker J, Krol AD, Kluin-Nelemans JC, Haak HL,* et al. Clinical significance of bcl2 and p53 protein expression in diffuse large B-cell lymphoma: a population-based study. J Clin Oncol 1996; 14(7): 2131–8.
24. *Zhang A, Ohshima K, Sato K, Kanda M, Suzumiya J, Shimazaki K,* et al. Prognostic clinicopathologic factors, including immunologic expression in diffuse large B-cell lymphomas. Pathol Int 1999; 49(12): 1043–52.
25. *de Jong D, Rosenwald A, Chhanabhai M, Gaulard P, Klapper W, Lee A,* et al; Lunenburg Lymphoma Biomarker Consortium. Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2007; 25(7): 805–12.
26. *Miller TP, Grogan TM, Dahlberg S, Spier CM, Braziel RM, Banks PM,* et al. Prognostic significance of the Ki-67-associated proliferative antigen in aggressive non-Hodgkin's lymphomas: a prospective Southwest Oncology Group trial. Blood 1994; 83(6): 1460–6.
27. *Jerkeman M, Anderson H, Dictor M, Kvaløy S, Akerman M, Cavallin-Ståhl E;* Nordic Lymphoma Group study. Assessment of biological prognostic factors provides clinically relevant information in patients with diffuse large B-cell lymphoma--a Nordic Lymphoma Group study. Ann Hematol 2004; 83(7): 414–9.

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K A Z U I S T I K A

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Stenting simptomatske visokogradusne stenoze bazilarne arterije

Stenting for symptomatic high-grade basilar artery stenosis

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Apstrakt

Uvod. Stenoze intrakranijalnih krvnih sudova, u koje spada i stenoza bazilarne arterije, su kod 5–10% bolesnika uzrok ishemijske bolesti mozga. Najčešći uzrok stenoze kod 95% bolesnika je arterioskleroza. Bolesnici sa stenozom bazilarne arterije i povratnim ishemijskim atacima koji se ne leče imaju lošu prognozu, sa mogućnošću razvoja infarkta kod 50% bolesnika u prve dve godine. **Prikaz bolesnika.** Prikazali smo bolesnika muškog pola, starog 48 godina, sa tranzitornim ishemijskim epizodama, povremenim slabljenjem vida i gubitkom ravnoteže u toku poslednjih 12 meseci. Urađena je multislajsna kompjuterizovana tomografija (MSCT) endokranijuma sa angiografijom intrakranijalnih krvnih sudova i dijagnostikovana je anularna stenoza bazilarne arterije od 85%. Digitalnom suptrakcionom angiografijom (DSA) potvrđeni su dužina, stepen i lokalizacija stenoze. Endovaskulna procedura sprovedena je u opštoj anesteziji kada je u prvom aktu urađena predilatacija stenoze balonom, a onda je plasiran samodilatirajući stent prečnika 3 × 12 mm. Kontrolnom angiografijom nakon stentinga potvrđena je potpuna dilatacija stenoze. **Zaključak.** Kombinacijom perkutane balon-angioplastike i samoekspandirajućeg stenta omogućeno je potpuno rešavanje simptomatske stenoze bazilarne arterije.

Ključne reči:
a. basilaris; angioplastika, balonska; stentovi; dijagnoza; lečenje, ishod; vertebrobazilarna insuficijencija.

Abstract

Background. Stenosis of brain vessels in 5–10% of cases causes ischemic disesase of the brain. Atherosclerosis is a cause of stenosis in 95% of cases. Patients with basilar artery stenosis and recurrent ischemic attacks are candidate for stroke in 50% of cases in the first two years. **Case report.** A 48-year old man presented with a 12-month history of transitory ischemic attacks, periodical loss of vision and balance disorder. Diagnostic cerebral angiography performed by MSCT revealed annular stenosis of basilar artery (85%). Digital subtraction angiography (DSA) confirmed dimensions, grade and localisation of stenosis. Endovascular stenting was performed in general anesthesia. The first step of procedure was preliminary balloon angioplasty and after that self- expandable stent (diameter of 3.0 mm, length of 12 mm) was placed. Check angiogram after stenting confirmed complete dilatation of basilar artery stenosis. **Conclusion.** Combination of balloon angioplasty and self-expandable stenting made possible non-surgical treatment of simptomatic basilar artery stenosis.

Key words:
basilar artery; angioplasty, balloon; stents; diagnosis; treatment outcome; vertebrobasilar insufficiency.

Uvod

Intrakranijalne stenoze visoko su rizične i često su uzrok infarkta mozga i smrti. Arterioskleroza je uzrok stenoze kod 95% bolesnika. Bolesnici sa stenozom bazilarne arterije koji se ne leče, imaju lošu prognozu sa mogućnošću razvoja infarkta kod 50% bolesnika u prve dve godine [1, 2]. Konzervativna terapija podrazumeva upotrebu antiagregacijskih i antikoagulantnih sredstava koja smanjuju rizik od ishemije, međutim ona ne može da reši redukovani protok kroz stenotični krvni sud [3]. Alternativna metoda za revaskularizaciju tokom zadnje dekade je ekstrakranijalna-intrakranijalna *by-pass* operacija, ali kao metoda izbora nije bila korisna kod bolesnika sa intrakranijalnim stenozama [4]. Perkutana balon angioplastika (PBA) kao procedura zbrinjavanja stenoze intrakranijalnih krvnih sudova počela je da se primenjuje 1980. godine, ali su početna iskustva bila povezna sa visokim rizikom od razvoja infarkta [5]. Tehnološki napredak u razvoju katetera, balona, kao i samoekspandirajućih intrakranijalnih stentova kojima može da se savlada krivina karotidnog sifona i verte-

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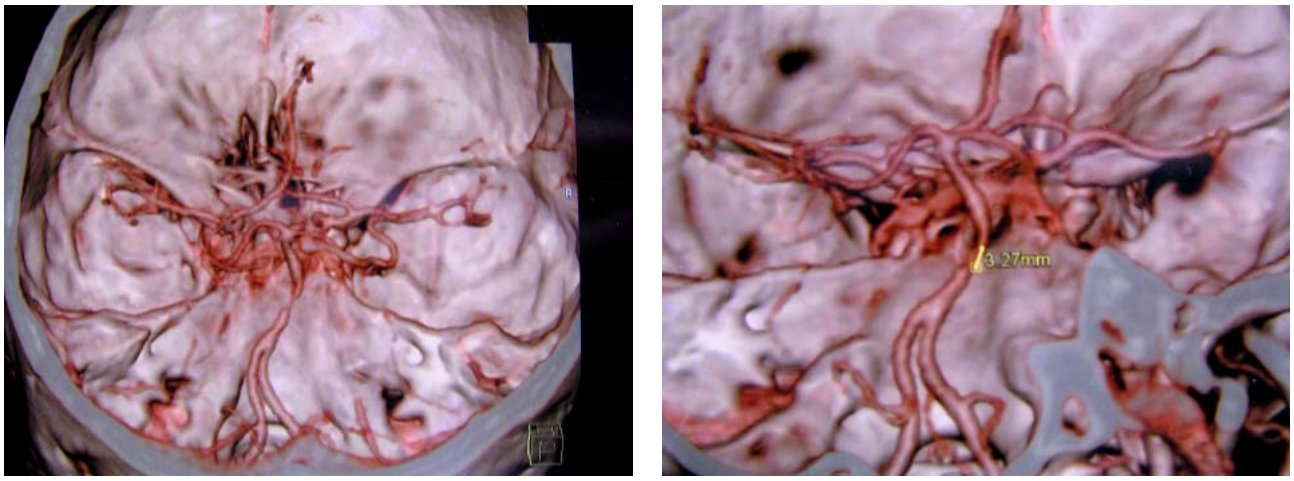
bralne arterije omogućio je znatno bezbednije rešavanje ovog problema [6].

Cilj ovog rada bio je da se pokaže da simptomatska, visokogradusna stenoza bazilarne arterije, koja je pretila da dovede do infarkta mozga, može biti uspešno zbrinuta interventnom neuroradiološkom metodom – angioplastikom i plasiranjem stenta.

Prikaz bolesnika

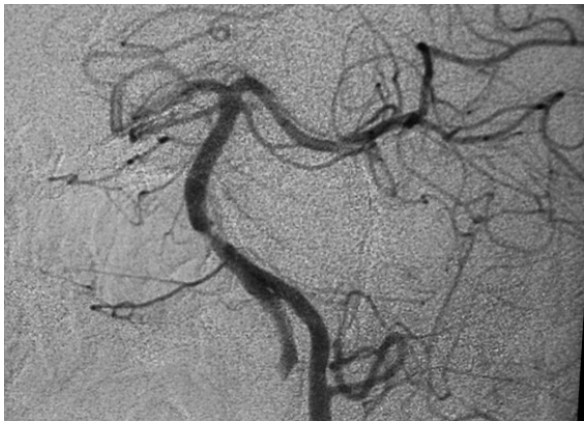
Bolesnik, star 48 godina, imao je nekoliko tranzitornih ishemijskih ataka tokom 12 meseci. Od ostalih simptoma postojale su smetnje sa vidom i poremećaj ravnoteže. Urađena je multislajsna kompjuterizovana tomografija (MSCT) endokranijuma sa angiografijom intrakranijalnih krvnih sudova kada je dijagnostikovana tubularna stenoza bazilarne arterije od 85% (slika 1a i 1b). Stenoza je potvrđena digitalnom suptrakcionom angiografijom (DSA) (slika 2). Bolesnik je nakon toga primao acetilsalicilnu kiselinu, 250 mg dnevno, ali su i pored terapije bili prisutni rekurentni ishemijski ataci. Zbog toga je odlučeno da se stenoza reši plasiranjem stenta endovaskularnim putem.



a) **b)**

Sl. 1 – Multislajsna kompjuterizovana tomografija endokranijuma sa angiografijom

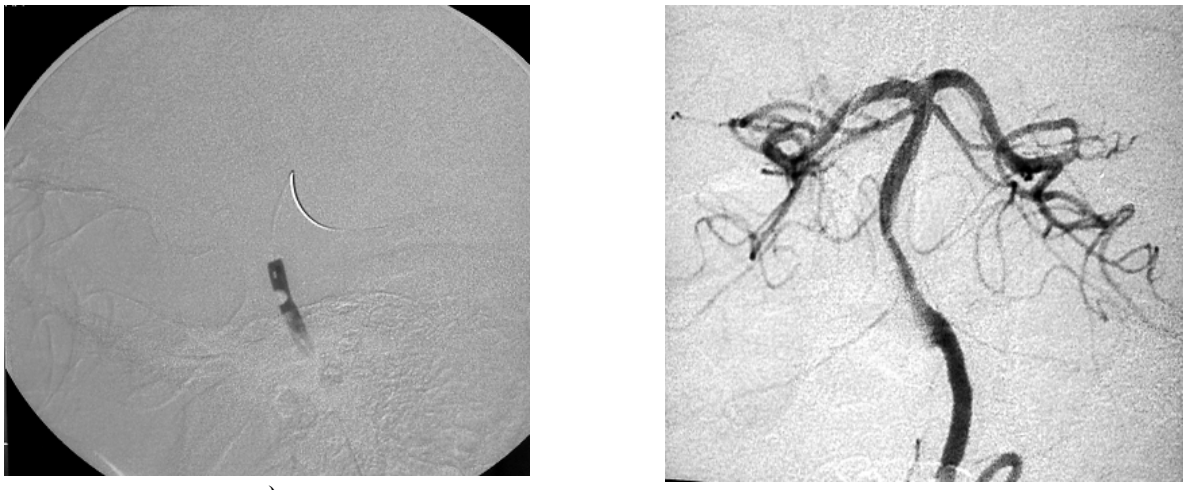
a) stenoza bazilarne arterije preko 85%; b) tubularni izgled u dužini od 3,27 mm



Sl. 2 – Digitalna suptrakciona angiografija - polukosa projekcija koja potvrđuje visokogradusnu stenozu

Na prijemu bolesnik nije imao neurološke ispade. Pre procedure urađena je premedikacija tokom 5 dana tabletama klopidogrela, (plaviks) 75 mg i acetilsalicilne kiseline, 100 mg. Endovaskularni tretman sproveden je u opštoj anesteziji na monoplan (jedna rendgenska cev) aparatu firme *General Electric*. Vaskularni put obezbeđen je plasiranjem *sheath*-a (uvodnik) lumena 6 *French*-a u desnu zajedničku femoralnu arteriju. Dijagnostičkim kateterom dijametra 5 *French*-a urađena je digitalna suptrakciona angiografija u lateralnoj i anteroposteriornoj projekciji pre plasiranja stenta kada je potvrđeno da perzistira stenoza lumena bazilarne arterije od 85%. Stenoza je bila lokalizovana u kaudalnom segmentu bazilarne arterije u dužini od 3,27 mm. Obe arterije *cerebri posterior* su se prikazivale i bile normalnog prečnika. Bolesnik je primio 5 000 IJ heparina intravenski u bolusu neposredno pre početka terapijske procedure. U toku procedure, na sat vremena, aplikovano je po 1 000 IJ heparina. Kateter uvodnik (Terumo 6 *French*-a) dužine 90 cm pozicioniran je u V2 segment leve vertebralne arterije. Vodič sajla 0,014 *inch*-a (Transcend; Medit-tech/Boston Scientific, Natick, MA) sprovedena je kroz stenozu bazilarne arterije u levu arteriju *cerebri posterior*.

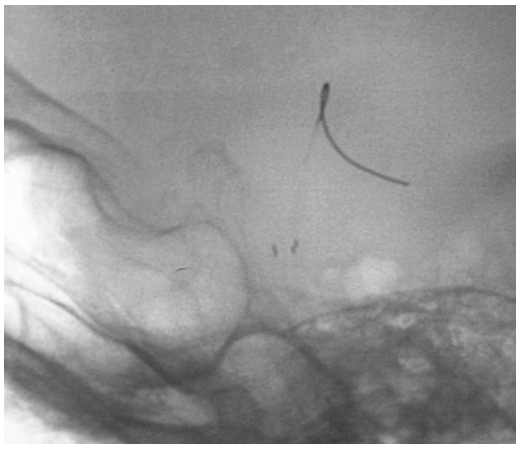
Wingspan Stent System sa *Gateway* PTA balon kateterom (Boston *Scientific Corporation*) upotrebljen je za rešavanje stenoze. Posle perkutane translumenske angioplastike (PTA) balonom prečnika 2,77 mm dužine 15 mm i pod pritiskom od 5 atmosfera postignuta je rekanalizacija stenoze od 70% (slika 3a i 3b). Nakon toga plasiran je samoekspandirajući *Wingspan* Stent prečnika 3 mm dužine 15 mm (slika 4). Kontrolnom angiografijom neposredno posle plasiranja stenta potvrđena je potpuna rekanalizacija lumena bazilarne arterije (slika 5a). Posle 30 minuta ponovo je urađen kontrolni angiografski pregled radi identifikacije eventualne akutne tromboze stenta. Pošto na završnoj angiografiji nije bilo komplikacija, procedura je završena. Naredna 24 časa bolesnik je primao 1 000 IJ heparina na sat vremena, a tokom šest meseci do kontrolnog pregleda tabletu klopidogrela, 75 mg dnevno. Dvanaest časova nakon procedure prestale su smet-



a) b)

Sl. 3 – a) Predilatacija balonom; b) rekanalizacija lumena arterije nakon angioplastike za 70%

nje sa vidom i poremećajem ravnoteže kod bolesnika. Na kontrolonom kliničkom pregledu posle šest meseci nije bilo neuroloških ispada, a na angiografskoj kontroli u istom periodu nije bilo restenoze.



