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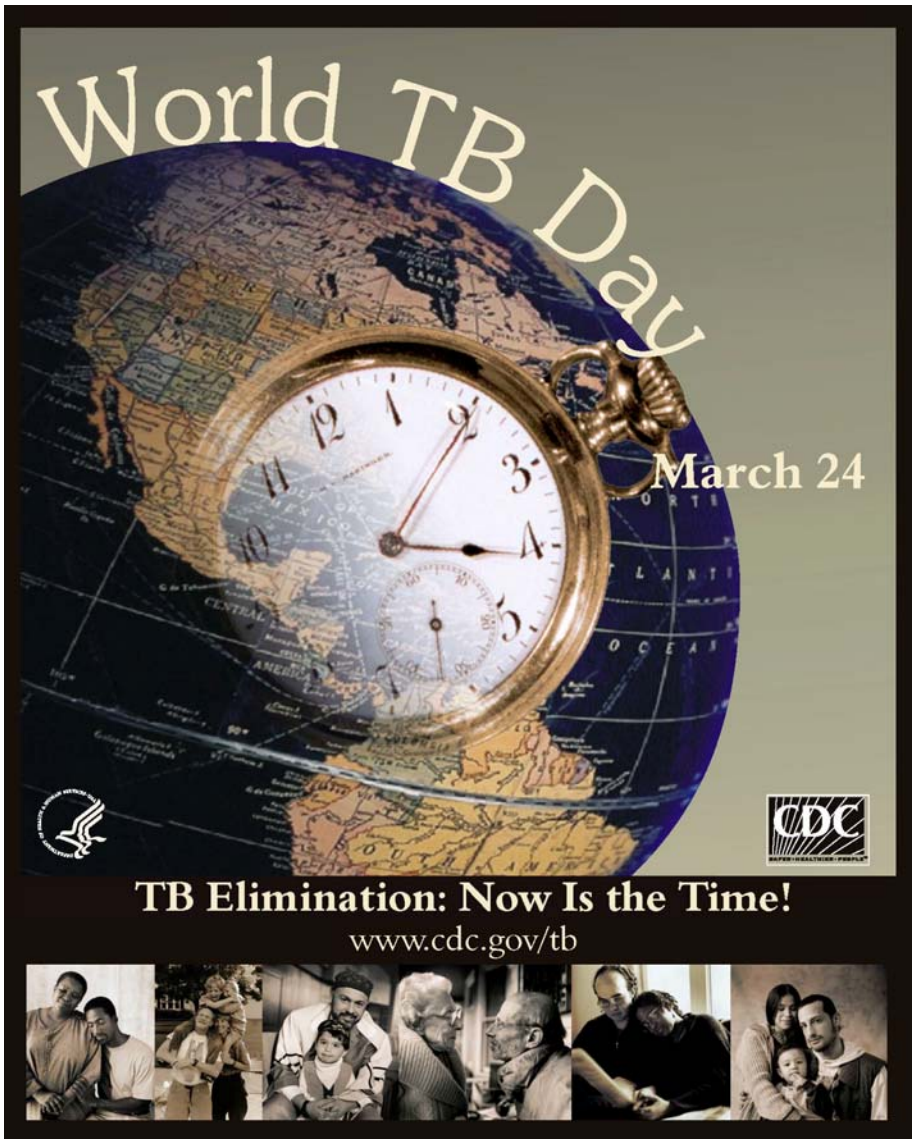

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SADRŽAJ / CONTENTS

UVODNIK / EDITORIAL

Silva Dobrić
Autor godine Vojnosanitetskog pregleda za 2011.
The Author of the Year 2011 by the *Vojnosanitetski Pregled* 223

ORIGINALNI ČLANCI / ORIGINAL ARTICLES

Dragica P. Pešut, Milica V. Bulajić, Aleksandar R. Lešić
Time trend and clinical pattern of extrapulmonary tuberculosis in Serbia, 1993–2007
Tendencije učestalosti i klinički oblici vanplućne tuberkuloze u Srbiji u periodu 1993–2007 227

Jasmina Djordjević-Jocić, Gordana Zlatanović, Dragan Veselinović, Predrag Jovanović, Vidosava Djordjević, Lilika Zvezdanović, Gordana Stanković-Babić, Milena Vujanović, Sonja Cekić, Matthias Zenkel, Ursula Schlotzer-Schrehardt
Transforming growth factor β1, matrix metalloproteinase-2 and its tissue inhibitor in patients with pseudoexfoliation glaucoma/syndrome
Transformišući faktor rasta β1, matriks metaloproteinaze-2 i njen tkivni inhibitor kod bolesnika sa pseudoeksfolijativnim sindromom/glaukomom 231

Zorica Brdareski, Aleksandar Djurović, Snežana Šušnjar, Mirjana Životić-Vanović, Andjelka Ristić, Ljubica Konstantinović,Ljiljana Vučković-Dekić, Mirjana Tankosić
Effects of a short-term differently dosed aerobic exercise on maximum aerobic capacity in breast cancer survivors: a pilot study
Uticaj kratkotrajnog aerobnog vežbanja različitog intenziteta na maksimalni aerobni kapacitet preživelih od karcinoma dojke 237

Marina Vučeljić, Olivera Ilić-Stojanović, Milica Lazović, Mirko Grajić
Vitamin D and parathyroid hormone in relation to bone mineral density in postmenopausal women
Vitamin D i paratireoidni hormon i povezanost sa mineralnom gustinom kostiju kod žena u postmenopauzi 243

Mirjana Janićijević Petrović, Tatjana Šarenac, Sunčica Srećković, Marko Petrović,Dejan Vulović, Katarina Janićijević
Evaluation of the patients with Grave's ophthalmopathy after the corticosteroids treatment
Ocena bolesnika sa Grejvsovom oftalmopatijom posle lečenja kortikosteroidima 249

Branko Košević, Predrag Aleksić, Novak Milović, Vladimir Bančević, Dušica Stamenković, Ivica Nikolić, Mirko Jovanović, Radovan Milošević
Urodynamic characteristics of the modified orthotopic ileal neobladder
Urodinamske karakteristike modifikovane ortotopne ilealne neobešike 253

AKTUELNA TEMA / CURRENT TOPIC

Aneta Lakić
Quality of life in childhood and adolescence: from concept to practice
Kvalitet života u detinjstvu i adolescenciji: od koncepta do prakse 257

Nataša M. Bakić-Mirić, Aleksandra S. Gogić, Nikola M. Bakić
Conceptual framework for communicating health and illness across cultures
Konceptualni okvir za interkulturalnu zdravstvenu komunikaciju 260

SEMINAR PRAKTIČNOG LEKARA / PRACTICAL ADVICE FOR PHYSICIANS

Jasna Jevdjić, Maja Šurbatović, Nebojša Stanković, Violetta Raffay, Zlatko Fišer, Duško Jovanović
Najvažnije promene u Preporukama za kardiopulmonalnu resuscitaciju Evropskog resustitacionog saveta za 2010. u oblasti osnovne i napredne podrške života kod odraslih
Major changes in the European Resuscitation Council Guidelines for Cardiopulmonary Resuscitation 2010 in the field of Adult Basic and Advanced Life Support 265

KAZUISTIKA / CASE REPORTS

Sašo Rafajlovski, Radoje Ilić, Branko Gligić, Vladimir Kanjuh, Vujadin Tatić, Andjelka Ristić, Slobodan Obradović,Dragan Dinčić, Nenad Ratković, Radoslav Romanović, Jasna Karić, Nemanja Djenić,Snježana Vukotić
Uticaj lokalizacije miksoma srca na klinički tok i ishod bolesti
Impact of heart myxoma localization upon its clinical course and outcome 270