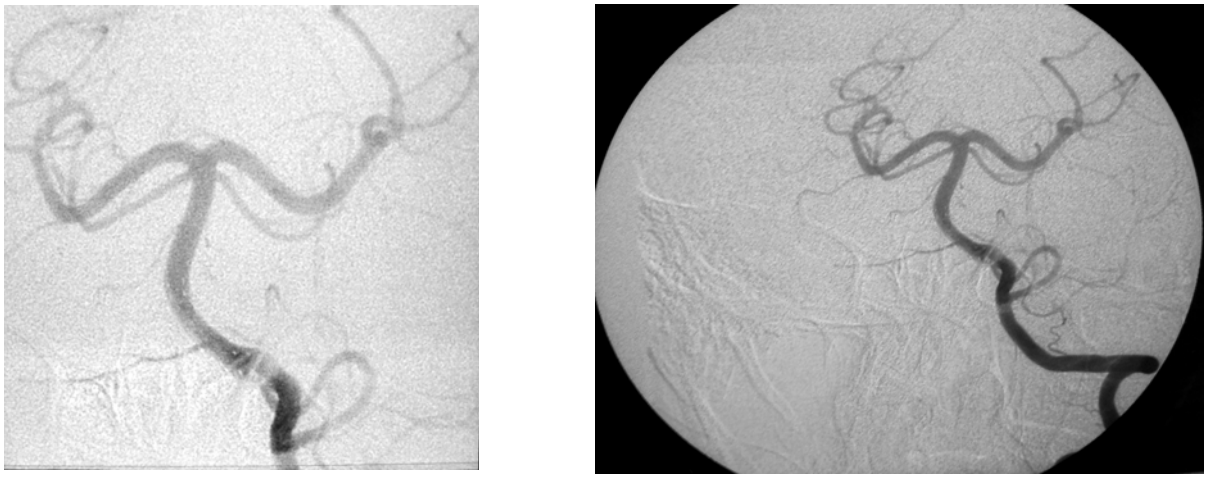
Sl. 4 – Vodič sajla u levu arteriju *cerebri posterior* preko koje je plasiran stent u lumen bazilarne arterije

Diskusija

Postoji nekoliko klasifikacija stenoza vertebrobazilarnog sliva. Jedna od njih je morfološka, bazirana na koronarnoj arterijskoj klasifikaciji i cerebralnoj angiografiji po Moriu i sar. [7].

Prema ovoj klasifikaciji stenoze se dele na tip A, dužina < 5 mm, cirkularna ili srednje ekscentrična, glatkih ivica zida; tip B, dužina 5–10 mm, izrazito ekscentrična, ili pod uglom > 45°, ili nepravilnog zida ili potpuna okluzija koja nije starija od 3 meseca; tip C, dužina > 10 mm, pod uglom > 90° ili potpuna okluzija starija od 3 meseca ili lezija sa brojnim kolateralama.

Po kriterijumu *North American Symptomatic Carotid Endarterectomy Trial* (NASCT) procena stepena stenoze pravi se na osnovu formule prečnik stenoze/normalni prečnik × 100. Normalni prečnik meri se proksimalno od stenoze, a tačka je normalni promer arterije. Po ovoj klasifikaciji postoje značajne stenoze > 75%, suptotalne stenoze 99% i okluzije.



a) b)

Sl. 5 – Kontrolna digitalna suptrakciona angiografija na kojoj je uočena potpuna rekanalizacija lumena bazilarne arterije

a) nakon plasiranja stenta, b) nakon 6 meseci ne postoji restenoza

Kod prikazanog bolesnika postojala je stenoza tipa A dužine 3,27 mm u distalnoj trećini bazilarne arterije i bila je visokogradusna, preko 85%. Stenoza je procenjena na osnovu MSCT i DSA.

Primena medikamentne antiagreagacijske terapije (acetilsalicilna kiselina, klopidogrel) samostalno ili u kombinaciji sa antikoagulantnom terapijom (varfarin) može usporiti razvoj infarkta mozga. Za prevenciju tromboze bazilarne arterije korišćena je antikoagulantna i antiagregacijska terapija. Međutim, novija istraživanja, u koja spada studija sa varfarinom, dokazala su da dugoročna dvojna terapija ne zaustavlja progresiju ateromatoze kao glavnog uzroka stenoze [8, 9]. S obzirom na to da se infarkt mozga uzrokovan stenozom bazilarne arterije i pored primenjene medikamentne terapije razvija kod preko 10% bolesnika godišnje, došlo se do zaključka da je neophodno rešavati visokogradusne stenoze interventnim endovaskulnim procedurama (angioplastika, stenting) [10, 11].

Kod prikazanog bolesnika postojali su tranzitorni ishemijski ataci, smetnje vida i ravnoteže koji su bili učestali u poslednja tri meseca i pored primenjene medikamentne terapije. Kako je postojala opasnost od razvoja infarkta mozga, jer je bolesnik bio refrakteran na medikamentnu terapiju, odlučeno je da se stenoza reši primenom kombinacije PTA i stenta. Intracerebralna perkutana translumenska angioplastika kao samostalna metoda podrazumeva upotrebu balona kojim se stenoza dilatira, pri čemu se širenje krvnog suda vrši postepeno uz izbor balona veličine manje od lumena stenoze. Tokom angioplastike zakrivljenost krvnog suda i ishodište perforatora za moždano stablo predstavljaju problem zbog mogućnosti nastanka tromboze, iznenadne rupture, intimalne disekcije i akutnog vazospazma. Potencijalne komplikacije angioplastike mogu biti smanjene upotrebom stenta [12]. Mi smo koristili sistem vingspan koji sadrži balon dimenzija 2,75 × 15 mm za predilataciju i stent 3 × 15 mm. Prema *Wingspan* studiji iz 2005. godine kod 25 bolesnika sa simptomatskim arteriosklerotskim stenozama bazilarne arterije korišćena je kombinacija balon dilatacije i samoekspandirajućeg mikrostenta. Početna srednja vrednost stenoza bila je 72%. Nakon balon dilatacije srednja vrednost preostalih stenoza iznosila je 54%, koja je ugradnjom stenta smanjena na 38%. Svi bolesnici imali su poboljšanje kliničke slike četiri nedelje nakon tretmana, bez ponovnog javljanja tranzitornog ishemijskog ataka [13]. Kod našeg bolesnika primenom ovog sistema došlo je do potpune rekanalizacije stenoze.

Veliki faktor rizika od razvoja akutne i subakutne tromboze nakon PTA i plasiranja stenta je lokalna agregacija trombocita u predelu stenta i oštećenog kompleksa intima/medija. Naša premedikacija podrazumevala je primenu 75 mg klopidogrela i 100 mg acetilsalicilne kiseline, tokom tri dana pre plasiranja stenta, koji su imali udruženi efekat u sprečavanju agregacije trombocita i primenu heparina neposredno pre i 24 časa nakon procedure [14]. Narednih 6 meseci do kontrolne angiografije bolesnik je oralno uzimao tabletu klopidogrela, 75 mg dnevno.

Neki autori preporučuju primenu abciksimaba (ReoPro®) intravenski u bolusu pre plasiranja stenta. Abciksimab je humani trombocitni glikoproteinski IIb/IIIa kompleks koji inhibira agregaciju trombocita. Abciksimab je znatno efikasniji od aspirina i heparina u prevenciji akutne tromboze tokom koronarne angioplastike. Ova terapija bila je efikasnija kod bolesnika sa akutnom trombozom bazilarne arterije od lokalne intraarterijske cerebralne trombolize i angioplastike. Abciksimab gotovo u potpunosti blokira agregaciju trombocita tokom plasiranja stenta [15]. Mi smo imali u rezervi abciksimab, ukoliko bi došlo do akutne tromboze stenta, zbog čega je rađen kontrolni angiografski pregled pola sata nakon plasiranja stenta.

Proliferacija neointime u predelu plasiranog stenta može dovesti do restenoze u periodu do šest meseci [16]. Iz tog razloga radili smo kontrolnu DSA nakon šest meseci kojom je ustanovljeno da nije došlo do restenoze (slika 5b).

Zaključak

Primenom perkutane balon angioplastike i samoekspandirajućeg stenta uspešno i potpuno je rešena visokogradusna simptomatska stenoza bazilarne arterije koja je bila refrakterna na medikamentnu terapiju.

L I T E R A T U R A

1. *de Rochemont Rdu M, Turowski B, Buchkremer M, Sitzer M, Zanella FE, Berkefeld J.* Recurrent symptomatic high-grade intracranial stenoses: safety and efficacy of undersized stents-initial experience. Radiology 2004; 231(1): 45–9.
2. *Sacco RL, Kargman DE, Gu Q, Zamanillo MC.* Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke 1995; 26(1): 14–20.
3. *Thijs VN, Albers GW.* Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. Neurology 2000; 55(4): 490–7.
4. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. N Engl J Med 1985; 313(19): 1191–200.
5. *Connors JJ 3rd, Wojak JC.* Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. J Neurosurg 1999; 91(3): 415–23.
6. *Gomez CR, Misra VK, Liu MW, Wadlington VR, Terry JB, Tulyapronchote R,* et al. Elective stenting of symptomatic basilar artery stenosis. Stroke 2000; 31(1): 95–9.
7. *Mori T, Kazita K, Chokyu K, Mima T, Mori K.* Short-term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease. AJNR Am J Neuroradiol 2000; 21(2): 249–54.
8. *Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR,* et al; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005; 352(13): 1305–16.
9. *Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS,* et al; Warfarin Aspirin Symptomatic Intracranial Disease Trial Investigators. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006; 113(4): 555–63.

10. *Marks MP, Marcellus ML, Do HM, Schraedley-Desmond PK, Steinberg GK, Tong DC,* et al. Intracranial angioplasty without stenting for symptomatic atherosclerotic stenosis: long-term follow-up. AJNR Am J Neuroradiol 2005; 26(3): 525–30.
11. *Chow MM, Masaryk TJ, Woo HH, Mayberg MR, Rasmussen PA.* Stent-assisted angioplasty of intracranial vertebrobasilar atherosclerosis: midterm analysis of clinical and radiologic predictors of neurological morbidity and mortality. AJNR Am J Neuroradiol 2005; 26(4): 869–74.
12. *Lylyk P, Cohen JE, Ceratto R, Ferrario A, Miranda C.* Angioplasty and stent placement in intracranial atherosclerotic stenoses and dissections. AJNR Am J Neuroradiol 2002; 23(3): 430–6.
13. *Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I,* et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. Stroke 2007; 38(5): 1531–7.
14. *Phatouros CC, Lefler JE, Higashida RT, Meyers PM, Malek AM, Dowd CF,* et al. Primary stenting for high-grade basilar artery stenosis. AJNR Am J Neuroradiol 2000; 21(9): 1744–9.
15. *Wojak JC, Dunlap DC, Hargrave KR, DeAlvare LA, Culbertson HS, Connors JJ 3rd.* Intracranial angioplasty and stenting: long-term results from a single center. AJNR Am J Neuroradiol 2006; 27(9): 1882–92.
16. *Kim DJ, Lee BH, Kim DI, Shim WH, Jeon P, Lee TH.* Stent-assisted angioplasty of symptomatic intracranial vertebrobasilar artery stenosis: feasibility and follow-up results. AJNR Am J Neuroradiol 2005; 26(6): 1381–8.

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P R I K A Z S L U Č A J A

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Embolizacija bronhijalnih arterija kao terapija izbora masivnih hemoptizija kod bronhiektazija

Bronchial artery embolization being the therapy of choice for massive hemoptyses in bronchiectases

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Apstrakt

Uvod. Među mnogobrojnim uzrocima hemoptizija, bronhiektazije su vrlo česte. Iako najveći broj krvarenja prođe spontano, u slučaju ponavljanih i masivnih hemoptizija one mogu da ugroze život bolesnika, te je neophodna brza dijagnostika i terapija. **Prikaz bolesnika.** Bolesnik, star 56 godina hospitalizovan je zbog masivnih hemoptizija sa nehomogenim zasenčenjem levo, parakardijalno. Kompjuterizovana tomografija grudnog koša ukazala je na atelektazu levog donjeg režnja i bronhiektazije. Bronhoskopski je viđena sveža krv i odlivci bronha u disajnim putevima levog plućnog krila. Nakon angiografije multislajsnim kompjuterizovanim tomografskim pregledom, urađena je embolizacija bronhijalnih arterija, nakon čega su hemoptizije potpuno prestale i bolesnik je otpušten bez simptoma. Na kontroli nakon mesec dana osećao se dobro, sa normalnim radiološkim nalazom i mirnim markerima inflamacije. **Zaključak.** Primenom embolizacije bronhijalnih arterija kod našeg bolesnika uspešno je zaustavljeno krvarenje koje mu je ugrožavalo život, a koje je uzrokovano inflamiranim bronhiektazijama. Na ovaj način izbegnuta je hirurška intervencija.

Ključne reči:
hemoptizije; bronhiektazije; arterije, bronhijalne; embolizacija, terapijska; dijagnoza; lečenje, ishod.

Abstract

Introduction. Hemoptyses may be very often due to bronchiectases. Although these bleedings are usually spontaneously resolved recurrent and massive hemoptyses may vitally endanger a patient. Therefore, an urgent diagnosis and treatment of hemoptyses is required. **Case report.** A 56-year old patient was admitted to the hospital due to massive hemoptyses, presented with a non-homogenous shadowing, paracardially on the left. The chest Computerized Tomography finding delineated atelectasis of the lower left lobe and bronchiectases. Bronchoscopy sampling of the left lung airways provided the fresh blood. The multislice angiography and embolization of the bronchial arteries was carried out, entirely ceasing hemoptyses so the patient was discharged with no symptoms. On the control examination one month later, he was well, with normal radiological finding and inflammation markers. **Conclusion.** In our patient, the life-threatening bleeding due to inflamed bronchiectases was successfully resolved by bronchial arterial embolization, thus avoiding surgery.

Key words:
hemoptysis; bronchiectasis; bronchial arteries; embolization, therapeutic; diagnosis; treatment outcome.

Uvod

Hemoptizije predstavljaju iskašljavanje krvi i uvek su alarmantan znak oboljenja disajnih puteva [1, 2]. Količina iskašljane krvi može varirati od tragova krvi u ispljuvku do iskašljavanja velikih količina čiste krvi [3]. Na osnovu stepena krvarenja hemoptizije se dele na nemasivne (iskašljavanje manje od 100 ml krvi tokom 24 časa) i masivne, obilne (iskašljavanje više od 100 do više od 600 ml krvi tokom 24 časa), koje direktno ugrožavaju život [1, 3, 4].

Mnogobrojni su etiološki uzroci hemoptizija. To su: bronhiektazije, infekcije respiratornih puteva, neoplazme, strana tela, trauma disajnih puteva i grudnog koša, kardijalni i plućni vaskularni uzroci, alveolarna hemoragija, jatrogeni i drugi uzroci [3, 4].

Kod brohiektazija, krvni sudovi postaju izuvijani i zbog istanjenog zida skloni pucanju. Ovi krvni sudovi su porekla bronhijalnih arterija. Iako najveći broj krvarenja prođe spontano, u slučaju ponavljanih hemoptizija mogu da ugroze život bolesnika, te je hirurška resekcija često indikovana [5].

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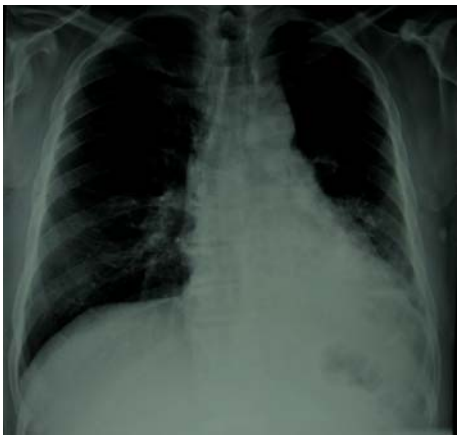
Prikaz bolesnika

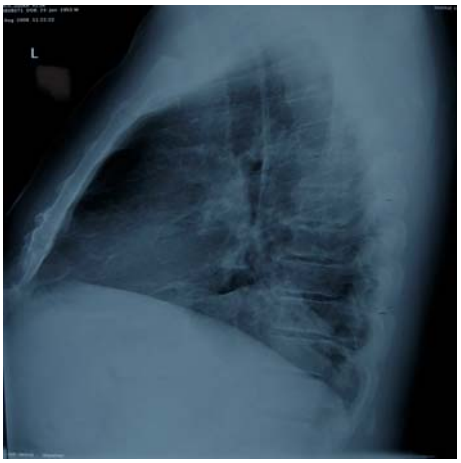
Bolesnik, star 56 godina, hospitalizovan je avgusta 2008. godine u Institutu za plućne bolesti Vojvodine (IPBV) u Sremskoj Kamenici. Tegobe su počele naglo, dva dana pred prijem, u vidu iskašljavanja veće količine sveže krvi u ranim jutarnjim časovima. Nakon ponovljenog ataka krvarenja u vidu masivnih hemoptizija, upućen je u Institut. Osam godina lečio se od arterijske hipertenzije koja je medikamentno korigovana.

Na prijemu, bio je svestan, orijentisan, pokretan, supfebrilan, u miru eupnoičan, klinički kardijalno kompenzovan, blede kože i vidljivih sluznica, a žalio se na kašalj i iskašljavanje krvavog ispljuvka.

Na radiogramu grudnog koša videlo se levo parakardijalno nehomogeno zasenčenje i elevirana leva hemidijafragma. Opisana promena na levom profilnom snimku projektovala se u donjem režnju (slike 1 i 2).



Sl. 1 – Radiogram grudnog koša na prijemu u Institut za plućne bolesti Vojvodine – levo parakardijalno nehomogeno zasenčenje i elevacija leve dijafragme

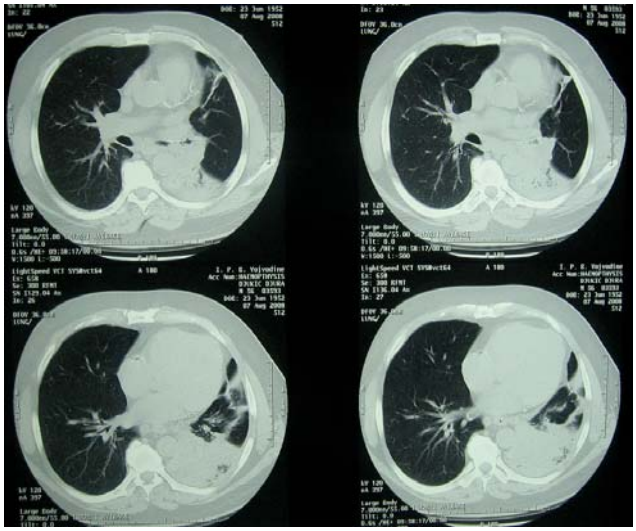


Sl. 2 – Profilni snimak grudnog koša na prijemu u Institut za plućne bolesti Vojvodine – nehomogeno zasenčenje u donjem režnju

Na prijemu, sedimentacija je bila ubrzana (100/-), u krvnoj slici bila je prisutna leukocitoza ($17{,}2 \times 10^9$/L). Vrednosti C-reaktivnog proteina (CRP)(> 100 mg/L) i fibrinogena (7,9 g/L) bile su povišene. Koagulacioni status bio je uredan. U gasnoj analizi otkrivena je parcijalna respiratorna insuficijencija. Bakteriološki pregledi sputuma, kao i pregledi sputuma na *Mycobacterium tuberculosis*, bili su negativani. Ehokardiografija je ukazivala na koncentričnu hipertrofiju miokarda leve komore.

Primenjena je kombinovana antibiotska terapija uz oksigenoterapiju, hemostiptike, obezbeđen venski put, nadoknada volumena i stalan monitoring vitalnih parametara.

Kompjuterizovana tomografija (KT) grudnog koša ukazala je na znake atelektaze donjeg lobusa levo, kao posledice potpune opturacije bronha za donji lobus. Levi glavni bronh bio je deformisan u svom završnom delu. U medijastinumu prikazivali su se limfni čvorovi paraaortno i u aortopulmonalnom prozoru veličine 12 mm, paraezofagusno i supkarinalno veličine do 17 mm (slika 3).



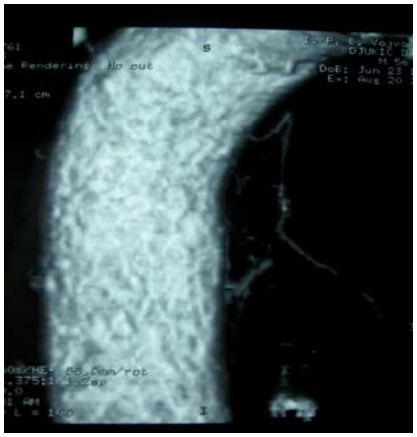
Sl. 3 – Kompjuterizovana tomografija grudnog koša – promene u glavnom levom bronhu

Hitno je urađena bronhoskopija, a endoskopski nalaz pokazao je normalan larings i prisutnu krv u traheji. Nakon aspiracije i traheja i desno bronhijalno stablo bili su uredni. U levom glavnom bronhu i svim ušćima nađeno je puno stare krvi, te su vađeni odlivci bronha. Urađeno je više aspiracija i ispiranja. I dalje se pratila stara krv u Kulmenu, koja se nije mogla u potpunosti aspirirati. Nelson i baza bili su prohodni a sluznica u bazi bila je edematozna. Nije bilo sveže krvi, te se nije moglo ustanoviti odakle je krvarenje. Bakteriološki, kultura bronholavata bila je bez bakterijskog porasta.

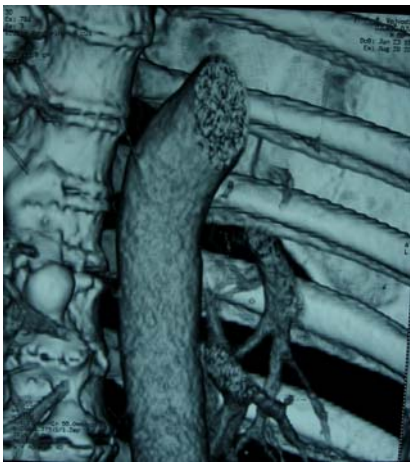
Nakon jednonedeljne terapije urađen je kontrolni KT pregled grudnog koša, koji je pokazao regresiju konsolidacije plućnog parenhima bazalno levo, uz prisustvo brojnih cilindričnih bronhiektazija segmentnih i supsegmentnih grana u ovom području.

S obzirom na to da hemoptizije nisu prestale, urađena je multislajsna KT (MSCT) angiografija grudnog dela aorte. U visini bifurkacije traheje sa ventralne strane zida videlo se mesto pomaka bronhijalne arterije za donji levi lobus, koja je bila prečnika oko 2 mm, a na oko 1 cm od pomaka video se kolenasto savijen segment „kniking“, posle koje se arterija

propagirala uz zid levog glavnog bronha u ranije opisano područje konsolidacije plućnog parenhima levog donjeg lobusa. Neposredno ispod pomaka navedene arterije video se arterijski trunkus prečnika 1,5 mm koji se po pomaku dihotomno granao, pri čemu je desna grana prelazila srednju liniju i pratila pravac prostiranja desnog glavnog bronha, dok je leva grana najpre oko 5 cm „silazila“ niz aortu, potom zauzimala položaj uz donji lobarni bronh, te je takođe bila okružena područjem konsolidacije plućnog parenhima (slike 4 i 5).



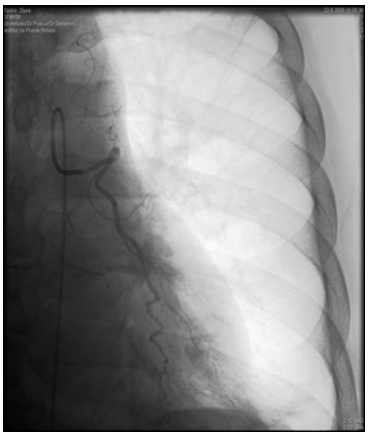
Sl. 4 – Multislajsna kompjuterizovana tomografska angiografija grudnog dela aorte



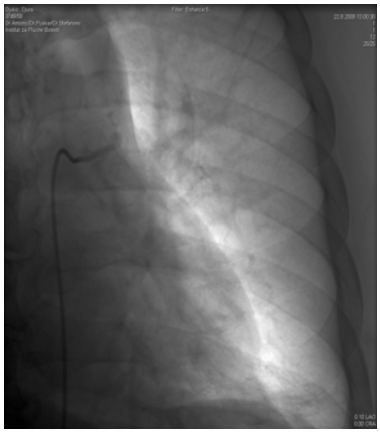
Sl. 5 – Multislajsna kompjuterizovana tomografska angiografija grudnog dela aorte

Nakon ovakvog nalaza odustalo se od hirurškog tretmana i indikovana je embolizacija bronhijalnih arterija za levi donji režanj. Selektivnom bronhijalnom angiografijom prikazana su dva trunkusa bronhialisa na prednjem zidu početnog dela descendentne aorte. Patološka vaskularna mreža viđena je u oba trunkusa bronhialisa, sa ekstravazacijom kontrasta. Gornji trunkus bio je prečnika 2,2 mm, a donji 1,2 mm. Urađena je selektivna embolizacija oba trunkusa sa „PVA mikrosferama“ prečnika 700–900 mikrona za gornji trunkus i 500–700 mikrona za donji. Prekid protoka kontrasta kroz oba trunkusa ukazao je na uspešnu embolizaciju (slike 6 i 7).

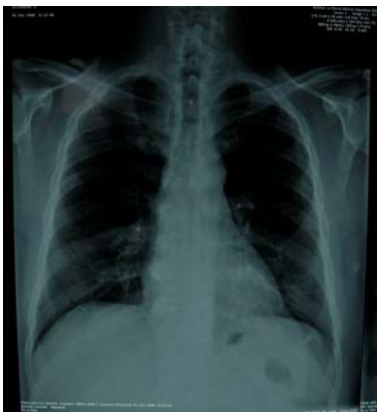
Hemoptizije nakon intervencije u potpunosti su prestale. Kontrolni markeri inflamacije bili su u padu. Kontrolni radiogram grudnog koša ukazivao je na primetnu regresiju zasenčenja leve strane (slika 8). Bolesnik je otpušten u dobrom opštem stanju, asimptomatičan.



Sl. 6 – Snimak pre embolizacije – prikaz vaskularne mreže sa ekstravazacijom kontratsa



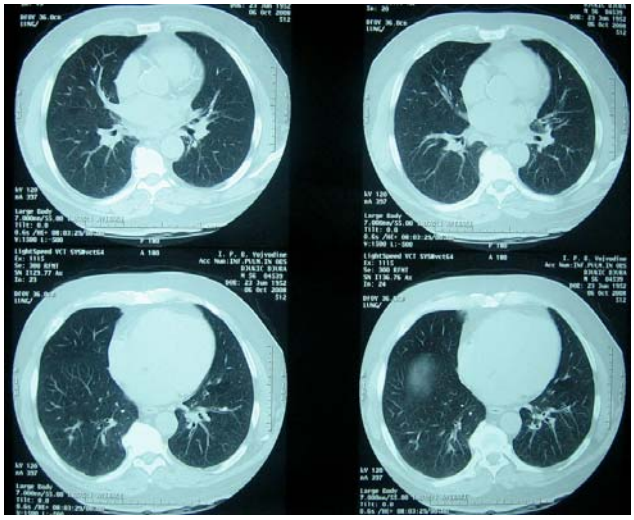
Sl. 7 – Snimak posle embolizacije – prekid protoka kontrasta kroz oba trunkusa



Sl. 8 – Kontrolni radiogram grudnog koša na otpustu iz Instituta za plućne bolesti Vojvodine – regresija promena sa leve strane

Na pregledu, mesec dana nakon otpusta, bolesnik je bio bez subjektivnih tegoba. Kontrolni radiogram grudnog koša bio je bez patoloških promena, a laboratorijske analize i markeri inflamacije bili su uredni. Na KT grudnog koša uočavalo se levo u S7, neposredno ispod ušća za bazalni buket, manje područje grubljeg mrežastog intersticijuma sa vidlji-

vim deformisanim i diskretno dilatiranim supsegmentnim bronhima. Medijastinum je bio lako povučen ulevo. Obostrano bila je prisutna bronhiektazija. Medijastinalni limfni čvorovi bili su fiziološke veličine (slika 9).



Sl. 9 – Kontrolna kompjuterizovana tomografija grudnog koša mesec dana nakon otpusta – levo, u S7, ispod ušća za bazalni buket manje područje grubljeg mrežastog intersticijuma sa vidljivo deformisanim i diskretno dilatiranim supsegmentnim bronhima

Diskusija

Prema podacima Hirshberga i sar. [1] bronhiektazije (20%) i karcinom pluća (19%) najčešći su uzroci hemoptizija. Swanson i sar. [6] ističu da su bronhiektazije (17%) najčešći uzrok hemoptizija, što navodi i Flores i sar. [4].

Mortalitet masivnih netretiranih hemoptizija je od 30–85%, sa čim se slaže i Hirshberg i sar. [1] dok je kod malih hemoptizija mortalitet 2,5% a kod srednjih 6% [4, 6].

Pravilan pristup hemoptizijama podrazumeva isključivanje drugih izvora krvarenja, pre svega iz nazofarinksa ili gastrointestinalnog trakta [4]. Nakon toga potrebna je hitna dijagnostika i terapija. Preporuke za procenu i tretman hemoptizija su: zaštita disajnog puta i stabilizacija opšteg stanja bolesnika; lokalizacija izvora krvarenja; primena odgovarajuće specifične terapije [4, 5, 7].

Radiogram grudnog koša je inicijalni korak u potrazi za uzrokom i lokalizacijom hemoptizija i od koristi je kod plućnih infiltrata, kavitarnih lezija ili alveolarnog krvarenja. Lokalizuje mesto krvarenja kod 60% slučajeva [4]. Kod 5–6% bolesnika sa hemoptizijama i normalnim radiogramom grudnog koša utvrđen je karcinom pluća [2].

Analizom brojnih podataka iz literature o dijagnostici i terapiji hemoptizija, stičemo uvid o pravilnom pristupu hemoptizijama.

Svaka potvrđena hemoptizija je indikacija za bronhološku obradu. Bronhoskopija lokalizuje krvarenje kod 49–93% masivnih hemoptizija [4, 8] a najbolje rezultate daje u kombinaciji sa KT grudnog koša [1, 4, 7, 8]. Analizom 80 bolesnika sa masivnim hemoptizijama, utvrđeno je da su fiberoptička bronhoskopija i KT visoke rezolucije (HRCT), komplementarne tehnike u lokalizaciji strane koja krvari, a HRCT je najbolja za otkrivanje uzroka hemoptizija [9].

Multislajsna kompjuterizovana tomografska angiografija je savremena i suverena metoda u dijagnostikovanju, lokalizaciji i planiranju tretmana hemoptizija i potrebno je da se uvek uradi pre endovaskularne intervencije [10]. Krvarenje iz bronhijalnih arterija češće je uzrok masivnih hemoptizija zbog većeg pritiska u sistemskom krvotoku od pritiska u plućnom krvotoku [3, 4, 11, 12].