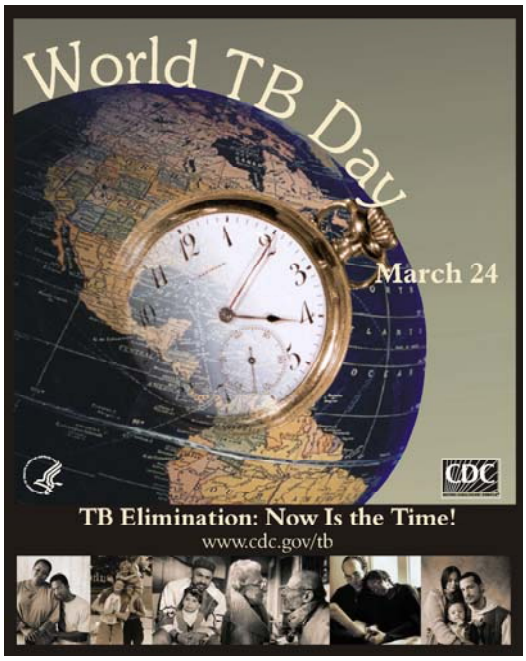
Marija Mačvanski, Dragana Ristić-Baloš, Brankica Vasić, Slobodan Lavrnić, Svetlana Gavrilović, Mihajlo Milićević, Sanja Milenković, Tatjana Stošić-Opinćal
Intracranial yolk sac tumor in an adult patient: MRI, diffusion-weighted imaging and 1H MR spectroscopy features
Intrakranijalni *yolk sac* tumor kod odraslog bolesnika: karakteristike snimanja magnetnom rezonancom (MR), difuzionom MR i protonskom MR spektroskopijom 277

Ivan Marjanović, Miodrag Jevtić, Sidor Mišović, Uroš Zoranović, Aleksandar Tomić, Siniša Rusović, Momir Šarac
Elektivna visceralna hibridna rekonstrukcija aneurizme torakoabdominalne aorte tipa III
Elective visceral hybrid repair of thoracoabdominal aortic aneurysm type III 281

Gordana Stanković-Babić, Ana Oros, Sonja Cekić, Milena Vujanović, Rade R. Babić
Unilateral optic nerve aplasia associated with microphthalmos
Jednostrana aplazija nervusa optikusa udružena sa mikroftalmusom 286

PRIKAZ KNJIGE / BOOK REVIEW 291

UPUTSTVO AUTORIMA / INSTRUCTIONS TO THE AUTHORS 293



Ove godine, 24. marta, 30. put zaredom obeležiće se Svetski dan protiv tuberkuloze (TB). To je prilika da se još jednom podsetimo na važnost borbe protiv ove bolesti koja, nažalost, u nekim zemljama još uvek predstavlja jedan od vodećih uzroka smrtnosti. Prema podacima Pešut i sar, objavljenim u ovom broju Vojnosanitetskog pregleda, poslednjih 10 godina beleži se blagi porast vanplućne TB u Srbiji (vidi str. 227–30).

This year, on March 24, for the 30th time continually, the World Tuberculosis Day will be denoted. It is an occasion to remind once again of importance to fight against tuberculosis that, unfortunately, in some countries continues to be one of the leading causes of death. According to data of Pesut et al., published in this issue of the *Vojnosanitetski pregled*, an increasing trend of extrapulmonary tuberculosis was registered in Serbia in the last 10-year period (see pages 227–30).

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

Autor godine Vojnosanitetskog pregleda za 2011.

The Author of the Year 2011 by the *Vojnosanitetski Pregled*

Silva Dobrić

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Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia

Stalni čitaoci Vojnosanitetskog pregleda (VSP) znaju da se već duži niz godina, 2. marta, na Dan Vojnomedicinske akademija, proglašava Autor godine časopisa za prethodnu godinu. Ova nagrada ustanovljena je 1995. godine sa željom da istakne značaj publikovanja u naučnim časopisima za širenje i unapređenje medicinske struke i nauke, ali i za podizanje ugleda i uticaja samih autora i njihovih institucija, kao i časopisa u kojima objavljuju.

Odavno je poznato da u naučnoj zajednici vredite onoliko koliko publikujete, odnosno onoliko koliko vaš rad, pretočen u publikacije, ima uticaja na oblast kojom se bavite. Merilo tog uticaja je citiranost radova pojedinog autora, pri čemu veliku ulogu igraju i časopisi u kojima se publikuju ti radovi. Naime, veća je verovatnoća da će rad biti čitan i citiran, ako se objavi u časopisu koji se više čita, a tu čitanost, upravo, i određuje citiranost radova koji se objavljuju u njemu. Na ovaj način, uspostavlja se zajednička uzročno-posledična veza, u kojoj, s jedne strane autor, a sa druge časopis, pomažu jedan drugom da ostvare svoj cilj – povećanje čitanosti i citiranosti, odnosno povećanje impakt faktora – faktora uticaja. Ali, osnovni preduslov za ovo jeste publikovanje, pa otuda i nagrada našeg časopisa najplodnijim autorima.

Kriterijumi za izbor Autora godine VSP baziraju se na broju radova objavljenih u godini za koju se nagrada dodeljuje, kategoriji kojoj objavljeni rad pripada i redosledu autora, pri čemu se u obzir uzimaju samo prva tri autora u radu (tabela 1).

U 2011. godini na stranicama VSP objavljeno je 177 radova iz kategorija koje se boduju sa ukupno 442 autora, a najveći broj bodova pripao je naučnom saradniku, prim. dr sc. med. Zoranu Stanojkoviću iz Zavoda za transuziju krvi u Nišu. Primarijus dr Stanojković je, ujedno, drugi po redu dobitnik našeg priznanja koji dolazi iz tzv. civilnih institucija. Naime, do sada su Autori godine VSP uglavnom bili autori iz struktura vojnog saniteta. Izuzetak je bila 2008. jer je za tu godinu titula Autora godine VSP pripala prof. dr Milanu Višnjiću, takođe iz Niša.

Regular readers of the *Vojnosanitetski pregled* (VSP) know that for a long period on March 2, the Day of the Military Medical Academy, the Author of the Year by the Journal for the previous year has been announced. The prize was established in 1995 intending to emphasize the significance of publishing in scientific journals for spreading and advancing medical fields and science, but also for enhancing reputation and impact of authors themselves and institutions they come from, as well as the journals they publish their papers in.

It has been known for a long time that the more an author publishes papers the higher he or she is rated within a scientific community, that is as much as a published paper impacts the field to which he or she belongs to. A measure reflecting that impact is citation of papers of an author, while a significant contribution, however, is made by journals that publish papers. Namely, it is much likely that a paper will be read and citated if published by a journal that is more read, and the rate of reading itself is determined by citations of papers published in it. A common cause-and-effect relationship set in this way with an author at one side and a journal at the other makes them help each other to obtain their aim – enhance reading rate and citation, that is to say to get a higher impact factor. The basic precondition for this, however, is the publishing itself, thus making the prize by our Journal to be awarded to the most fruitful authors.

The Author of the Year selecting criteria are based on the number of the papers published in the year for which the prize is awarded, the category to which the published paper belongs, and the order of authors (only the first three authors are considered) (Table 1).

Within 2011 there were 177 papers published on pages of the VSP of the categories that are rated with a total of 442 authors. The highest score was won by a research fellow, Primarius Doctor, Ph.D., Zoran Stanojković, Blood Transfusion Institute, Niš. Primarius Doctor, Ph.D., Zoran Stanojković is at the same time the second our prize winner coming from civil institutions since till now prize winners mainly came from military

Correspondence to: Silva Dobrić, Institut za naučne informacije, Vojnomedicinska akademija, Crnotravska 17, 11040 Beograd, Srbija. Tel.: +381 11 3609 311. E-mail: vsp@vma.mod.gov.rs

Primarijus Zoran Stanojković, Autor godine VSP za 2011. godinu, objavio je u toku prošle godine tri rada u našem časopisu, sva tri iz kategorije originalni članci (tabela 2). U dva rada bio je prvi autor, a u jednom drugi što mu je, shodno kriterijumima navedenim u tabeli 1, donelo 30 bodova i prvo mesto (tabela 3).