Embolizacija bronhijalnih arterija (*bronchial artery embolization* – BAE) je tretman izbora kod masivnih hemoptizija. Primenjuje se kod ponavljanih hemoptizija, koje ne mogu da se zaustave konzervativnim tretmanom. Indikovana je pre svega kod obostranih hemoptizija, kod neadekvatne plućne funkcije i kod nemogućnosti hirurškog lečenja [2, 13]. Embolizacija bronhijalnih arterija je metoda koja kontroliše krvarenje kod 75–90% bolesnika i omogućava dugoročnu kontrolu hemoptizija kod većine, pri čemu se hemoptizije ponovo javljaju ako je embolizacija bila nekompletna ili kod progresije bolesti [2, 4, 14]. Komplikacije BAE su: torakalni bol, disfagija, leukocitoza, a retke su lezije kičmene moždine zbog anastomoze bronhijalne cirkulacije i prednje spinalne arterije, subintimalna disekcija aorte [2, 6, 13, 14].

U studiji sa 46 BAE zaustavljanje krvarenja postignuto je kod 77% uz dugoročnu kontrolu hemoptizija [14]. Swanson i sar. [6] prikazuju iskustvo sa bronhijalnom arteriografijom kod 54 bolesnika sa hemoptizijama, najčešće uzrokovanim bronhiektazijama, kod kojih je BAE bila veoma uspešna u zaustavljanju i kontroli krvarenja, što je slučaj i sa našim bolesnikom [6].

Hiruške resekcije primenjuju se kod lokalizovanih lezija kao i kada se krvarenje nastavlja nakon BAE [2, 13]. Manje od 10% bolesnika sa masivnim hemoptizijama zahteva hitan hirurški tretman [4].

Sirajuddin i sar. [2] prikazuju bolesnika sa masivnim hemoptizijama, kavitarnom lezijom levog gornjeg režnja, aspergilomom, kod koga je plućna funkcija onemogućavala hirurški zahvat, pa je urađena angiografija i uspešna embolizacija bronhijalne arterije.

U tretmanu hemoptizija preporučuje se BAE, pri čemu se ističe značaj radiograma, KT grudnog koša i bronhoskopije u lokalizovanju mesta krvarenja, kao i MSCT angiografije kao inicijalne intervencije pre BAE [2, 6, 10, 13].

Zaključak

Jedna od najtežih i najurgentnijih komplikacija bronhiektazija je krvarenje. Većinom, krvarenja se zaustavljaju konzervativnim tretmanom, a kod masivnih i ponavljanih hemoptizija godinama je metoda izbora bila hirurška terapija. Kod prikazanog bolesnika, zahvaljujući multislajsnoj KT angiografiji, blagovremeno je postavljena dijagnoza bolesti i primenom embolizacije bronhijalnih arterija, uspešno je zaustavljeno krvarenje i izbegnuta hirurška intervencija.

L I T E R A T U R A

1. *Hirshberg B, Biran I, Glazer M, Kramer MR*. Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. Chest 1997; 112(2): 440–4.
2. *Sirajuddin A, Mohammed TL*. A 44-year-old man with hemoptysis: a review of pertinent imaging studies and radiographic interventions. Cleve Clin J Med 2008; 75(8): 601–7.
3. *Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL*. Harrison's Principles of Internal Medicine. 16th ed. New York: Mcgraw-Hill 2005. p. 207–9.
4. *Flores R, Sandur S*. Massive hemoptysis. Hospital Physician 2006; 5: 37–43.
5. *Fishman AP, Elias JA, Fishman JA, Grippi MA, Senior RM, Ackl Al*.. Fishman's Pulmonary Diseases and Disorders. 3rd ed. New York: NY: McGraw-Hill; l998. p. 1261–96.
6. *Swanson KL, Johnson CM, Prakash UB, McKusick MA, Andrews JC, Stanson AW*. Bronchial artery embolization : experience with 54 patients. Chest 2002; 121(3): 789–95.
7. *Jean-Baptiste E*. Clinical assessment and management of massive hemoptysis. Crit Care Med 2000; 28(5): 1642–7.
8. *Valipour A, Kreuzer A, Koller H, Koessler W, Burghuber OC*. Bronchoscopy-guided topical hemostatic tamponade therapy for the management of life-threatening hemoptysis. Chest 2005; 127(6): 2113–8.
9. *Khalil A, Soussan M, Mangiapan G, Fartoukh M, Parrot A, Carette MF*. Utility of high-resolution chest CT scan in the emergency management of haemoptysis in the intensive care unit: severity, localization and aetiology. Br J Radiol 2007; 80(949): 21–5.
10. *Khalil A, Parrot A, Nedelcu C, Fartoukh M, Marsault C, Carette MF*. Severe hemoptysis of pulmonary arterial origin: signs and role of multidetector row CT angiography. Chest 2008; 133(1): 212–9.
11. *Håkanson E, Konstantinov IE, Fransson SG, Svedjeholm R*. Management of life-threatening haemoptysis. Br J Anaesth 2002; 88(2): 291–5.
12. *Remy J*, *Remy*-Jardin M, *Voisin C*. Endovascular management of bronchial bleeding. In: *Butler J*,editor. The Bronchial circulation. New York, NY: Dekker; 1992. p. 667–723.
13. *Ghaye B, Dondelinger RF*. Imaging guided thoracic interventions. Eur Respir J 2001; 17(3): 507–28.
14. *Mal H, Rullon I, Mellot F, Brugière O, Sleiman C, Menu Y*, et al. Immediate and long-term results of bronchial artery embolization for life-threatening hemoptysis. Chest 1999; 115(4): 996–1001.

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Rabdomioliza nakon ekstremnog fizičkog napora

Exercise induced rhabdomyolysis

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Apstrakt

Uvod. Rabdomioliza je potencijalno vitalno ugrožavajuće oboljenje. Patofiziološka osnova ovog oboljenja je oslobađanje intraćelijskog kalcijuma iz skeletnih mišića u cirkulaciju, što može da dovede do akutne bubrežne insuficijencije. **Prikaz bolesnika.** U Kliniku za infektivne bolesti u Novom Sadu primljen je devetnaestogodišnji mladić, kod koga je bolest nastupila postepeno, sa malaksalošću, bolovima u mišićima i pojavom tamne boje urina. U laboratorijskim nalazima uočena je patološka aktivnost aminotransferaza, zbog čega je, posle četiri dana od početka bolesti hospitalizovan, pod uputnom dijagnozom akutnog virusnog hepatitisa. U toku hospitalizacije došlo je do daljeg porasta aktivnosti aminotransferaza, kreatin kinaze i laktat dehidrogenaze. Serološkim analizama isključen je akutni virusni hepatitis. Neurološki nalaz ukazivao je na produženu dekontrakciju kvadricepsa, a nalaz elektromiografije bio je suspektan na neuromiozitis. **Zaključak.** Vodeći, a najmanje prepoznat uzročnik rabdomiolize kod zdrave populacije je ekstenzivan fizički napor. Nekontrolisana fizička aktivnosti može da dovede do značajnog porasta aktivnosti aminotransferaza u serumu i sumnje na hepatitis.

Ključne reči:
rabdomioliza; dijagnoza, diferencijalna; vežbanje.

Abstract

Introduction. Rhabdomyolysis is a potentially life-threatening disease, characterized by the release of intracellular calcium from skeletal muscles and can result in acute renal failure. **Case report.** A nineteen year old boy was admitted to the Clinic for Infective Diseases of Clinical Center Novi Sad. The disease was developing gradually and the symptoms were dizziness, muscle pain and dark color of urine. Due to the pathological level of aminotransferase he was hospitalized on the fourth day of the disease beginning with a suspicious diagnosis of acute viral hepatitis. In the hospital course of the disease, a further elevation of serum aminotransferases, creatine kinase and lactate dehydrogenase were registered. Additional serological analyses were done to exclude other possible causes of acute liver lesion. In the neurological status prolonged decontraction of quadriceps muscle was detected and the electromyography was suspicious on neuromyositis. **Conclusion.** Excessive muscular activity with the strenuous exercise is the leading, but very frequently overlooked, cause of rhabdomyolysis in healthy people. Excessive physical exercise may lead to elevation of the serum activity of aminotransferases and to suspicion of hepatitis.

Key words:
rhabdomyolysis; diagnosis, differential; exercise.

Uvod

Rabdomioliza je potencijalno vitalno ugrožavajuće oboljenje, čija je patofiziološka osnova u oslobađanju intracelularnog sadržaja skeletnih mišića, što u krajnjem može rezultirati akutnom bubrežnom insuficijencijom [1, 2]. Vodeći, a najmanje prepoznat uzročnik rabdomiolize je ekstenzivan fizički napor u sklopu vežbanja kod zdrave populcije ("*overtraining*" sindrom – kumulativni efekat mišićne lezije bez dovoljnog odmora) [3–7], a naročito kod osoba sa miogenim citopatijama (rekurentne rabdomiolize koje nastaju usled deficita enzima koji učestvuju u oksidaciji masnih kiselina: fosforilaza, karnitin – palmitoiltransferaza, mioadenilat – dezaminaza) [8, 9].

Pri intenzivnom radu miofibrila dolazi do sarkoplazmatskog ulaska Na^+, Cl^- i vode u ćeliju što dovodi do edema, destrukcije mišićne ćelije i oslobađanja mioglobina i kalcijuma u cirkulaciju. Oslobođeni mioglobin dovodi do tubularnog bloka, dok kalcijum aktivira fosforilazu A. Fosforilaza A je po funkciji proteaza, pa njena aktivacija ima za posledicu oslobađanje slobodnih radikala i nastanak oksidativnog stresa. Nekroza tubula ("*cast*" formacije), uz stanje oksidativnog stresa, rezultira akutnom bubrežnom insufici-

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jencijom [4]. Usled toksičnog dejstva slobodnih radikala i elektrolitskog disbalansa, u sklopu rabdomiolize mogu se javiti i lezije drugih vitalnih organa [1, 2]. Provocirajući faktori za nastanak rabdomiolize vežbanjem najčešće su visoka atmosferska temperatura, visoka vlažnost vazduha, dehidratacija i virusne infekcije (*Coxackie* B4 i B5, *Influenza*, *Hepatitis* A virus i drugi) [5, 6].

Klinički slika rabdomiolize je nespecifična, manifestuje se bolovima i napetošću u mišićima, aritmijama, konfuzijom i pojavom tamnog urina (boja crnog čaja). Dijagnoza se postavlja nalazom mioglobinurije, patološke aktivnosti kreatin kinaze (CPK) i mioglobinemije [10, 11]. Može se javiti patološka aktivnost aminotransferaza (ALT, AST), gama GT, hiperkalemija, hiperkalcemija, hiperfosfatemija kao rezultat destrukcije miofibrila i isticanja ćelijskih komponenata u cirkulaciju [12, 13]. Radiološke metode (kompjuterizovana tomografija, ultrasonografija, magnetna rezonanca i scintigrafija skeletne muskulature) su nespecifične [14–16]. Definitivna dijagnoza postavlja se biopsijom mišića. Histopatološki i imunoenzimski pregled mišića najznačajniji je za dijagnozu rabdomiolize povezane sa metaboličkim miopatijama [3].

Primarni terapijski cilj kod ustanovljene rabdomiolize je prevencija akutne bubrežne insuficijencije što se postiže obezbeđivanjem diureze od 200 mL/h (dobra hidracija, diuretici, manitol 20% 10 mL/h), korekcijom acidoze (odmah ordinirati 100 mL bikarbonata, a sledeće doze u zavisnosti od baznog ekcesa) i kontrolom hiperkalijemije (hipertoni rastvori glukoze, bikarbonati, kalcijum karbonat). Ukoliko se diureza ne uspostavi i dođe do razvoja akutne bubrežne insuficijencije, neophodna je hemodijaliza. U terapiji rabdomiolize mogu se ordinirati alopurinol i pentoksifilin [2].

U eri popularizacije zdravog načina života i održavanja fizičke kondicije uvek treba imati u vidu posledice koje se mogu javiti usled nekontrolisanih fizičkih aktivnosti. Prikaz ovog bolesnika ima za cilj da pomogne lekarima u prepoznavanju rabdomiolize, kao i da proširi diferencijalno-dijagnostička razmatranja patološkog biohemizma jetre.

Prikaz bolesnika

U Kliniku za infektivne bolesti Kliničkog centra Vojvodine 12.09.2005. godine upućen je devetnaestogodišnji mladić pod sumnjom na akutni virusni hepatitis. Bolest je počela četiri dana pre prijema, u toku kvalifikacionog treninga za takmičenje „Može biti samo jedan“. Posle 45 sklekova, 85 „gušterovih letova“ i 60 kolutova, osetio je mučninu i povratio više puta. Odmah se javio lekaru, koji mu je dao ampulu metiklopramida posle čega je prestao da povraća, dok je i dalje imao osećaj blagog zatezanja u mišićima celog tela. Narednog dana dobro se osećao i po podne je otišao na posao. Po zanimanju je konobar u noćnom klubu. U toku rada javili su mu se intenzivni bolovi u mišićima natkolenica i leđa, zbog čega je prekinuo rad, uzeo jednu tabletu acetilsalicilne kiseline, i legao da spava. Noć je proveo mirno. Trećeg dana od početka bolesti osećao se izuzetno loše, trpeo je bolove u gotovo svim mišićima tela i primetio je tamnu boju mokraće (boja crnog čaja). Bolovi u mišićima su se pojačali do te mere da više nije mogao da pokreće donje ekstremitete. Sledećeg dana javio se lekaru, uzete su mu laboratorijske analize i zbog patoloških nalaza funkcijskih testova jetre upućen je u Kliniku za infektivne bolesti pod sumnjom na akutni virusni hepatitis. Prilikom prijema u kliničkom nalazu dominirala je uvećana jetra i slezina i izražena palpatorna bolnost mišića ekstremiteta. Pregledom urina ustanovljeni su proteinurija i povećan nivo urobilinogena. U biohemijskim nalazima zapažena je 33 puta povišena aktivnost aspartat aminotransferaze (AST 1230 U/L, referentna vrednost do 37 U/L), oko 10 puta povišena aktivnost alanin aminotransferaze (ALT 382 U/L, referentna vrednost do 40 U/L), oko 8 puta povišena aktivnost laktat dehidrogenaze (LDH 3860 U/L, referentna vrednost do 460 U/L). Kompletna krvna slika, sedimentacija eritrocita, fibrinogen i biohemijski parametri bubrežne funkcije bili su uredni.

Po prijemu uvedena je simptomatska terapija (rehidratacija, hepatoprotektivi i analgetici) na koju dolazi do postepene regresije bolova u mišićima.

U kontrolnim laboratorijskim nalazima i dalje je bio prisutan porast aktivnosti AST (1 800 U/L, 45 puta povišena), ALT (684 U/L, 20 puta povišena) i LDH (6 240 U/L, 15 puta povišena). Kreatin kinaza (CPK) bila je iznad 42 000 U/L (referentna vrednost do 195 U/L), a MB frakcija CPK 250 U/L (referentna vrednost do 38 U/L). Ultrasonografijom gornjeg abdomena uočena je hepatosplenomegalija, dok su radiografija pluća i srca i ehokardiografija bili uredni. Neurološki nalaz ukazao je na produženu dekontrakciju kvadricepsa, a elektomiografija (EMG) na polineuropatiju. Ultrasonografski nalaz mišića ekstremiteta bio je uredan. Zatražena je konsultacija specijaliste sportske medicine koji je posumnjao da intenzitet fizičkog napora može biti jedini etiološki faktor postojećih tegoba, s obzirom da su vežbe koje je izveo bile izrazito anaerobnog tipa sa velikim, ali kratkotrajnim porastom koncentracije laktata. Ukoliko su dezaminacioni parametri funkcionalni, eliminacija laktata iz periferne krvi traje najduže 48 h.