U ime Izdavača, Uređivačkog odbora i Redakcije časopisa čestitam prim. dr Zoranu Stanojkoviću na tituli Autora godine VSP za 2011. godinu uz želje za još mnogo sličnih uspeha i ubuduće i s nadom se da će, i u godinama koje slede, nastaviti da objavljuje svoje radove na stranicama našeg časopisa. Čestitke i želje za što veći broj publikacija u narednom periodu upućujem i ostalim autorima našeg časopisa, od kojih će neki, sigurno, biti naši novi Autori godine VSP.

medical institutions. The only exception was in 2008 when the winner, Prof. Dr. Milan Višnjić, also came from the town of Niš.

Primarius Doctor Zoran Stanojković, the Author of the Year 2011 by the VSP, in the previous year published three papers in the VSP, each of them of the category Original articles (Table 2), as the first author in two papers, and the second in one paper, that in compliance with the criteria got him 30 scores and the first position (Table 3).

In the name of the Publisher, Editorial Board, Editorial Srtaff, I congratulate to Primarius Doctor Zoran Stanojković to the title the Author of the Year 2011 by the VSP wishing him more success in future, hoping that in years that come he will keep on publishing papers on pages of the VSP. My congratulations and good wishes for more publications I also send to other authors of our Journal, some of whom will certainly be the new winners of the Author of the Year by the VSP.

Tabela 1
Table 1

Kriterijumi za bodovanje autora i članaka u VSP /
Criteria for authors and articles scoring in the *Vojnosanitertski Pregled*

Kategorija rada/ Article category	Broj bodova/ Score		
	prvi autor/ first author	drugi autor/ second author	treći autor/ third author
Originalni članak/ Original article	12	6	3.6
Prethodno saopštenje/ Preliminary report	5	2.5	1.5
Pregledni članak/ General review	10	5	3
Aktuelna tema/ Curreent topic	8	4	2.4
Kazuistika/ Case report	4	2	1.2
Istorija medicine/ History of medicine	5	2.5	1.5
Uvodnik/ Editorial	5	2.5	1.5

Tabela 2
Table 2

Radovi prim. dr sc. med. Zorana Stanojkovića objavljeni u Vojnosanitetskom pregledu u 2011. /
/ Articles by Dr. Zoran Stanojkovic, PhD, published in the *Vojnosanitetski Pregled* in 2011

Broj/ Number	Autori i naziv rada / Authors and title of article
1	*Antić A, Stanojković Z.* Red blood cells transfusions in oncological patients treated with radio- and chemotherapy. Vojnosanit Pregl 2011; 68(1): 28–34. (Serbian)
2	*Stanojković Z, Antić A.* Pathogen inactivation in fresh friozen plasma using riboflavin and ultraviolet light: effects on plasma proteins and coagulation factor VIII. Vojnosanit Pregl 2011; 68(1): 51–6. (Serbian)
3	*Stanojković Z, Antić A, Stojanović M.* Effects of use of riboflavin and ultraviolet light for pathogen inactivation on quality of platelet concentrates. Vojnosanit Pregl 2011; 68(6): 489–94. (Serbian)

Tabela 3
Table 3

Autori Vojnosanitetskog pregleda u 2011. godini koji po broju osvojenih bodova zauzimaju prvih pet mesta (vidi tabelu 1) /
/ Authors of the *Vojnosanitetski pregled* in 2011 at the first five positions on the rang-list according to the score (see Table 1)

Redni broj / Number	Autori / Authors	Institucije / Institutions	Bodovi/ Score
1	Zoran Stanojković	Zavod za transfuziju, Niš, Srbija Blood Transfusion Institute, Niš, Serbia	30
2	Ana Antić	Zavod za transfuziju, Niš, Srbija Blood Transfusion Institute, Niš, Serbia	24
3	Ivan Leković	Vojnomedicinska akademija, Beograd, Srbija Military Medical Academy, Belgrade, Serbia	24
4	Silva Dobrić	Vojnomedicinska akademija, Beograd, Srbija Military Medical Academy, Belgrade, Serbia	21
5	Zoran Bjelanović	Vojnomedicinska akademija, Beograd, Srbija Military Medical Academy, Belgrade, Serbia	19.2

Napomena: Navedena su imena samo prvih pet autora jer se na pozicijama od 6. do 10. mesta nalazi više autora sa istim brojem bodova
Note: Only the first five authors are mentioned because the positions 6 to 10 are occupied by more authors having the same score.

Kratka biografija Autora godine Voojnosanitetskog pregleda za 2011.

Prim dr sc.med Zoran Stanojković rođen je 27.12.1963. u Kumanovu. Medicinski fakultet Univerziteta u Nišu završio je 1988. godine, a specijalizaciju iz transfuziologije 1996. godine na Medicinskom fakultetu Univerziteta u Beogradu sa odličnim uspehom. Trenutno se nalazi na supspecijalističkim studijama iz oblasti hematologije.

Short *Curriculum Vitae* of the Author of the Year 2011 by the *Vojnosnaitetski pregled*

Primarius Dr. Zoran Stanojković, PhD, was born on December 27, 1963, at the town of Kumanovo. He graduated from the Medical Faculty in Niš in 1988, and became a Transfusion Medicine Specialist in 1996, at the Medical Faculty in Belgrade. Currently, he is subspecializing in hematology.

Primarijus dr sc. med Zoran Stanojković, autor godine Vojnosanitetskog Pregleda za 2011.
Zoran Stanojković, MD, PhD, the Author of the Year 2011 by the *Vojnosanitetski Pregled*

Magistrirao je 2000. godine na Medicinskom fakultetu Univerziteta u Nišu odbranivši rad pod nazivom „Inhibitori faktora VIII kod bolesnika sa hemofilijom A“, a osam godine kasnije na istom fakultetu uspešno je odbranio i doktorsku disertaciju „Procena vrednosti lokalne primene fibrinskog lepka sa antibioticima u prevenciji dehiscencije anastomoze kolona“.

Od 1990. godine stalno je zaposlen u Zavodu za transfuziju krvi u Nišu gde je od 1998. do 2002. godine obavljao dužnost načelnika Odeljenja za kolekciju krvi i laboratorije za ispitivanje poremećaja hemostaze, a od 2002. godine nalazi se na mestu direktora Zavoda. Od samog početka svoje profesionalne karijere aktivno je učestvovao u implementaciji novih transfuzijskih metoda i tehnologija. Tako je, najpre, učestvovao u izradi i sprovođenju strategije autologne transfuzije krvi u Kliničkom centru u Nišu, a od 2001. godine započinje pripremu fibrinskog lepka za potrebe eksperimentalne studije iz oblasti hirurgije, a kasnije i za kliničku primenu. U isto vreme uvodi testove za ispitivanje na trombofilije, a 2006. godine najsavremeniji informacioni sistem za rad služ-

He got the Master's Degree in 2000 from the Medical Faculty in Niš on “Factor VIII inhibitors in patients with haemophilia A”, while eight years later he successfully defended his PhD thesis “Assessment of local application of fibrin glue with antibiotics in prevention of colon anastomosis dehiscences”.