U daljem toku hopsitalizacije mladić se dobro osećao, bolovi u mišićima su se smirili, zaostala je samo otežana dekontrakcija mišića natkolenica. Sedmog dana od početka bolesti kontrolni laboratorijski nalazi ukazali su na regresiju aktivnosti ALT (10 puta povišena), AST (5 puta povišena), CPK (8 puta povišena) uz normalizaciju LDH. Dopunske serološke analize (HBsAg, anti HCV, IgM anti HAV), analize na prisustvo virusa influence A i B, adenoviruse, *Mycoplasma pneumoniae, Toxoplasma gondii* i Paul-Bunellova reakcija bile su negativne. Imunološke pretrage (ANF, autoantitela na zbirnom supstratu, serumski imunoglobulini IgA, IgG, IgM, C3, C4) bili su u granicama referentnih vrednosti. Potpuna normalizacija ALT, AST i CPK zabeležena je 21. dana od početka bolesti.

Diskusija

Nalaz hepatosplenomegalije i poremećaj testova za funkcijsko ispitivanje jetre daju osnove za sumnju na akutni virusni hepatitis. Godište bolesnika i nepouzdani podaci o socijalnom ponašanju obavezuju razmatranje jetrene lezije uzrokovane hepatotoksičnim supstancama, na prvom mestu alkoholom i

steroidima. Međutim, anamnestički podataci o naglom početku bolesti sa bolom u mišićima ekstremiteta, laboratorijski nalazi u kojima dominira patološka aktivnost AST u odnosu na ALT, enormno visoka aktivnost CPK i LDH proširuju dijagnostiku na mišićnu leziju. Isključivanjem infekcije aktuelnim, primarno i sekundarno hepatotropnim virusima, infekcije leptospirama, sistemskih autoimunih bolesti i porfirije, dijagnoza rabdomiolize postala je sve izvesnija.

Mioglobinurija (urin tamne boje sa prisutnim hemoglobinom, cilindrima i mioglobinom, a bez prisutnih eritrocita), koja se javlja 24–48 sati od akcidenta prvi je simptom koji je ukazao na rabdomiolizu. Mioglobinurija se ne javlja ako nema rabdomiolize, ali rabdomioliza ne rezultira obavezno mioglobinurijom [2, 12]. Da bi se javila mioglobinurija destrukcijom mora biti zahvaćeno minimalno 100 g mišićne mase [10]. Kod prikazanog bolesnika tamna boja urina javila se trećeg dana od početka tegoba. Četvrtog dana bolesti urin je bio zamućen, kisele pH reakcije, proteini su bili označeni sa 2+, urobilinogen je bio povećan, a u sedimentu urina nađena su 3–4 erirtocita, 4–6 leukocita, retke epitelne ćelije, cilindri, nešto bakterija i dosta sluzi. Mioglobin u urinu nije određivan pošto ova analiza ne ulazi u standarne dijagnostičke procedure nadležne laboratorije. Mioglobin se može određivati i u serumu, ali to nije senzitivna dijagnostička metoda pošto se mioglobin brzo eliminiše iz seruma putem jetre [2].

Glavni marker rabdomiolize u serumu je povišena aktivnost kreatin kinaze koja može dostići vrednosti do 500 puta viši od referentnih. Porast aktivnosti CPK javlja se 24–48 h od akcidenta i perzistira do 2 nedelje [10–12, 18]. Upravo ovakva dinamika aktivnosti kreatin kinaze zapažena je kod prikazanog bolesnika aktivnost CPK bila je povećana preko 200 puta šestog dana od početka bolesti uz tendenciju normalizacije u naredne tri nedelje. Kao rezultat fizičke aktivnosti povećava se aktivnost CPK u samom mišiću, a usled produžene fizičke aktivnosti dolazi do oštećenja mišićnih vlakana i izlaska enzima iz ćelije. Povećani permeabilitet membrane mišićne ćelije, koji nastaje kao posledica fizičke aktivnosti, može dovesti do oslobađanja CPK u cirkulaciju i bez nekroze mišićne ćelije [19]. Vrednosti MB frakcije CPK kod prikazanog bolesnika bile su minimalno povišene, te je uz uredan nalaz elektrokardiografije i ehokardiografije isključena lezija miokarda. Uzrok povišene vrednosti CPK mogu biti mišićne lezije kod intramuskularnih (*im*) injekcija, što je kod prikazanog bolesnika isključeno. Kod *im* injekcija aktivnost CPK oko 5 puta je povišena u odnosu na normalu, i održava se dva do najduže sedam dana nakon takve aplikacije leka [20].

Pored izlaska CPK iz mišićne ćelije, u toku fizičke aktivnosti izlaze i ALT, AST i LDH. Osim u hepatocitu, alanin i aspartat aminotransferaza nalaze se u velikim količinama i u mišićnim ćelijama. Alanin aminotransferaza je specifičniji pokazatelj hepatocelularne lezije, dominatno je citosolni enzim, za razliku od AST (40% AST je koncentrisano u mitohondrijama). Porast aktivnosti ALT ukazuje na oštećenje ćelije i izmenjen permeabilitet ćelijske membrane, dok porast aktivnosti AST ukazuje na „dublje“, teže, mitohondrijalno oštećenje ćelije. Diferencijalno-dijagnostički bitno je odrediti i De Rittisov indeks (odnos ALT:AST), čija je referentna vrednost oko 1. Indeks manji od 1 ukazuje na mitohondrijalnu leziju. Poluživot ALT je 3 puta duži od poluživota AST, tako da se patološka aktivnost ALT održava duže u odnosu na AST [13]. Kod prikazanog bolesnika aktivnost aminotransferaza bila je 30 do 40 puta povišena u odnosu na referentne vrednosti, a De Rtitisov indeks iznosio je manje od 1. Laktat dehidrogenaza bila je oko 8 puta povišena u odnosu na referetne vrednosti, dok mišićni izoenzim LDH5 nije određen.

Kao rezultat destrukcije mišićne ćelije u početku bolesti se u serumu može zapaziti hiperkalijemija, hiperkalcemija i hiperfosfatemija. Prikazani bolesnik nije imao porast nivoa serumskog kalijuma, kalcijuma i fosfora što se može objasniti brzom i dobrom rehidratacijom. Iz istog razloga, i pored opsežne destrukcije mišićne mase nije došlo do razvoja najteže komplikacije rabdomiolize – akutne bubrežne insuficijencije [2, 21].

Definitivna dijagnoza rabdomiolize postavlja se biopsijom mišića i histopatološkom i imunoenzimskom obradom uzorka [3]. Biopsija mišića kod prikazanog bolesnika nije urađena s obzirom da je bolest imala povoljan klinički tok (povlačenje subjektivnih tegoba, normalizacija kliničkog i laboratorijskih nalaza), pa smo smatrali da nije neophodno bolesnika izlagati navedenoj invazivnoj dijagnostičkoj proceduri.

Zaključak

Rabdomioliza može da dovede do akutne bubrežne insuficijencije, zbog čega se svrstava u potencijalno vitalno ugrožvajuće oboljenje. Vodeći, a najmanje prepoznat, uzročnik rabdomiolize je ekstenzivan fizički napor u sklopu vežbanja kod zdrave populcije, a naročito kod osoba sa miogenim citopatijama. U eri popularizacije zdravog načina života i održavanja fizičke kondicije ne sme se zaboraviti na posledice koje se mogu javiti usled nekontrolisane fizičke aktivnosti.

L I T E R A T U R A

1. *Kokko JP.* Rhabdomyolysis. In: *Goldman L, Bennett JC,* editors. Cecil Textbook of Medicine. 21st ed. Philadelphia: W.B. Saunders; 2000. p. 522–5.
2. *Vanholder R, Sever MS, Erek E, Lameire N.* Rhabdomyolysis. J Am Soc Nephrol 2000; 11(8): 1553–61.
3. *Grobler LA, Collins M, Lambert MI, Sinclair-Smith C, Derman W, St Clair Gibson A,* et al. Skeletal muscle pathology in endurance athletes with acquired training intolerance. Br J Sports Med 2004; 38(6): 697–703.
4. *Brown JA, Elliott MJ, Sray WA.* Exercise-induced upper extremity rhabdomyolysis and myoglobinuria in shipboard military personnel. Mil Med 1994; 159(7): 473–5.
5. *MacIntyre DL, Reid WD, McKenzie DC.* Delayed muscle soreness. The inflammatory response to muscle injury and its clinical implications. Sports Med 1995; 20(1): 24–40.
6. *Juray RM.* Exertional rhabdomyolysis in unsupervised exercises in a correctional setting: a case study. Urol Nurs 2005; 25(2): 117–9.

7. *Marinella MA*. Exertional rhabdomyolysis after recent coxsackie B virus infection. South Med J 1998; 91(11): 1057–9.
8. *Omar MA, Wilson JP, Cox TS*. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacother 2001; 35(9): 1096–107.
9. *Schaefer J, Jackson S, Dick DJ, Turnbull DM*. Trifunctional enzyme deficiency: adult presentation of a usually fatal beta-oxidation defect. Ann Neurol 1996; 40(4): 597–602.
10. *Ahsan SK, Washington RJ, Ahsan N*. Myoglobinuria: evaluation of methods in the clinical diagnosis acute renal failure. Indian J Med Sci 2001; 55(8): 443–52.
11. *Koskinen SOA, Höyhtyä M, Turpeenniemi-Hujanen T, Martikkala V, Mäkinen TT, Oksa J*, et al. Serum concentrations of collagen degrading enzymes and their inhibitors after downhill running. Scand J Med Sci Sports 2001; 11(1): 9-15.
12. *Beetham R*. Biochemical investigation of suspected rhabdomyolysis. The Annals of Clinical Biohemistry 2000; 37(5): 581–7.
13. *Johnston DE*. Special considerations in interpreting liver function tests. Am Fam Physician 1999; 59(8): 2223–30.
14. *Messing ML, Feinzimer ET, Brosnan JJ, Rochester D*. CT of rhabdomyolysis associated with malignant hyperthermia and seizures. Clin Imaging 1993; 17(4): 258–9.
15. *Lamminen AE, Hekali PE, Tiula E, Suramo I, Korhola OA*. Acute rhabdomyolysis: evaluation with magnetic resonance imaging compared with computed tomography and ultrasonography. Br J Radiol 1989; 62(736): 326–30.
16. *Kneeland JB*. MR imaging of masle and tendon injury. Eur J Radiol 1997; 25: 199–208.
17. *Lane R, Phillips M*. Rhabdomyolysis. BMJ 2003; 327(7407): 115–6.
18. *Clark CJ, Nolan RL*. Answer to case of the month ≠93: exercise-induced rhabdomyolysis. JACR 2003; 54: 5.
19. *Cooper CE, Vollaard NB, Choueiri T, Wilson MT*. Exercise, free radicals and oxidative stress. Biochem Soc Trans 2002; 30(2): 280–5.
20. *Kasper D, Brauwald E, Fauci A, Hauser S, Longo D, Jameson L*. Harisons's principles of intrnal medicine. 16th ed. New York: McGraw Hill; 2005.
21. *Visweswaran P, Guntupalli J*. Rhabdomyolysis. Crit Care Clin 1999; 15(2): 415–28.

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P R I K A Z S L U Č A J A

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Akutno trovanje glifosat-surfaktantom sa neurološkim sekvelama i letalnim ishodom

Acute glyphosate-surfactant poisoning with neurological sequels and fatal outcome

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Apstrakt

Uvod. Klinička slika teškog trovanja glifosat-surfaktantima najčešće uključuje gastroenteritis, respiratorne poremećaje, poremećaje svesti, hipotenziju refrakternu na terapiju, bubrežnu insuficijenciju, šok. U medicinskoj literaturi opisan je jedan slučaj sa neurološkim sekvelama i promenama u beloj masi koji se dovodi u vezu sa trovanjem glifosat-surfaktantom. Kod bolesnice koju prikazujemo došlo je do masivnog oštećenja bele mase s posledičnim razvojem vigilne kome i smrtnim ishodom. **Prikaz bolesnika.** Bolesnica stara 56 godina, u cilju samotrovanja popila je oko 500 mL herbicida koji sadrži izopropilamin glifosat. Najznačajnije manifestacije trovanja bile su hipotenzija, koma, acidoza, hiperkalijemija, respiratorna i bubrežna insuficijencija. Mere intenzivne terapije uključivale su simptomatsku i suportivnu terapiju uz mehaničku ventilaciju i hemodijalizu. Bolesnica je preživela akutnu fazu trovanja, ali je došlo do razvoja vigilne kome. Magnetnom rezonancom registrovane su multiple lezije u strukturama bele mase i moždanom mostu. **Zaključak.** Osim mogućeg neurotoksičnog efekta glifosat-surfaktnata, ishodu bolesti verovatno je u značajnoj meri doprinela ishemija, pogotovu u periodima izražene hipotenzije tokom hemodijalize. Kako se hemodijaliza preporučuje kao jedna od mera detoksikacije i pre nastanka bubrežne insuficijencije, ističemo da je zbog hemodinamske nestabilnosti potrebno adekvatno planiranje modaliteta dijalizne terapije, pri čemu prednost treba dati metodama kontinuirane dijalize.

Ključne reči:
herbicidi; trovanje; dijagnoza; neurotoksičnost, sindromi; dijaliza; disanje, veštačko; lečenje lekovima; lečenje, ishod.

Abstract

Introduction. Clinical picture of severe glyphosate-surfactant poisoning is manifested by gastroenteritis, respiratory disturbances, altered mental status, hypotension refractory to the treatment, renal failure, shock. Single case report indicated possible neurotoxic sequels of glyphosate-surfactant exposure with white matter lesions and development of Parkinsonism. We described a patient with massive white matter damage which led to vigil coma and lethal outcome. **Case report.** A 56-year old woman ingested about 500 mL of herbicide containing glyphosate isopropylamine salt. The most prominent manifestation of poisoning included hypotension, coma, hyperkaliemia, respiratory and renal failure. The patient was treated in intensive care unit by symptomatic and supportive therapy including mechanical ventilation and hemodialysis. The patient survived the acute phase of poisoning, but she developed vigil coma. Nuclear magnetic imagining revealed extensive bilateral lesions of the brain stem white matter and pons. **Conclusion.** The outcome of reported poisoning may be the consequence of glyphosate-surfactant neurotoxic effect or/and ischemia, especially in the episodes of marked hypotension during hemodialysis. Considering recommendation of early hemodialysis as the treatment of choice, even before renal failure development, we point out the importance of careful planning of dialysis modality in hemodynamically instable patient and recommend continuous dialysis methods.

Key words:
herbicides; poisoning; diagnosis; neurotoxicity syndrome; dialysis; respiration, artificial; drug therapy; treatment outcome.

Uvod

Glifosat (N-fosfonometilglicin) predstavlja jedan od najčešće upotrebljavanih herbicida širom sveta. Ovo jedinjenje deluje prvenstveno na metabolizam aminokiselina u biljkama i bakterijama preko mehanizama koji ne postoje kod životinjskog sveta i ljudi [1]. Ispitivanja na pacovima pokazala su da utiče i na enzimske sisteme kod životinja, tako što do-

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vodi do smanjenja aktivnosti enzima koji imaju važnu ulogu u detoksikaciji (citohroma P-450 i monoamiono oksigenaze u jetri i hidroksilaze u sluznici crevnog trakta) [2]. Procene toksičnosti glifosata zasnivaju se na ispitivanjima sprovedenim na eksperimentalnim životinjama u cilju registracije pesticida koji sadrže ovu aktivnu materiju. Slabo se resorbuje preko kože, respiratornog ili digestivnog trakta, i malo je toksičan za sisare (srednja oralna letalna doza za pacova veća je od 4 320 mg/kg) [3, 4]. Međutim, u komercijalnim proizvodima, glifosat je rastvoren u surfaktantima, supstancijama koje se dodaju herbicidima da bi pospešile njihovu resorpciju i koje mogu značajno da doprinesu toksičnosti preparata [5]. Ovo se naročito odnosi na preparate na bazi glifosata, za koje se ispostavilo da su višestruko toksičniji od pojedinačnih komponenti [6, 7]. Zbog toga je ispravnije u trovanjima ovim formulacijama kao toksični agens imenovati glifosat-surfaktant, nego sam glifosat.