He started to work at the Blood Transfusion Institute in Niš in 1990, and from 1998 he had been working as a Head of the Department for Blood Collection and laboratory for Testing of Hemostatic Disorders. He became a director of the Institute in 2002. From the very beginning of his professional career he participated in new transfusion methods and technology implementation. Thus, he participated first in the development of strategy of implementing autologous transfusion in the Clinical Center in Niš, and in 2001 he introduced fibrin glue preparation, firstly for experimental study purposes in surgery, and later for clinical use. At the same time he introduced testings for trombophilia at the Blood Transfusion Institute in Niš, and in 2006 the most modern information system for transfusion services which allows traceabilty

be transfuzije koji omogućava apsolutno praćenje traga jedinice krvi od davaoca do primaoca. Poslednjih par godina obeležile su njegovo zalaganje za uvođenje inaktivacije patogena u krvnim produktima, implementaciju gel-aglutinacione tehnike u pretransfuzijska ispitivanja, praćenje antiagregacione terapije, kao i automatizaciju u testiranju dobrovoljnih davalaca krvi.

Primarijus dr sc. med. Zoran Stanojković bio je član Upravnog odbora Projekta reorganizacije transfuziološke službe u Srbiji, u okviru projekta Evropske agencije za rekonstrukciju i Ministarstva zdravlja Republike Srbije, 2002–2006. godine, kao i predstavnik Republike Srbije za oblast transfuzije krvi u Zdravstvenom sektoru Saveta Evrope (SP-GS) u Upsali 2005. godine i Briselu 2006. godine. U istom periodu bio je jedan od koautora Preporuka za pripremu, primenu i kontrolu kvaliteta krvi i komponenata krvi (12–14. izdanje) Saveta Evrope. Član je i Međunarodnog udruženja transfuziologa (ISBT).

Bio je saradnik u projektu „Istraživanje mogućnosti primene i poboljšanja karakteristika autolognog fibrinskog lepka u hirurgiji – klinička i eksperimentalna studija“, odobrenog od Ministarstva za nauku i tehnologiju Republike Srbije 2002. godine. Trenutno je angažovan na projektu Ministarstva prosvete i nauke Republike Srbije od 2011. godine pod nazivom „Monitoring elektromagnetnog zračenja mobilnih telekomunikacionih sistema u životnoj sredini, analiza molekularnih mehanizama i biomarkera oštećenja kod hronične izloženosti sa razvojem modela za procenu rizika i metoda za zaštitu“.

U periodu od 2004. do 2007. godine prim dr sc. med Zoran Stanojković bio je predsednik Sekcije za transfuziologiju Srpskog lekarskog društva. Od 2005. godine član je Republičke stručne komisije za transfuziologiju pri Ministarstvu zdravlja Republike Srbije, a 2010. godine izabran je za predsednika Udruženja transfuziologa Srbije. Takođe, od 2003. godine mentor je specijalističkog staža iz transfuziologije na postdiplomskim studijama na Medicinskom fakultetu u Beogradu i Medicinskom fakultetu u Nišu. Član je uređivačkog odbora Biltena za transfuziologiju od 2006. godine, a od aprila 2011. godine i jedan od njegovih urednika. Januara 2010. godine dobio je zvanje primarijus, a iste godine izabran je za naučnog saradnika na Medicinskom fakultetu u Nišu.

Objavio je preko 90 naučnih i stručnih radova u međunarodnim i domaćim časopisima, od kojih je devet publikovano u časopisima sa SCI liste. Učetvovao je na brojnim kongresima u zemlji i inostranstvu, i bio potpredsednik III i IV Kongresa transfuziologa Srbije i Crne Gore 2006. i 2010. godine. Autor je poglavlja u knjigama Transfuziologija (2004; izdavač: Zavod za udžbenike i nastavna sredstva, Beograd) i Hirurgija (2011; izdavač: Medicinski fakultet, Niš).

of all blood units, from donors to recipients. The last two years were marked by his efforts to introduce pathogen inactivation in blood products, gel agglutination technique in pretransfusion testings, monitoring of anti-aggregation therapy and automatization in blood donors testings.

Dr. Zoran Stanojković was a member of the Steering Comittee of the Project of Reorganization of Transfusion Services in Serbia, as a part of the Project of European Council and Ministry of Health of the Republic of Serbia from 2002 to 2006, and a member of the Expert Working Group (SP-GS), as a representative of Serbia in the European Comittee of Blood Transfusion (Uppsala, 2005; Brussells, 200.). Also, he participated in writing a book “Guide to the preparation, use and quality assurance of blood components” 12th, 13th and 14th edition (Council of Europe Publishing). He is a member of International Society Blood Transfusion (ISBT).

Dr. Stanojković was a contributor in the Project “Researching the possibilty for application and improvement of characteristics of autologous fibrin glue in surgery – experimental and clinical study“, improved by the Ministry of Science and Technology of Republic of Serbia in 2002. Currently, he is engaged in the Project of the Ministry of Education and Science od the Republic of Serbia from 2011 „Monitoring of electromagnetic radiation of mobile telecommunication systems in the enviroment, analysis of molecular mechanisms and biomarkers of damages in chronic exposure with model development for risk assessment and protection methods“.

From 2004 to 2007 Dr. Stanojković was a president of the Section of Transfusiology in Serbian Medical Society, a member of the Republic Blood Transfusion Committee of the Serbian Ministry of Health from 2005, and in 2010 he was elected for the president of the Association of Transfusion Specialists of Serbia. Also, from 2003 he is a mentor to specialization training in transfusion at Postgraduate studies at the Medical Faculty in Belgrade and Medical Faculty in Niš. Dr. Stanojković is a member of Editorial Board of the Bulletin of Transfusion Medicine from 2006, and from the last year he is one of the editors of the Journal. In January 2010 he got the title “Primarius” and later that year he was selected for a Research Fellow at the Medical Faculty in Niš.

Dr. Stanojković published more than 90 scientific articles in international and domestic journals, nine of which were published in the journals from the SCI list. He participated in numerous congresses in Serbia and abroad, and he was a Vice-President of the 3rd and 4th Transfusion Medicine Congress of Serbia and Montenegro 2006 and 2010. He is the author of chapters in books “Transfusiology” (2004; Belgrade: Institute for Textbooks and Teaching Aids), and “Surgery” (2011; Niš: Medical Faculty).

ORIGINAL ARTICLE

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Time trend and clinical pattern of extrapulmonary tuberculosis in Serbia, 1993–2007

Tendencije učestalosti i klinički oblici vanplućne tuberkuloze u Srbiji u periodu 1993–2007.

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Abstract

Background/Aim. Increased incidence of extrapulmonary tuberculosis (XPTB) is reported worldwide. Serbia is a country in socio-economic transition period with low-middle HIV prevalence and intermediate-to-low tuberculosis (TB) incidence rate, 100% directly observed treatment (DOT) coverage, and mandatory BCG vaccination at birth. The aim of the study was to examine the incidence trend and clinical features of XPTB in Serbia during a 15-year period. **Methods.** This retrospective observational study included XPTB cases diagnosed in the period between 1st January 1993 and 31st Decembre 2007, according to the reports of the National Referral Institute of Lung Diseases and Tuberculosis in Belgrade and Central Tuberculosis Register. Population estimates with extrapolations were based on 1991 and 2002 census data. **Results.** While the overall TB incidence rate showed a slight, not significant decreasing trend (p = 0.535), a significant increase was found for XPTB (y = 1.7996 + 0.089x; R^2 = 0.4141; p = 0.01). A total of 2,858 XPTB cases (newly diagnosed and 10% relapses) gave an average age specific incidence rate of 2.51/100,000 population (95% confidence interval, SD = 0.6182) with 8.9% annual increase. The male-to-female ratio was 0.54. Lymph nodes were most frequently affected site (48.5%) followed by genitourinary (20.5%), pleural (12%), and osseo-arthicular (10.3%) TB. Treatment outcome was successful in 88.29% of patients (cured and completed), 3.64% died, 5.18% interrupted, 0.57% displaced, and 2.3% unknown. **Conclusion.** Increasing trend of XPTB incidence rate may be a result of increased morbidity due to still present risk factors, possible higher detection rate in Serbia and better notification. A high coverage of newborns with BCG vaccination at birth might contribute to a decreased number and rare XPTB cases in children.