Akutnu toksičnost herbicida koji sadrže glifosat i surfaktante prvi put u medicinskoj literaturi opisali su japanski autori koji su objavili seriju od 56 slučajeva samotrovanja, među kojima je bilo devet smrtnih ishoda [8]. Po njihovim procenama, letalna doza peroralno unetog preparata bila je oko 200 mL. S obzirom na nisku akutnu toksičnost glifosata, ova grupa autora iznela je pretpostavku da se radi o toksičnosti polioksietilenamina (POEA), koji je bio surfaktant u većini proizvoda. Na osnovu publikovanih slučajeva, simptomi i znaci trovanja preparatima koji sadrže glifosat i surfaktante uključivali su bol u trbuhu, povraćanje, zastojne promene na plućima, pneumoniju, akutno oštećenje pluća, poremećaj svesti od somnolencije do kome, hemolizu, hipotenziju, bubrežnu insuficijenciju, šok, erozije gastrointestinalnog trakta i oštećenje larinksa [9–16]. Iako se u navedenoj medicinskoj literaturi opisuju poremećaji svesti i metabolički i cirkulatorni poremećaji koji bi mogli da ih prouzokuju, nema podataka o morfološkim promenama u tkivu centralnog nervnog sistema. U slučaju koji smo prikazali došlo je do razvoja masivnog oštećenja moždanog tkiva koje je dovelo do vigilne kome i smrtnog ishoda bolesnice.

Prikaz bolesnika

Bolesnicu, staru 56 godina, zatekli su ukućani u jutarnjim časovima bez svesti, sa otežanim disanjem. Odmah je prevežena u najbliži bolnički centar, gde je konstatovano da je somnolentna, dispnoična, sa masom inspirijumskih pukota obostrano, hipotenzivna (90/50 mmHg). Pošto se pretpostavilo da se radi o akutnoj srčanoj slabosti, otpočeto je sa simptomatskom terapijom koja je uključivala intravensku primenu kristaloidnih rastvora, inotropnih lekova, diuretika, bronhodilatatora, antibiotika. Učinjena je hitna ehosonografija srca čiji je nalaz bio normalan. Kako se radilo o bolesnici koja se psihijatrijski lečila, posumnjalo se da je u pitanju trovanje lekovima. Ordiniran je antidot za trovanja benzodiazepinima (flumazenil), nakon čega se stanje svesti bolesnice popravilo, te je i dobijen podatak da je u cilju samotrovanja popila 3–4 tablete midazolama i dve bočice nekog pesticida. Posle ovog saznanja bolesnica je premeštena u našu ustanovu. Naknadno, tek trećeg dana od ingestije, ukućani su javili da su pronašli dve ispražnjene bočice od herbicida (Glifosaf od 250 mL i Dominator od 300 mL, u oba slučaja koncentracije 480 g/L) za koje su pretpostavili da ih je bolesnica popila. Oba herbicida kao aktivnu materiju sadrže izopropilamonijumovu so glifosata.

Pri prijemu bolesnica je bila somnolentna, afebrilna, acijanotična, anikterična, lako dispnoična i tahipnoična (23 respiracije/min), tahikardna (102/min). Auskultatorno, na plućima registrovan je neznatno produžen ekspirijum sa niskotonskim zvižducima obostrano. Srčana radnja bila je ritmična, tonovi tihi, bez šumova. Arterijski krvni pritisak na prijemu iznosio je 100/50 mmHg. Trbuh je bio lako distendiran i lako bolno osetljiv u epigastrijumu, jetra i slezina se nisu palpirale. Ostali nalaz bio je normalan.

Analizom gasova arterijske krvi dobijeni su sledeći rezultati: pH 7,35, pCO2 35,1 mmHg, pO2 54,7 mmHg, sO2 87,9%, laktati 6,3 mmol/L, bikarbonati 20,1 mmol/L, ABE -5,2 mmol/L. U krvnoj slici registrovane su normalne vrednosti leukocita ($3{,}66 \times 10^9$/L), eritrocita ($4{,}3 \times 10^{12}$/L) i trombocita (300×10^9/L), uz lako snižene vrednosti hemoglobina od 118 g/L i hematokrita 0,29. Biohemijskom analizom krvi određeni su sledeći parametri: glikoza 6,1 mmol/L, urea 13,4 mmol/L, kreatinin 298 μmol/L, Na^+ 143 mmol/L, K^+ 5,7 mmol/L, aspartat aminotransferaza (AST) 57 IJ/L, alanin aminotransferaza (ALT) 28 IJ/L, kreatin kinaza (CK) 2690 IJ/L.

Nalaz elektrokardiografije (EKG) bio je normalan, osim sinusne tahikardije. Radiografijom grudnog koša otkriveno je postojanje konsolidacije plućnog parenhima obostrano parakardijalno.

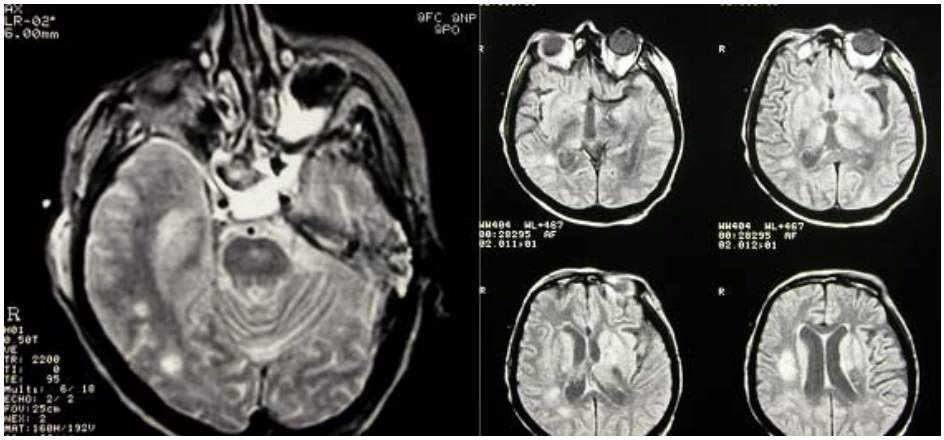
Prilikom prijema, na osnovu vrednosti serumske i eritrocitne holinesteraze i kvalitativnog testa urina isključena je mogućnost trovanja organofosfornim insekticidima i bipiridilijumskim herbicidima. Tek trećeg dana, po saznanju o vrsti preparata koje je bolesnica popila, HPLC metodom dokazan je glifosat u krvi koncentracije 83,06 mg/L.

Bolesnica je primljena u jedinicu intenzivne nege i otpočeto je sa simptomatskom terapijom. Uprkos adekvatnoj nadoknadi tečnosti koja je uključivala primenu 3 L infuzionih rastvora u prvih nekoliko časova, došlo je do pada vrednosti arterijskog pritiska na 80/40 mmHg, pri čemu je vrednost centralnog venskog pritiska (CVP) iznosila 12 mm H_2O, te je otpočeto sa dopaminskom stimulacijom. Kako je na prijemu konstatovano postojanje hipoksije, a stanje svesti i poremećaj respiratorne funkcije nisu se popravljali pri primeni kiseonika preko maske, bolesnica je priključena na mehaničku ventalciju (MV) modaliteta SIMV. S obzirom na konstantovan poremećaj bubrežne funkcije, primenjivan je diuretik (furosemid) i u toku prvog dana lečenja ostvarena je diureza od 1 400 mL. Takođe, otpočeto je sa primenom antibiotika u lečenju pneumonije. U toku prvog dana hospitalizacije zapažen je i laki gastroenteritis sa pojačanom peristaltikom creva i nekoliko tečnih stolica.

Narednog dana stanje bolesnice donekle se stabilizovalo – stanje svesti se normalizovalo, ali je i dalje bila neophodna adrenergička stimulacija zbog hipotenzije, pri čemu su postignute vrednosti srednjeg arterijskog pritiska do maksimalno 85 mmHg.

Trećeg dana lečenja došlo je do ponovnog pogoršanja stanja svesti do nivoa kome, sa reakcijom na draži i razvoja oligurične bubrežne insuficijencije sa smanjenjem dnevne diureze na oko 400 mL, porastom CVP na 23 mm H_2O i povećanjem vrednosti kalijuma (8,3 mmol/L), uree (31 mmol/L) i kreatinina (593 μmol/L) u krvi. Istovremeno, ana-

(pojačanog intenziteta signala u sekvenci T1 i smanjenog u sekvencama TW2 i PD), koje su bile najizraženije u *centrumu semiovale* sa leve strane. Lezije su bile prisutne u kapsuli interni obostrano, izraženije levo, koroni radijati i supkortikalnim strukturama obostrano. Sličan poremećaj dijagnostikovan je i u predelu moždanog mosta (slika 1).



Sl. 1 – Zone smanjenog denziteta u ponsu i temporalno paraventrikularno

lizom arterijske krvi otkriveno je pogoršanje acidoze, pri čemu su zabeležene sledeće vrednosti praćenih parametara: pH 7,19, pCO2 47,6 mmHg, pO2 88 mmHg, sO2 95,1%, laktati 2,9 mmol/L, bikarbonati 16,6 mol/L i ABE-9,2 mmol/L. Zbog nastanka akutne bubrežne insuficijencije, otpočeto je sa primenom hemodijalizne terapije. Takođe, u terapiju su uvedeni bikarbonati radi korekcije acidoze.

U daljem toku bolesnica je sve vreme bila u stanju kome, na mehaničkoj ventilaciji. Tokom prva četiri dana lečenja održavala se hipotenzija, zbog koje je bila neophodna dopaminska stimulacija. Hemodijaliza je sprovođena na 24-48 h u zavisnosti od kliničkog nalaza i biohemijskih pokazatelja, pri čemu su prilikom prva dva tretmana zabeleženi padovi krvnog pritiska na 77/37 mmHg, odnosno 65/25 mmHg. Nakon 26 dana bolesnica je ušla u poliurijsku fazu bubrežne insuficijencije, uz postepen pad vrednosti uree i kreatinina u krvi, čije su se vrednosti normalizovale oko 40. dana hospitalizacije. Mehanička ventilacija sprovođena je tokom 30 dana. Nakon tri nedelje od početka primene, učinjena je traheotomija; bolesnica je još devet dana bila na mehaničkoj ventilaciji, a potom je spontano disala. Takođe, primenjivana je antibiotska i druga simptomatska i suportivna terapija.

Praćenjem biohemijskih parametara uočeno je povećanje enzimske aktivnosti koje je bilo najizraženije 5-6 dana nakon ingestije – AST do 2032 IJ/L, ALT do 1232 IJ/L i CK do 17619 IJ/L.

S obrizom na to da je sve vreme perzistirao poremećaj stanja svesti na nivou vigilne kome, 20. dana hospitalizacije učinjena je kompjuterska tomografija (KT) glave. Nalaz je ukazivao na nejasne granice kortikalnih i supkortikalnih struktura mozga, pri čemu su u obe kapsule interne viđene zone smanjenog denziteta. Dijagnostika uočenih promena je, nakon odvajanja od mehaničke ventilalacije, dopunjena magnetnom rezonancom glave. Viđene su multiple promene u beloj masi

Bolesnica je nakon 52 dana hospitalizacije u našoj ustanovi premeštena u ustanovu za lečenje cerebrovaskularnih oboljenja, gde je posle osam dana preminula.

Diskusija

U medicinskoj literaturi postoji nekoliko radova u kojima je na osnovu serija slučajeva ukazano na klinički i prognostički značaj razvoja pojedinih poremećaja u trovanjima glifosat-surfaktantom. Talbot i sar. [9] ukazuju da se slučajevi sa letalnim ishodom karakterišu sindromom koji uključuje hipotenziju refrakternu na terapiju i, u pojedinim slučajevima, edem pluća uz normalne vrednosti CVP. Lee i sar. [14] ističu da edem pluća, acidoza i hiperkaliemija predstavljaju parametre koji ukazuju na verovatan letalni ishod u ovim trovanjima. Kao prognostički parametri letaliteta, takođe, navode se respiratorna insuficijencija, tahikardija i povišene vrednosti kreatinina [17].

U slučaju prikazane bolesnice, najznačajnije manifestacije trovanja uključivale su hipotenziju, poremećaj svesti do nivoa kome, acidozu, hiperkaliemiju, respiratornu i bubrežnu insuficijenciju.

Hipotenzija refrakterna na primenu intravenskih tečnosti i vazopresornih lekova jedna je od najznačajnijih karakteristika teških i letalnih trovanja herbicidima koji sadrže glifosat i surfaktante. Etiologija ove pojave je kompleksna. Iako pojedini autori ističu oštećenje digestivnih sluznica uz masivan gubitak tečnosti iz gastrointestinalnog trakta, novija saznanja ukazuju da ovi poremećaji nisu od velikog kliničkog značaja u pogledu preživljavanja u teškim trovanjima [10, 18]. Iako ingestija herbicida koji sadrže glifosat može da dovede do gastroenteritisa sa pojavom erozija na sluznici jednjaka, želuca i duodenuma i gastrointestinalnog krvarenja, u našem slučaju nisu verifikovane promene te vrste na sluznicama, već je zapaženo

samo postojanje ubrzane peristaltike uz pojavu dijareje prvog dana lečenja [8, 16].

Ispitivanja uticaja pojedinih aktivnih supstancija, surfaktanata i komercijalnih proizvoda koji sadrže kombinacije ovih materija na vazorelaksaciju i kardijalnu funkciju pokazala su da komercijalni preparati deluju toksičnije nego pojedinačne komponente. U eksperimentima na pacovima, sam glifosat nije uticao na kontraktilnost miokarda, kao ni izopropilamin (drugi sastojak herbicida koji je bolesnica popila), ali su preparati koji sadrže obe materije dovodili do smanjenja kontraktilnosti [19]. Glifosat i izopropilamin, ni pojedinačno, ni zajednički, nisu ispoljili značajno vazorelaksaciono dejstvo, za razliku od kombinacija glifosata sa drugim surfaktantima. Uobičajeno, herbicidni preparati sadrže više surfaktanata, ali proizvođači nisu u obavezi da pruže informacije o vrsti i količini svake „inertne" materije u formulaciji. Bez ovih podataka, teško je proceniti potencijalni doprinos svakog sastojka u komercijalnom proizvodu. Kod prikazane bolesnice na prijemu u lokalnom zdravstvenom centru učinjena je ehosonografija srca koja je bila u fiziološkim granicama, te se održavanje hipotenzije uprkos adekvatnoj nadoknadi tečnosti i primeni vazokonstriktornih lekova pre može shvatiti kao posledica vazodilatacije, nego smanjene kontraktilnosti miokarda.

Respiratorni poremećaji u trovanju glifosatom posledica su akutnog oštećenja pluća, pneumonije i edema pluća [16]. Kod prikazane bolesnice registrovana je masivna bilateralna pneumonija, čije je napredovanje dovelo do respiratorne insuficijencije i neophodnosti mehaničke ventilacije.

Bubrežna insuficijencija predstavlja karakterističan poremaćaj u teškim trovanjima glifosatom. Ona je verovatno velikim delom posledica hipoperfuzije bubrega, ali treba imati u vidu i mogućnost doprinosa direktnog toksičnog dejstva preparata, s obzirom da se glifosat prvenstveno izlučuje urinom u nepromenjenom obliku [4]. Iako su već na prijemu registrovane povišene vrednosti uree i kreatinina kod prikazane bolesnice, uz primenu infuzionih rastvora, dopaminske stimulacije i diuretika tokom prva dva dana lečenja postignuta je zadovoljavajuća diureza. Međutim, uprkos terapiji, trećeg dana došlo je do oligurije, hiperkalijemije i acidoze, zbog čega je otpočeto sa hemodijaliznim lečenjem.