Key words:
tuberculosis, urogenital; tuberculosis, miliary; tuberculosis, lymph node; tuberculosis, meningeal; tuberculosis, osteoarthicular; serbia; incidence.

Apstrakt

Uvod/Cilj. Incidencija vanplućne tuberkuloze (VPTB) je u porastu širom sveta. Srbija, koja se nalazi u periodu socioekonomske tranzicije je zemlja niske-srednje prevalencije infekcije HIV i srednje-niske stope incidencije tuberkuloze (TB) sa 100% primenjenom strategijom neposredno nadzirane terapije (DOT) i obaveznom BCG vakcinacijom po rođenju. Cilj našeg rada bio je da se ispita incidencija i klinički oblici VPTB u Srbiji tokom 15 godina. **Metode.** Retrospektivna opservaciona studija obuhvatila je sve slučajeve VPTB dijagnostikovane u periodu od 1. januara 1993. do 31. decembra 2007. godine, prema Godišnjim izveštajima Instituta za plućne bolesti i tuberkulozu u Beogradu (nacionalna referentna ustanova) i Centralnog registra za tuberkulozu. Procena broja stanovnika izvršena je na osnovu popisa stanovništva od 1991. i 2002. godine. **Rezultati.** Dok je ukupna stopa incidencije TB pokazala blagu neznatnu tendenciju opadanja (p = 0,535), našli smo značajan porast stope incidencije VPTB (y = 1,7996 + 0,089x; R2 = 0,4141; p = 0.01). Ukupno 2 858 bolesnika sa VPTB (novodijagnostikovani i 10% recidiva) dalo je prosečnu starosno specifičnu stopu incidencije od 2,51/100 000 stanovnika (interval poverenja 95%, SD = 0,6182) sa godišnjim porastom od 8,9%. Odnos broja obolelih osoba muškog i ženskog pola bilo je 0,54. Najčešće su bile zahvaćene limfne žlezde (48,5%), potom urogenitalni organi (20,5%), pleura (12%) i koštanozglobni sistem (10,3%). Kod 88,29% bolesnika lečenje je uspešno završeno, 3,64% bolesnika je umrlo, 5,18% prekinulo lečenje, 0,57% premešteno, dok je za 2,3% ishod leče-

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nja bio nepoznat. **Zaključak.** Tendencija porasta incidencije VPTB u Srbiji može da bude rezultat porasta morbiditeta usled još uvek prisutnih faktora rizika, moguće veće stope otkrivanja slučajeva i boljeg prijavljivanja. Visoki obuhvat novorođenčadi BCG vakcinacijom može da objasni što je VPTB u Srbiji kod dece retka.

Ključne reči:
tuberkuloza, urogenitalna; tuberkuloza, milijarna; tuberkuloza limfnih žlezda; tuberkuloza moždanica; tuberkuloza, osteoartikularna; srbija; incidenca.

Introduction

Although TB usually affects lungs, it can be spread through the blood stream and involve other sites leading to extrapulmonary TB (XPTB) [1]. This latter usually happens easier in immune compromised host [2, 3]. Thus, increasing number of XPTB cases worldwide is due to increasing number of immunodefficient persons, predominantly human immunodeficiency virus (HIV)-positive ones [2–4]. Nowadays, Serbia is an intermediate-low TB incidence country [4]. It ranks among HIV/AIDS low-middle prevalence countries and both HIV infection and drug resistance seem not to be major problems in current TB control [4]. Some other risk factors are of higher importance in developing TB such as stress and malnutrition, diabetes mellitus, chronic alcohol and tobacco abuse, and coexisting malignant disease, which are especially prominent in the existed and newly appeared risk groups [5-7]. Despite a slight decreasing trend of reported overall cases of TB in Serbia in recent years, we observed an increasing trend in some selected age groups and reported rare forms of XPTB in the setting [5,8–14].

Among all forms of XPTB, only pleural TB is equally likely to develop in male and female TB patients (adjusted for age, race/ethnicity and country of origin). All the other extrapulmonary forms (lymphatic, osteo-articular, peritoneal, pericardial, meningeal, and rarer forms) are consistently more likely to develop in female than in male patients [15].

The aim of our study was to examine the time trend of XPTB incidence rate in Serbia from 1993 to 2007 and to analyze the clinical pattern of the disease.

Methods

In this retrospective descriptive study, we analyzed annual data on diagnosed active TB cases for a 15-year-period, 1993–2007, categorized by sex and age. In the analysis, we used the proportion of notifications by age group and sex, and notification rate of TB per population by age-group as the main indicators over time.

The sources of data were Annual Summaries of the Research and Epidemiology Department of the National Referral Institute of Lung Diseases and Tuberculosis in Belgrade, and Central TB register [9–12].

The setting characteristics: South-East European country in socioeconomic transition period with population of 7,481,579 and TB incidence rate 27/100,000 population in 2007 [9]. Since 1952, the Serbian national TB reporting system provided age- and sex-specific morbidity figures for the year the cases were reported (cross-sectional reports). The age groups were defined as five-year intervals except for the first two intervals (0 years and 1–4 years) with 65–69 and ≥ 70 available age intervals for the elderly. According to the number and distribution of the XPTB cases notified, as well as the importance of the first years of age in TB pathogenesis and control, we used the age interval 0–4 years followed by the next three 20-year intervals (5–24, 25–44, 45–64), and the ≥ 65 years, to present the data most effectively.

Population estimates based on 1991 and 2002 census data with extrapolation were used for the calculations of TB incidence rates in the observed period. Incidence rates were expressed as the number of TB patients per 100,000 (No/100,000) population.

A regression line was fitted to the annual age specific incidence rates to ascertain the *p* value. For the estimation of regression coefficients, Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 was used. We used the following formula for linear regression to test the trends: value on vertical axis = intercept +/- slope multiplied by value on horizontal-axis ($y = a + bx$). Trendline was fitted by the sum of least squares.

Results

A total of 2,858 XPTB cases were registered in Serbia from 1993 to 2007. They presented the proportion of overall TB cases that ranged from 7–11.5% being 8% on average over the observed 15-year-period. While the overall TB incidence rate showed a slight, not significant decreasing trend ($y = 35.241–0.2643x$; $R^2 = 0.1712$; $p = 0.535$), a significant increase was found in patients with XPTB ($y = 1.7996 + 0.089x$; $R2 = 0.4141$; $p = 0.01$). An average age specific incidence rate of XPTB was 2.51/100,000 population (95% confidence interval, SD = 0.6182) with annual increase of 8.9% (Figure 1).

Distribution of XPTB cases by sex and age showed peak number in the 45–64-year age interval for male and female cases (Figure 2). Only two cases were recorded in the age interval 0–4 years over the observed period and both were girls. The female cases have prevailed in all the other ages with the average male-to-female ratio 0.54, being 0.6, 0.45, 0.59 and 0.55 for the age intervals 5–24, 25–44, 45–64, and 65 years and over, respectively (Figure 2).