Istovremeno, stanje svesti kod bolesnice pogoršava se do nivoa kome, koja se održava i nakon korekcije metaboličkog disbalansa i normalizacije kardiocirkulatornog statusa. Nuklearna magnetna rezonanca pokazala je postojanje multiplih bilateralnih lezija u beloj masi i moždanom mostu. U medicinskoj literaturi opisan je samo jedan slučaj moguće neurotoksičnosti glifosat-surfaktanta kod bolesnika sa razvojem Parkinsonove bolesti mesec dana nakon inhalacionog trovanja herbicidima, pri čemu su magnetnom rezonancom otkrivene bilateralne zone smanjenog intenziteta u beloj masi (*globus pallidus* i *substantia nigra*) [20]. U slučaju prikazane bolesnice, takođe, kao definitivna sekvela trovanja, najizraženije lezije registrovane su u beloj masi, a klinički su se manifestovale kao vigilna koma.

Terapaija trovanja glifosat-surfaktantom je simptomatska i suportivna. U teškim trovanjima koja se inicijalno manifestuju poremećajima koji ukazuju na lošu prognozu bolesti, pojedini autori preporučuju primenu hemodijalize i pre razvoja akutne bubrežne insuficijencije [21, 22]. Ovi stavovi prvenstveno su bazirani na činjenici da bi ekstrakorporalna detoksikacija mogla da ubrza eliminaciju glifosata iz organizma. Osim toga, hemodijalizom se može uticati na korekciju acidobaznih i elektrolitnih poremećaja koji se često javljaju u ovim trovanjima. Međutim, treba imati u vidu da se teška trovanja glifosat-surfaktantom manifestuju cirkulatornim šokom koji često nije moguće korigovati nadoknadom tečnosti i vazopresornim lekovima. Kod prikazane bolesnice, tokom dijaliznih tretmana dolazilo je do pogoršanja hipotenzije, što je moglo da utiče na težinu bolesti, a pogotovo na oštećenje moždanog tkiva.

Zaključak

Trovanje herbicidima koji sadrže glifosat posledica je sinergističkog delovanja aktivne materije i surfaktanata. Iako pojedinačno male toksičnosti, ove materije mogu da dovedu do teških i fatalnih intoksikacija. U slučaju prikazane bolesnice, zapaženi su poremećaji karakteristični za ova trovanja, koji su uključivali hipotenziju, poremećaj svesti, acidozu, hiperkalijemiju, respiratornu i bubrežnu insuficijenciju. Uz primenjene mere intenzivne terapije, bolesnica je preživela akutnu fazu trovanja, ali je došlo do trajnog oštećenja moždanog tkiva, prvenstveno bele mase, sa razvojem vigilne kome. Osim mogućeg neurotoksičnog efekta glifosat-surfaktanata, ovakvom ishodu bolesti je verovatno u značanoj meri doprinela ishemija, pogotovo u periodima izražene hipotenzije tokom hemodijalize. Kako se hemodijaliza preporučuje kao jedna od mera detoksikacije i pre nastanka bubrežne insuficijencije, ističemo da je zbog hemodinamske nestabilnosti potrebno adekvatno planiranje modaliteta dijalizne terapije, pri čemu prednost treba dati metodama kontinuirane dijalize.

L I T E R A T U R A

1. *Gilchrist DG, Kosuge T* .Aromatic amino acid biosynthesis and its regulation. In: *Miflin BJ,* editor. The biochemistry of plants. New York: Academic Press; 1980. p. 507–13.
2. *Hietanen E, Linnainmaa K, Vainio H.* Effects of phenoxyherbicides and glyphosate on the hepatic and intestinal biotransformation activities in the rat. Acta Pharmacol Toxicol (Copenh) 1983; 53(2): 103–12.
3. *Cox C.* Glyphosate. Part 1: Toxycology. J Pestic Reform 1995; 15(3): 14–20.
4. *U.S. EPA.* (1993) *EPA R.E.D* Facts: Glyphosate. Available from: www.epa.gov/oppsrrd1/REDs/factsheets/0178fact.pdf
5. SERA. Effects of surfactants on the toxicitiy of glyphosate, with specific reference to RODEO. Syracuse Evnironmental Research Associates. [1997 February 6]. Available from: www.fs.fed.us/foresthealth/pesticide/pdfs/Surfactants.pdf
6. *Martinez TT, Long WC, Hiller R.* Comparison of the toxicology of the herbicide roundup by oral and pulmonary routes of exposure. Proc West Pharmacol Soc 1990; 33: 193–7.

7. *Martinez TT, Brown K.* Oral and pulmonary toxicology of the surfactant used in roundup herbicide. Proc West Pharmacol Soc 1991; 34: 43–6.
8. *Sawada Y, Nagai Y, Ueyama M, Yamamoto I.* Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. Lancet 1988; 1(8580): 299.
9. *Talbot AR, Shiaw MH, Huang JS, Yang SF, Goo TS, Wang SH,* et al. Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. Hum Exp Toxicol 1991; 10(1): 1–8.
10. *Menkes DB, Temple WA, Edwards IR.* Intentional self-poisoning with glyphosate-containing herbicides. Hum Exp Toxicol 1991; 10(2): 103–7.
11. *Tominack RL, Yang GY, Tsai WJ, Chung HM, Deng JF.* Taiwan National Poison Center survey of glyphosate--surfactant herbicide ingestions. J Toxicol Clin Toxicol 1991; 29(1): 91–109.
12. *Temple WA, Smith NA.* Glyphosate herbicide poisoning experience in New Zealand. N Z Med J 1992; 105(933): 173–4.
13. *Lin CM, Lai CP, Fang TC, Lin CL.* Cardiogenic shock in a patient with glyphosate-surfactant poisoning. J Formos Med Assoc 1999; 98(10): 698–700.
14. *Lee HL, Chen KW, Chi CH, Huang JJ, Tsai LM.* Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: a review of 131 cases. Acad Emerg Med 2000; 7(8): 906–10.
15. *Stella J, Ryan M.* Glyphosate herbicide formulation: a potentially lethal ingestion. Emerg Med Australas 2004; 16(3): 235-39.
16. *Bradberry SM, Proudfoot AT, Vale JA.* Glyphosate poisoning. Toxicol Rev 2004; 23(3): 159–67.
17. *Lee CH, Shih CP, Hsu KH, Hung DZ, Lin CC.* The early prognostic factors of glyphosate-surfactant intoxication. Am J Emerg Med 2008; 26(3): 275–81.
18. *Chang CY, Peng YC, Hung DZ, Hu WH, Yang DY, Lin TJ.* Clinical impact of upper gastrointestinal tract injuries in glyphosate-surfactant oral intoxication. Hum Exp Toxicol 1999; 18(8): 475–8.
19. *Chan YC, Chang SC, Hsuan SL, Chien MS, Lee WC, Kang JJ,* et al. Cardiovascular effects of herbicides and formulated adjuvants on isolated rat aorta and heart. Toxicol In Vitro 2007; 21(4): 595–603.
20. *Barbosa ER, Leiros da Costa MD, Bacheschi LA, Scaff M, Leite CC.* Parkinsonism after glycine-derivate exposure. Mov Disord 2001; 16(3): 565–8.
21. *Moon JM, Min YI, Chun BJ.* Can early hemodialysis affect the outcome of the ingestion of glyphosate herbicide? Clin Toxicol (Phila) 2006; 44(3): 329–32.
22. *Sampogna RV, Cunard R.* Roundup intoxication and a rationale for treatment. Clin Nephrol 2007; 68(3): 190–6.

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I S T O R I J A M E D I C I N E UDC: 616-051:355.084(497.1)(091)

Sanitetski pukovnik dr Dragutin S. Petković, prvi upravnik Pasterovog zavoda u Nišu

Medical Corps Colonel Dr Dragutin S. Petković, the first director of the Pasteur's Institute in the town of Niš

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Key words:
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Uvod

Sanitetski pukovnik dr Dragutin S. Petković (1873–1947) bio je prvi stalni upravnik Pasterovog zavoda u Nišu (1. januar 1900), osnivač Antirabičnog, Bakteriološkog i Hemijskog odelenja u tom zavodu, profesor, patriota i ratnik (slika 1).

Sl. 1 – Sanitetski pukovnik dr Dragutin S. Petković (1873–1947)

Dr Dragutin S. Petković rođen je 8. jula 1873. u Ćićevcu, od oca Save (sveštenik, streljan sa grupom pravoslavnih sveštenika kod Bele Palanke za vreme Prvog svetskog rata od strane bugarskog okupatora) i majke Perside (domaćica, poginula sa ćerkom Ivanom u železničkoj nesreći kod Beograda za vreme Drugog svetskog rata). Osnovnu školu završio je u mestu rođenja, a gimnaziju s maturom u Kruševcu (1892). Po maturiranju upisuje Prirodno-matematički fakultet Velike škole u Beogradu. Nakon završene prve godine na Prirodno-matematičkom fakultetu u Beogradu Dragutin S. Petković odlazi u Beč kao vojni pitomac Ministarstva vojnog i upisuje Medicinski fakultet (1893) na kome diplomira 1899, a na dan rođenja iste godine (8. jul 1899) biva promovisan za doktora celokupnog lekarstva .

Bio je poliglota: govorio je nemački, francuski, engleski i italijanski.

Dr Dragutin S. Petković umro je 1947. g. u Nišu. Sahranjen je na groblju u Ćićevcu. Na ovom groblju, crkvu i mauzolej porodice Petković u kojem se nalaze mošti dr Dragutina S. Petkovića, podigao je njegov sin, urolog, akademik dr Sava Petković.

Dr Dragutin S. Petković imao je četvoro dece: sina Ivana (advokat), kći Ivanu (muzikolog), sina Milana (lekar) i sina Savu (lekar).

Profesionalno opredeljenje dr Dragutina S. Petkovića nastavilo je da živi u delima njegova dva sina koji su bili čuveni doktori u Jugoslaviji i svetu (profesor dr Milan Petković, gastroenterolog – Niš i akademik Sava Petković, urolog – Beograd), i unuka dr Vladimira Petkovića, sina profesora dr Milana Petkovića, doajena niške radiologije [1–6].

Stručno usavršavanje dr Dragutina S. Petkovića

Dr Dragutin S. Petković jula i avgusta 1900. godine odlazi na stručno usavršavanje u Peštu (Austrougarska) gde

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izučava i stiče nova saznanja o antirabičnom lečenju lica sa ujedima besnih životinja. Po povratku iz Pešte 1. januara 1901. g. dr Dragutin S. Petković preuzima rad Pasterovog zavoda u Nišu. Znanje koje je stekao u Pešti o antirabičnom lečenju lica sa ujedima besnih životinja dr Dragutin S. Petković oživljava, prenosi i primenjuje u praksi puštanjem u rad Pasterovog zavoda u Nišu koji je zvanično otvoren 1. januara 1901; to je bio prvi Pasterov zavod na Balkanu (slika 2) [1, 3–6].

Roux Tierre Taul Emile, Mečnikova Ilije Iliča i Nicolle Charles. Nakon studijskog boravka u Parizu dr Dragutin S. Petković odlazi u Hamburg (Nemačka) i nastavlja svoje školovanje u tamošnjem Higijenskom zavodu, u sklopu najčuvenijeg Tropskog instituta na izučavanju higijene (od septembra 1903. do marta 1904). Edukuje se u oblasti borbe protiv zaraznih bolesti, pregleda životnih namirnica i dezinfekcije. Predavao je higijenu u Muškoj gimnaziji u Nišu, školske 1921/22. godine [1, 3, 5].

Sl. 2 – Dr Dragutin S. Petković u Pasterovom zavodu u Parizu 1902. godine (označen krugom, u drugom redu desno)

Njegov pomoćnik u to vreme i, ujedno, šef Odeljenja za animalnu limfu, bio je sanitetski poručnik dr Miloš Stevanović (1873–1915). On ga je zamenjivao na funkciji upravnika za vreme specijalizacije 1902–1904. godine [1].

Sa stečenim znanjem o antirabičnom lečenju lica sa ujedima besnih životinja dr Dragutin S. Petković se ne zadovoljava i ne zadržava na tome, već svoj naučnoistraživački rad nastavlja i odlazi u Pariz (Francuska), u tamošnji Pasterov zavod radi izučavanja bakteriologije (15. mart 1902. – 15. septembar 1903) (slika 3). Usavršava se kod akademika i nobelovaca,

Saopšteni i štampani radovi dr Dragutina S. Petkovića

Dr Dragutin S. Petković štampao je i saopštio preko 20 radova.

Neki od radova dr Dragutina S. Petkovića su:

– O Pasterovom zavodu u Nišu, Srpski arhiv za celokupno lekarstvo, 1901,

– O apendicitisu od Dijelafoa, prevod, Srpski arhiv za celokupno lekarstvo, 1902,

Sl. 3 – Učesnici Prvog kursa za dezinfekciju (1904-1905); kurs je organizovao dr Dragutin S. Petković (u sredini, označen strelicom) za vojne pitomce

– O medicinskoj statistici, Srpski arhiv za celokupno lekarstvo, 1903,

– O antirabičnom lečenju, Vojnolekarski godišnjak, 1905. g,

– Jedan slučaj besnila, Vojnolekarski godišnjak, 1905,

– *Beitrage zur des Diagnostischen Wertes einiger Nahrboden fur di Typhusbakterien. Centralblatt für die Bakteriologie etc. Abt. Originale Bd.* 36, No 02,

– Moralna higijena u vojsci, Glasnik Ministarstva narodnog zdravlja, 1921,

– Moja higijenska iskustva u našim ratovima, Istorija srpskog vojnog saniteta, 1925. g, i drugi radovi.

Na Prvom kongresu srpskih lekara i prirodnjaka održanom 1904. godine u Beogradu dr Dragutin S. Petković učestvovao je sa dva naučna rada: „Iz Kraljevskog srpskog Pasterovog zavoda u Nišu o antirabičnom lečenju uopšte i o lečenju u Kraljevskom srpskom Pasterovom zavodu s trogodišnjom statistikom“ i „O higijenskome pregledu i oceni pijaće vode“ [1].

Mada su oba rada od značaja, najpre zbog prirode problema koji obrađuju, vremena koje obuhvataju i, u to doba, krupnih događaja koji se dešavaju u Srbiji, osvrnućemo se i prokomentarisaćemo rad „Iz Kraljevskog srpskog Pasterovog zavoda u Nišu o antirabičnom lečenju uopšte i o lečenju u Kraljevskom srpskom Pasterovom zavodu s trogodišnjom statistikom“ budući da se u tom radu pominju osnovni motivi za otvaranje Pasterovog zavoda u Nišu, a to je borba protiv besnila u Srbiji. Ovaj rad dr Dragutin S. Petković napisao je na 19 štampanih stranica, sa 7 tabelarnih prikaza i sa jednim grafikonom, uz dodatak koji predstavljaju dva ministarska raspisa (Raspis svima načelstvima i upravi grada Beograda, od 16. januara 1901. i Raspis ministra unutrašnjih dela o taksi za lečenje u niškom Pasterovom zavodu).