The most frequently affected sites were lymph nodes (48.5%), and the next three ranked genitourinary (20.5%), pleural (12%), and osteo-articular TB (10.1%) (Figure 3). Only three XPTB patients have been reported to be HIV-positive. Individual data for the last three years of the analysis showed that the treatment of XPTB was successful in 88.29%, 3.64% of the patients died, 5.18% interrupted treat-

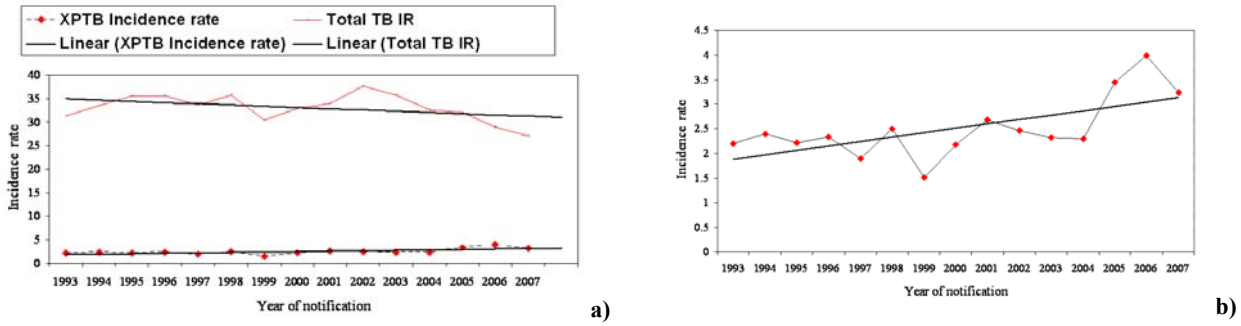

Fig. 1 – Time trends of the overall tuberculosis (TB) (a) and extrapulmonary tuberculosis (XPTB) (b) incidence rates in Serbia (1993–2007)

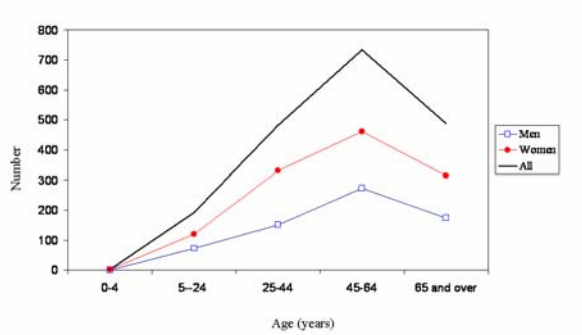

Fig. 2 – Distribution of extrapulmonary tuberculosis cases in Serbia by sex and age

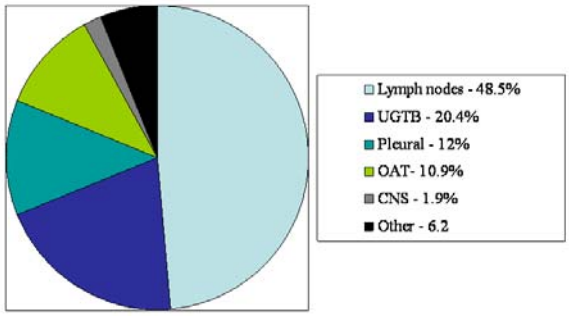

Fig. 3 – Distribution of extrapulmonary tuberculosis cases in Serbia by the sites involved

ment, 0.57% were displaced, and none was still on treatment at the time of the evaluation, 18 months from the treatment initiation. The disease outcome was unknown for the 2.3% of the cases [9–11].

Discussion

The results of our study showed a total of 2,858 cases of XPTB over 15 years giving an average incidence rate of 2.51/100,000 population, and a significant increase over the study period. In the United States of America, after a steady decline during several decades, there was an increase in the rate of TB in the 1980s that coincided with the acquired immunodeficiency syndrome (AIDS) epidemic. Disease patterns since have changed, and there is now a higher incidence of disseminated and extrapulmonary disease [16]. In the American study, common extrapulmonary sites of TB included lymph nodes, pleura, and osseoarthicular areas while Sos et al. [17] reported lymph nodes (42.6%), miliary and disseminated (19.5%), and pleura (12.8%) as the three first ranked sites. The lymph node affection is the first ranked XPTB site in many studies although the proportion may vary in different settings [17–19]. The proportion in our study is similar to the results of Parimon et al. [18].

Although HIV infection is the greatest single risk factor for developing active TB in infected person, it is still not considered major problem of TB management in Serbia due to the overall low HIV infection prevalence by 2003 [4]. Due to the lack of systematic HIV-testing of TB patients, it is uncertain were the three reported HIV-positive patients the only HIV-positive XPTB cases in the study period. However, we assume that some other risk factors, which have been proved to dicrease humman immunity, might be of higher importance for developing active TB [2–4]. The 1990s in the country were characterized by complex and unique socioeconomic crisis enriched with a wide spectrum of TB risk factors. These have led to both higher risk of infection and, in infected, higher risk of developing TB active disease. Worsening of economic crisis with the highest hyperinflation ever has brought poverty, which is strongly associated with TB incidence [2, 20–22]. Stress and malnutrition are also well-known risk factors for developing TB [2]. In the countries with low TB and HIV-infection prevalence, the data about foreign origin might indicate the possibility of TB disease especially if a patient belongs to any of the risk groups for developing TB [23, 24].

While the overall male-to-female ratio of pulmonary TB in Serbia accounts for 2 : 1, when it comes to XPTB, the two thirds of the patients are female. We found similar findings in some other studies on XPTB [15]. In the study of XPTB in Cambodian refugees in Thailand, lymphatic tuberculosis was equally frequent among male and female children, but it was much more common among adult females than among adult males [25], suggesting that underlying genetic and maturational factors may impact on the expression of TB [2].

The results of our study also showed that XPTB was rare in children over the observed 15-year-period. This could be explained by systematic Bacille Calmette-Guerin (BCG) vaccination, mandatory in Serbia at birth, which has been

proved to protect the youngest from the most serious forms of TB and the TB related death [26].

Although recording and reporting of both pulmonary and XPTB through the pulmonary facilities network has a long-term tradition in Serbia, a possible underreporting may present a limitation of our study, which might affect incidence values. The retrospective character of a study represents limitation. The other limitation originates from the disease itself. XPTB can be difficult to diagnose and requires a high index of suspicion. Thus, it is possible that some of the cases remained not diagnosed and/or not reported over the observed period. Despite the possible limitations, our study showed significant increasing trend of XPTB with 8.9% annual increase.

Conclusion

To prevent, diagnose and treat XPTB in a timely manner, physicians should be aware of TB epidemiological situation in the world and in the local setting. The knowledge on TB risk factors, existing risk groups for TB, as well as the importance of proper recording and reporting of all the cases may contribute to better TB control and decrease TB related death.

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Transforming growth factor β1, matrix metalloproteinase-2 and its tissue inhibitor in patients with pseudoexfoliation glaucoma/syndrome

Transformišući faktor rasta β1, matriks metaloproteinaza-2 i njen tkivni inhibitor kod bolesnika sa pseudoeksfolijativnim sindromom/glaukomom

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Abstract

Background/Aim. Transforming growth factor-β1 (TGF-β1), oxidative stress and imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) may play an important role in pathogenesis of pseudoexfoliation syndrome/glaucoma (PEX Sy/Gl). The aim of the study was to measure concentrations of TGF-β1, MMP-2, TIMP-2 in the aqueous humor in the examined group, as well as to compare the biochemical findings with the following clinical parameters: degree of chamber angle pigmantation, presence of pseudoexfoliation and the value of intraocular pressure (IOP). **Methods.** Aqueous samples from 30 patients with cataract, 30 patients with PEX Sy, 36 patients with PEX Gl, and 42 patients with primary open-angle glaucoma (POAG) were collected during phacoemulsification cataract surgery. TGF β1, MMP-2, TIMP-2 Fluotokine Multi Analyze Profiling kits and Luminex technology were used to simultaneously measure TGF β1, MMP-2 and TIMP-2. **Results.** TGF-β1, MMP-2, TIMP-2 were detected in human aqueous from all the groups with the highest level in the group with PEX Gl. Statistically, a significant correlation between the levels of TGF β1, MMP-2, TIMP-2 in the aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, the positive correlations between the TGF β1 concentration in the aqueous humor and the presence of pseudoexfoliation ($p < 0.01$), on the one hand, and between the TIMP-2 level and the presence of pseudoexfoliation ($p < 0.05$), on the other, were reported. A statistically significant positive correlation of TGF-β1 and MMP-2, and the degree of chamber angle pigmentation in the PEX Gl group was confirmed ($p < 0.05$). In the POAG group, TIMP-2 values were in a negative correlation with the degree of pigmentation ($p < 0.05$), and the IOP value ($p < 0.05$). **Conclusion.** TGF β1 and MMP-2 affect the degree of chamber angle pigmentation and the degree of pseudoexfoliation in patients with pseudoexfoliative glaucoma.

Key words:
transforming growth factor beta 1; matrix metaloproteinase 2; tissue inhibitor of metaloproteinase-2; exfoliation syndrome.

Apstrakt

Uvod/Cilj. Transformišući faktor rasta ß1 (TGF-ß1), oksidativni stres i disbalans između matriks metaloproteinaza (MMPs) i njihovih tkivnih inhibitora (TIMPs) igraju važnu ulogu u patogenezi pseudoeksfolijativnog sindroma/glaukoma PEX Sy/Gl. Cilj ove studije bio je da se utvrdi koncentracija TGF-ß1, MMP-2, TIMPs-2 u očnoj vodici izabranih grupa bolesnika, kao i da se uporede biohemijski nalazi sa odgovarajućim kliničkim parametrima: stepen pigmentacije komornog ugla, prisustvo pseudoekfolijacija i vrednost intraokularnog pritiska (IOP). **Metode.** Tokom operacije fakoemulzifikacije katarakte prikupljena je očna vodica od 30 bolesnika sa kataraktom, 30 bolesnika sa PEX Sy, 36 bolesnika sa PEX Gl i 42 bolesnika sa primarnim glaukomom otvorenog ugla (POAG). Za određivanje nivoa TGF-ß1, MMP-2 i TIMP-2 korišćen je komplet Quantikine (R&D System, UK), a vrednosti su iščitavane pomoću Luminex analizataora. **Rezultati.** Vrednosti TGF-ß1, MMP-2 i TIMP-2 u očnoj vodici bile su povišene u grupi bolesnika sa PEX Gl. Postojala je statistički značajna korelacija između nivoa TGF-ß1, MMP-2 i TIMP-2 u očnoj vodici i visine IOP kod bolesnika sa PEX Gl ($p < 0,05$). U ovim grupama je nađena statistički značajna korelacija između koncentracije TGF-ß1 u očnoj vodici i prisustva pseudoeksfolijacija ($p < 0,01$), sa jedne strane i nivoa TIMP-2 i prisu-

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stva pseudoeksfolijacija sa druge strane ($p < 0,05$). Potvrđena je i statistički značajna pozitivna korelacija nivoa TGF-ß1, MMP-2 i stepena pigmentacije komornog ugla ($p < 0,05$) u grupi bolesnika sa PEX Gl. U grupi bolesnika sa POAG vrednost TIMP-2 je u negativnoj korelaciji sa stepenom pigmentacije komornog ugla i vrednostima IOP ($p < 0,05$). **Zaključak.** TGF-ß1 i MMP-2 utiču na stepen pigmentacije komornog ugla i prisustva pseudoeksfolijacija kod bolesnika sa PEX glaukomom.

Ključne reči:
faktor rasta, transformišući, beta 1; matriks metaloproteinaza 2; tkivni inhibitor matriks metaloproteinaze-2; eksfolijativni sindrom.

Introduction

Pseudoexfoliation syndrome (PEX Sy) is an elastosis-like systemic disease characterized by the production and progressive accumulation of extracellular fibrillar material, known as pseudoexfoliative material, on the tissues of the anterior segment of the eye and different visceral organs [1–3]. In many countries PEX Sy is common in population over the age of 60, and in many cases it leads to the appearance of pseudoexfoliation glaucoma (PEX Gl), one of the most frequent causes of poor visual acuity and blindness [4, 5]. The real pathogenesis of PEX Sy is still not known enough. Recent studies have shown that PEX Sy is a microfibrilopathy and that transforming growth factor β1 (TGF-β1), oxidative stress and an imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play a role in its appearance. The aim of the study was to determine concentrations of TGF-β1, MMP-2, TIMP-2 in the aqueous humor in patients with PEX Gl, PEX Sy, primary open-angle glaucoma (POAG) and cataract (Cat), and also, to compare the biochemical findings with the following clinical parameters: degree of angle pigmantation, presence of pseudoexfoliation and the value of intraocular pressure (IOP).

Methods

Four groups of patients were included in this prospective study: the group I – 42 patients with PEX Gl, group II – 30 patients with PEX Sy, group III – 36 patients with POAG, and the group IV – 30 patients with Cat.

The ophthalmological examination was conducted at the Clinic of Ophthalmology, Clinical Center Niš (Niš, Serbia).

Biochemical analyses were done in the Center of Medical Biochemistry of Clinical Center Niš, and the Ophtholmology, Department of the University of Erlangen-Nürnberg (Germany).

Tranforming growth factor β1 was determined by the ELISA method using a commercially available kit (Quantikine; R&D System, UK).

The MMP-2 vlaues in the aqueous humor of patients were determined with the multiplex method for quantitative measurement using a commercially available test (Quantikine; R&D System, UK). The values were read by the Luminex analyser.

For this study the aqueous humor of the patients was used. Aqueous humor was extracted by paracentesis through the limbus of the cornea during the trabeculectomy or routine phacoemulsification paying special attention not to touch the endothelium, iris or lens as well as extracting the aqueous humor without any traces of blood. After its aspiration and securing in sterile test tubes, aqueous humor samples (80–100 μl) were immediately frozen in liquid nitrogen and then stored and kept at the temperature of -80°C.

All the patients gave their written informed consent. All the patients underwent pupillary dilation a day before the surgery so that the presence of pseudoexfiliation could be confirmed. The classification of the presence of pseudoexfoliation was done from I^0 to III^0. Thus, I^0 marked that PEX material was visible only on the anterior side of the lens after the pupillary dilation; II^0 – PEX material was occasionally visible on the pupillary edge, and III^0 – pseudoexfoliation was costantly visible along the whole circumference of the pupillary edge and on the anterior side of the lens, with or without iridodonesis and phacodonesis. The width and pigmentation of the chamber angle were classified according to the Scheie classification.

A one-way analysis of variance (One –Way ANOVA) and a Post Hoc (Tukey HSD) analysis were used to check the difference in the average age between the examined groups. To check the hypotheses that there are differences in the presence of certain attributes between the groups, Fisher's Exact Probability Test was used. To evaluate the differences in IOP values between the patients with different kinds of glaucoma, the Mann-Whitney *U*-Wilcoxon Rank Sum *W*-test was used. This test was also used to compare the values of the concentration of certain enzymes in the aqueous humor of the patients. The level of significance was adapted by the Bonferoni inequality and for the time being it is 0.01. The correlation between enzymes and clinical parameters was conducted with the help of Pearson's linear correlation coefficient. For the statistical analysis of the data, SPSS Windows (Ver. 8.0) was used.

Results

The average age of the patients with PEX Gl was 68.9 ± 7.6 years; of the patients with PEX Sy 66.8 ± 4.6 years; of the patients with POAG 62.8 ± 8.8 years; and, finally, of the patients with cataract 64.8 ± 3.7 years. Statistically, the patients with PEX Gl were significantly older in relation to the patients with POAG ($p < 0.001$). The average value of IOP was 43.1 ± 13 mm Hg in the group with PEX Gl, while in the group with POAG the average value of IOP was 34.8 ± 11.4 mm Hg and this difference proves to be statistically significant ($p < 0.001$).

The presence of pseudoexfoliation is shown in Figure 1. The patients with PEX Gl had significantly higher grade of pseudoexfoliation compared to the patients with PEX Sy ($p < 0.001$).