U ovom radu dr Dragutin S. Petković iznosi istorijat otkrivanja antirabičnog lečenja sa osvrtom na besmrtnost Pasterovog dela, dela njegovih saradnika, pa i dr Hedješa. U to vreme, Pasterov zavod u Nišu koristio je Hedješeov metod rada. Dr Dragutin S. Petković tabelarno prikazuje da je za trogodišnji period (1901–1903) rada Pasterovog zavoda u Nišu antirabično lečio ukupno 824 lica, pri čemu je prosečna smrtnost iznosila 0,48% (računajući tu lica koja su lečena i kod kojih se za prvih 15 dana nakon poslednjeg ubrizgavanja nisu pojavili znaci besnila). Prema dr Dragutinu S. Petkoviću, ovi rezultati rada poklapaju se sa rezultatima rada u Pasterovom zavodu u Parizu za period prvih 10 godina (1885–1895), za koje vreme je lečeno 17 337 ujedenih lica, sa 0,47% umrlih. U isto vreme, po Hedješu, prosečna smrtnost u 24 Pasterova zavoda, kod 54 620 lečenih lica, iznosila je 0,77%. U zaključku dr Dragutin S. Petković ističe: „S radom u Antirabičnom odeljenju našeg Pasterovog zavoda za ove minule tri godine mi možemo bez preterivanja biti zadovoljni i postignuti uspeh daje nam opravdane nade da na započetom poslu u pravcu istrajemo sa željom: da uskoro vidimo osnovana i druga odeljenja pri našem Pasterovom zavodu, gde će se obrađivati sve grane iz mikrobiologije ponikle iz radova i otkrića Pasterova, koga se zauvek zadužено čovečanstvo mora s pijetetom sećati, a čijoj se uspomeni mi odužujemo kličući: Slava mu!“ [1].

Na ovom kongresu dr Dragutin S. Petković preuzeo je akciju reorganizacije Srpskog lekarskog društva u kojem su do tada redovni članovi bili samo doktori iz Beograda, dok su doktori iz unutrašnjosti bili dopisni članovi.

Dr Dragutin S. Petković – vojni lekar u tri rata

Dr Dragutin S. Petković bio je lekar Drugog pešadijskog puka „Knez Mihajlo“ (1899–1900), Moravskog artiljerijskog puka (1900) i šef Unutrašnjeg odeljenja Moravske stalne bolnice sve do septembra 1912. godine. Učesnik je Stepinog manevra izvedenog na terotoriji niške divizijske komande u mirnodopskim uslovima 1911. godine (isprobavana je varijanta rata sa Turskom) i Stepinog manevra izvedenog tokom bitke na Ceru 1914. (Prvi svetski rat). Učestvuje u regrutaciji 2. pukovske komande. Od dana mobilizacije (20. septembar 1912) komandir je bolničke čete 2. poziva na kojem ostaje za vreme Prvog i Drugog balkanskog rata.

Srbija je u Prvom balkanskom ratu izgubila 43 000 ljudi, a u Drugom balkanskom ratu srpski vojni gubici iznosili su 44 500 ljudi [11]. Ukupno, u balkanskim ratovima srpski vojni gubici iznosili su oko 88 000: poginulo je 14 000 ljudi, ranjeno 54 000, a 17 000 umrlo od rana i bolesti (5 000 od kolere) [7–10].

U pobedonosnoj bici na Jadru (Cer 3–6. avgusta 1914) srpska vojska izgubila je blizu 17 000 oficira i vojnika, a od toga je bilo 11 519 ranjenika [7].

Neposredno pred Prvi svetski rat, dr Dragutin S. Petković od 1. januara do 20. jula 1914. godine biva imenovan za šefa Unutrašnjeg odeljenja stalne Moravske vojne bolnice, a od dana mobilizacije za Prvi svetski rat do 10. januara 1916, odnosno do povlačenja na Krf, bio je imenovan za referenta saniteta Moravske divizije 2. poziva.

Prema podacima đenerala dr Sime Karanovića, do dolaska na Krf (Grčka) poginulo je 45 861 vojnika, umrlo od rana i bolesti 68 458 vojnika, ostalo u bolnicama u Srbiji 138 600, a 306 603 nestalo „kroz Albaniju, zarobljeno ili propalo pri povlačenju“. Do 16. jula 1916. od mobilnih 711 343 vojnika na Krf je stigao 151 821 vojnik [7–10].

Kada je Srpska vojska stigla na Krf, dr Dragutin S. Petković biva imenovan za šefa saniteta na ostrvu Lazaret (februar 1916, Grčka), gde je trebalo da rukovodi kupanjem i dezinfekcijom iskrcanih srpskih vojnika.

Moravska bolnica iz Niša smeštena je na malom ostrvu Lazaret, gde je vršena trijaža i dezinfekcija, da bi kasnije hitnom naredbom prešla na ostvo Vido. Tada se njen rad odvija ispod četiri velika šatora [5].

Po zamisli komande Srpske vojske, kupanju i dezinfekciji na ostrvu Lazaret trebalo je da bude podvrgnuta cela srpska vojska, ali se od toga vrlo brzo odustalo zbog malog kapaciteta. Zbog toga je dr Dragutin Petković bio poslat u Solun gde je imenovan za člana Međusavezničke antiepidemijske komisije za higijenu sve do sredine 1918, kada se vratio u operativnu vojsku [1–5].

Za vreme Prvog svetskog rata sanitet Kraljevine Srbije podneo je velike žrtve što se vidi iz sledećih podataka: poginulih lekara – 3, umrlih lekara – 119, umrlih stomatologa – 1,

umrlih lekara, stranaca u srpskoj vojsci – 25, umrlih zarobljenih lekara na radu u srpskim vojnim bolnicama – 11, umrlih studenata medicine – 20 i umrlih starijih doktoranata – 4. Njihova dela i žrtve ostaće zauvek utkane u istoriji srpskog vojnog saniteta [10].

Od 1. marta do 31. maja 1916. dr Dragutin S. Petković bio je član Srpske misije za uređivanje logora na Halkidikiju (Grčka) za prijem Srpske vojske za Solunski front. Između ostalog, za vreme Prvog svetskog rata dr Dragutin S. Petković bio je šef Saniteta srpske komande u Solunu, član superrevizione komisije pri Vrhovnoj komandi u Solunu, član Međunarodne komisije u Solunu, član Komisije za suzbijanje vašljivosti kod vojnika na Solunskom frontu, član Antimalarične komisije pri Vrhovnoj komandi, član Komisije za suzbijanje veneričnih bolesti u Solunu, lekar Srpskog kaznenog zavoda u Solunu, a od 1. juna do 19. jula 1918. referent saniteta Jugoslovenske divizije i načelnik saniteta Prve armije u selu Dragomanci kod Bitolja, sve do dana demobilizacije.

Bolnica u Dragomancima smatrana je za jednu od najznačajnijih sanitetskih ustanova srpske vojske, pa su je ispomagali mnogobrojni poznati lekari kao npr. Ludvik Hirsfeld, poljski epidemiolog iz Varšave koji je vodio srpsku bakteriološku laboratoriju, dr Nikola I. Sičev iz Hrakova i dr. [5].

Bolnica u Dragomancima ostaće zabeležena u analima velikog rata na Solunskom frontu, duž bojišta Moglenske ravnice. Po rečima vojvode Stepe Stepanovića „ona će služiti u istoriji srpskog ratnog saniteta kao model i škola, kako treba hirurška poljska bolnica da izgleda“ [5].

Kada je počeo proboj Solunskog fronta, najveći problem srpskog vojnog saniteta bio je njegovo zaostajanje, jer nije mogao da prati furiozni povratak Srpske vojske u otadžbinu. Nemački car Vilhelm II (1918), neverujući u poraz bugarske vojske i neprestano povlačenje nemačke vojske, rekao je: „Trebalo je biti Srbin ..... pa učiniti nemoguće mogućim“ [7].

U periodu 1914–1918. na čelu vojnog saniteta nalazili su se: pukovnik dr Sima Karanikolić, načelnik Sanitetskog odeljenja Ministarstva vojnog; pukovnik dr Roman Sondermajer, načelnik Sanitetskog odeljenja Vrhovne komande do 19. jula 1917; posle njega pukovnik dr Đoka Vladisavljević, do kraja rata.

U I armiji načelnik saniteta bio je pukovnik dr Đoka Vladisavljević, do 19. juna 1918, i pukovnik dr Dragutin Petković, do kraja rata, a u II armiji načelnik saniteta do kraja rata bio je pukovnik dr Sava Petrović [9].

Pošto je dr Dragutin S. Petković bio lekar Srpskog kaznenog zavoda u Solunu, po službenoj dužnosti je konstatovao smrt Apisa nakon sprovedene kazne streljanjem, izvršene zbog neuspelog atentata na regenta Aleksandra Karađorđevića u Solunu [11, 12].

Nakon demobilizacije, po prethodno podnetoj molbi, vraća se u Niš (20. mart 1918) za referenta saniteta Moravske divizijske oblasti i na tom položaju ostaje do 20. avgusta 1922. godine.

Sanatorijum dr Dragutina S. Petkovića – prvi u Nišu, drugi u Srbiji

Dr Dragutin S. Petković 1. oktobra 1922. godine otvara svoj privatni sanatorijum u Nišu, pod imenom „Niški sanatorijum dr Petkovića“. Taj sanatorijum bio je prvi u Nišu, a drugi u Srbiji (prvi sanatorijum u Srbiji osnovao je dr Lazar Genčić) [1, 4, 12, 13]. Zgrada sanatorijuma srušena je za vreme Drugog svetskog rata, tokom bombardovanja 1944. godine, dok su pomoćne zgrade ostale sačuvane.

„Niški glasnik“ iz 1925. godine objavio je tekst pod naslovom „Sanatorijum dr Petkovića“ : „...Sanatorijum dr Petkovića je prava blagodet za Niš i okolinu. Leži u jednom od najlepših delova grada, a sama zgrada je solidna, suva i izložena suncu.....sobe za bolesnike pune svetla, sunca i života; operaciona sala snadbevena je svim modernim hirurgičkim rekvizitima, ostale sobe i kancelarije uzorne. Bolesnicima se posvećuje upravo maternja briga i nega. Hrana je onakva kakva samo može biti. Iz Sanatorijuma izvedene su dosad upravo neverovatne operacije i to sa najboljim uspehom. Uzrok tome je i to, što Niš ima dosta lekara i specijalista, a bolesnici kada dođu u Sanatorijum mogu po volji da izaberu sebi lekara specijalista. Sanatorijum ima i lepu baštu, u kojoj bolesnici mogu da udišu, od jela i borova, aromatizovani vazduh koji krepi, osvežava i oživljuje...“ Sanatorijum je mogao da hospitalizuje 23 bolesnika, a brojao je sedam zaposlenih radnika [13].

Priznanja dr Dragutina S. Petkovića

Dr Dragutin S. Petković nosilac je mnogobrojnih priznanja i odlikovanja: Spomenice kralja Petra, Zlatne medalje za revnosnu službu (dva puta), Spomenice srpsko-turskog rata, Spomenice srpsko-bugarskih ratova, Krsta milosrđa, Albanske spomenice, Crvenog krsta, Ordena Svetog Save 3. reda, Ordena belog orla 4. reda, Počasne legije, Francuskog ratnog krsta, Francuske medalje za epidemiju, Grčkog ordena Svetog Spasa, Grčkog ratnog krsta i Medalje kralja Petra [1, 3, 4].

Zaključak

Sanitetski pukovnik dr Dragutin S. Petković bio je prvi upravnik Pasterovog zavoda u Nišu, osnivač Antirabičnog, Bakteriološkog i Hemijskog odelenja u tom zavodu, profesor, poliglota, patriota, vojni lekar u tri rata, dobitnik mnogobrojnih priznanja i ordenja.

Najveći deo svog života posvetio je medcini i otadžbini. Ostvario je velika dela, ne samo u sklopu vojnog saniteta, već i celokupnog srpskog zdravstva onog vremena.

L I T E R A T U R A

1. *Milojević V.* Pasteur's Institute in the town of Niš, 1900–1985. Niš: Prosveta Niš; 1990. (Serbian)
2. *Milojević V.* History of the town of Niš. Niš: Gradina i Prosveta; 1984. (Serbian)
3. *Živić R.* Encyclopedia. Niš: Gradina; 1996. (Serbian)
4. *Živić R.* Great mens in medicine of the town of Niš. Niš: Prosveta; 1997. (Serbian)
5. *Đenić N, Cirić S, Popović-Filipović S.* On 130th anniversary of Military Hospital in the town of Nis: January, 1878–January, 2008. Vojnosanit Pregl 2008; 65(1): 69–80. (Serbian)
6. *Kovačević A.* history of development of urology in the town of Niš. Niš: Poligraf; 2008. (Serbian)
7. *Ignjatović M.* Serbian war surgical doctrine (1912–1918). Vojnosanit Pregl 2008; 65(suppl): 49–58. (Serbian)
8. *Popović B, Zeljković J, Mikić D, Vidanović M.* The Serbian army in 1917–1918. Vojnosanit Pregl 2008; 65(suppl.): 41–8. (Serbian)
9. *Nedok A.* The Serbian army medical corps in 1917–1918. Vojnosanit Pregl 2008; 65(1): 19–26. (Serbian)
10. *Nedok A, Sekulić M.* The epilogue: total numbers of casualties in World War I. Vojnosanit Pregl 2008; 65(1):98–100. (Serbian)
11. *Savković D.* Apis – blood and rage. Beograd: Sloboda; 1988. (Serbian)
12. *Živić R.* Book on hospital. Niš: Prosveta; 2001. (Serbian)
13. Sanatorium dr Petković. Niš: Niški glasnik 1925; 7: 73. (Serbian)

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I N M E M O R I A M

Primarijus dr Miroslav Živković pukovnik u penziji (1933–2009)

Posle duge i teške bolesti napustio nas je pukovnik u penziji, primarijus dr Miroslav Živković, dugogodišnji član kolektiva Klinike za anesteziologiju i intenzivnu terapiju Vojnomedicinske akademije.

Doajen vojne anesteziologije, primarijus dr Miroslav Živković rođen je u Pirotu 1933. godine. Svoj radni vek proveo je u VMA Beograd, prvo u Odeljenju za plastičnu hirurgiju, a potom u Klinici za anesteziologiju i intenzivnu terapiju. Počeci su bili teški i, kako je sam govorio, teško je bilo razvijati anesteziološku službu pošto je anesteziolog bio sam i prepušten brojnim problemima i zahtevima koji su pred njega postavljani. Međutim, tokom tih dugih i teških godina, primarijus Živković je „ispekao zanat“ i postao anesteziolog od ugleda, čovek na koga se uvek moglo osloniti i anesteziolog koji je, zajedno sa svojim kolegama, stvorio današnju Kliniku za anesteziologiju i intenzivnu terapiju u Vojnomedicinskoj akademiji. Iskustvo i umeće primarijusa Živkovića bili su beskrajni i on je to nesebično delio sa mlađim kolegama. Dobroćudan po naravi, veliki prijatelj i stariji kolega od ugleda, uvek se nalazio nama mlađima u nevolji i uvek je njegova pomoć bila brza i neprocenjiva. Skroman i tih, kao i većina njegovih sunarodnika, nikada nije isticao sebe ali je uvek bio tu, spreman da pomogne. O tome su svedočili i brojna rodbina, prijatelji i kolege koji su došli da ga isprate na poslednji put.

U ime svih koji su od primarijusa dr Miroslava Živkovića učili anesteziologiju i reanimatologiju i koji su imali tu čast i zadovoljstvo da ga poznaju i rade sa njime, odajem mu poslednju počast i pozdrav. Neka počiva u miru.

Načelnik Klinike za anesteziologiju
i intenzivnu terapiju
pukovnik prof. dr Predrag Romić

UPUTSTVO AUTORIMA

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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)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

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

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Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

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. 413-428.

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

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Type each table double-spaced on a separate sheet. Number tables consecutively in the order of their first citation in the text in the upper right corner **(Table 1)** and supply a brief title for each. Place explanatory matter in footnotes, using the following symbols, in this sequence: ***, †, ‡, §, ||, ¶, **, ††, ...** Each table has to be mentioned in the text. If you use data from another source, acknowledge fully.

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