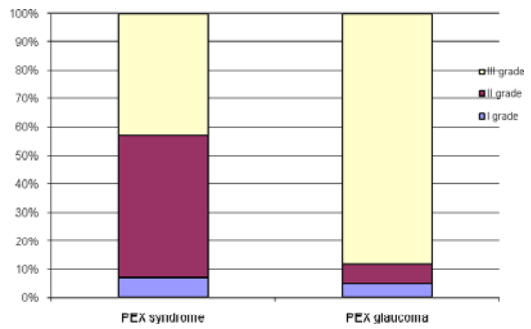

Fig. 1 – The presence of pseudoexfoliation (PEX) in the patients with PEX glaucoma and PEX syndrome

Figure 2 shows a degree of chamber angle pigmentation (according to Scheie) in the patients with POAG and those with pseudoexfiloation syndrome.

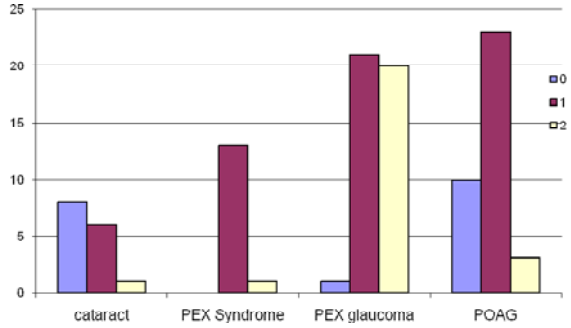

Fig. 2 – Degree of chamber angle pigmentation (according to Scheie) in the patients with primary open-angle glaucoma (POAG) and pseudoexfiloation (PEX) syndrome

The greatest number of POAG patients had I^{o} chamber angle pigmentation according to Scheie (96.7%). In the PEX Gl group, the gonioscopic findings mostly showed II^{o} ili III^{o} chamber angle pigmentation (86.7%). The observed difference in the chamber angle pigmantation degree between these two groups was statistically highly significant ($p < 0.0001$).

The values of TGF-β1, MMP-2 i TIMP-2 in the aqueous humor of the patients in all the groups is shown in Table 1. The average level of TGF-β1 in the aqueous humor of the patients with PEX Gl was 147.29 ± 76.54 pg/mL, while in the group with senile cataract it was 38.85 ± 28.47 pg/mL ($p < 0.0001$).

The mean values of this protease were 29031.5 ± 16725.8 pg/mL in the PEX Gl group, 24250.12 ± 42741.74 pg/mL in the PEX Sy group, 19346.07 ± 10871.13 pg/mL in the POAG group, and 15195.40 ± 11225.02 pg/mL in the Cataract group. Significant differences were found between MMP-2 in PEX Gl and both POAG and cataract groups ($p < 0.001$, and $p < 0.0001$, respectively). The difference in the values of MMP-2 in the aqueous humor of the patients with PEX Sy in comparison with the senile Cataract and POAG groups, respectively, was significant ($p < 0.05$).

The levels of TIMP-2 in aqueous humor ranged from 19.947 pg/mL in the patients with cataract to 43.521 pg/mL in the patients with PEX Gl. A significant increase in aqueous humor TIMP-2 levels was mesaured in both PEX Gl and POAG groups compared with PEX Sy and Cataract groups ($p < 0.001$ and $p < 0.01$, respectively).

Table 2 shows a correlation of the levels of TGF-β1, MMP-2, TIMP-2 in the aqueous humor of patients with the degree of pigmentation, the presence of pseudoexfoliation and IOP value. Statistically, a significant correlation between

Table 1

Concentration of transforming growth factor β1 (TGF-β1), matrix metaloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) in aqueous humor of the patients

Group	TGF- β1 (pg/mL)	MMP-2 (pg/mL)	TIMP-2 (pg/mL)
PEX Gl	147.29 ± 76.54 **, ***	29031.5 ± 16725.8 *, **, ***	43521 ± 19737 **, ***
POAG	73.96 ± 48.50 ##	19346.07 ± 10871.13	26103 ± 14989
PEX Sy	108.26 ± 30.85 ***, #	24250.12 ± 42741.74 #	39103 ± 4961
Senile cataract	38.85 ± 28.47	15195.40 ± 11225.02	19947.7 ± 5181

PEX Gl – pseudoexfoliation glaucoma; PEX Sy – pseudoexfoliation syndrome;
POAG – primary open-angle glaucoma.
***p* < 0.05 in relation to PEX syndrome**
****p* < 0.001 in relation to POAG**
*****p* < 0.0001 in relation to senile cataract**
#*p* < 0.05 in relation to POAG
##*p* < 0.01 in relation to senile cataract

Table 2

Correlation of transforming growth factor β1 (TGF-β1), matrix metaloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) in aqueous humor of the patients with the degree of pigmentation, presence of pseudoexfoliation (PEX) and intraocular pressure (IOP) values

Biochemical parameters	PEXGl			POAG	
	Degree of PEX	IOP	Pigmentation of the chamber angle	Pigmentation of the chamber angle	IOP
MMP-2		c = 0.33 $p < 0.05$	c = 0.36 $p < 0.05$		
TIMP-2	c = 0.46 $p < 0.05$	c = 0.43 $p < 0.05$		c = -0.48 $p < 0.01$	c = -0.36 $p < 0.05$
TGF-β1	c = 0.47 $p < 0.01$	c = 0.48 $p < 0.01$	c = 0.312 $p < 0.05$		

POAG – primary open-angle glaucoma
PEXGl – pseudoexfoliation glaucoma

the levels of TGF-β1, MMP-2, TIMP-2 in the aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, positive correlations were established between the level of TGF β1 and TIMP-2 in aqueous humor and the presence of pseudoexfoliation ($c = 0.47$; $p < 0.01$ and $c = 0.46$, $p < 0.05$, respectively). In the PEX Gy group a statistically significant positive correlation of TGF-β1 and MMP-2, and the degree of angle pigmentation was confirmed ($c = 0.312$; $p < 0.05$). In the POAG group, the TIMP-2 values were in a negative correlation with the degree of angle pigmentation ($c = -0.48$, $p < 0.05$), and the IOP value ($c = 0.36$; $p < 0.05$).

Discussion

The pathological accumulation of abnormal fibrillar extracellular material, which is a characteristic of PEX Sy in numerous extra- and intraocular tissues, can result in a great number of clinical complications and the development of PEX Gl [1–4]. PEX syndrome is one of the main causes of PEX Gl. Clinical changes in the eye are often asymmetrical and can be manifested as trabeculopathy, iridopathy, zonulopathy, endotheliopathy, pigment dispersion and increased trabecular pigmentation, high values of IOP, as well as great daily fluctuations of IOP accompanied by the rapid deterioration of the optic nerve head and a progressive visual field loss [3, 6–10].

However, a precise etyology of this systemic disease of extracellular matrix still remains unknown, though it is considered TGF β1 causes an imbalance between MMPs and their TIMPs, leading to a progressive accumulation of exfoliation material in the trabecular tissue, which further results in elevated IOP [11–13]. The normal balance requires a balanced interaction of MMPs and TIMPs, and the normal relation of enzymes to the inhibitor is 1 : 1. Any changes in the balance can result in the excessive accumulation or degradation of extracellular matrix (ECM) [6, 7, 14, 15].

In this study the values of total TGF-β1 in aqueous humor of the patients with PEX Gl and PEX Sy, respectively, were significantly higher in relation to the values of this enzyme in aqueous humor of the patients with POAG and cataract, respectively ($p < 0.0001$), while the activity of total TGF-β1 in the aqueous humor of the patients with PEX Gl was different from and higher than the activity of this enzyme in the aqueous humor of patients with PEX Sy, but the difference was not statistically significant – it can be said that it was at the verge of statistical significance ($p < 0.01$).

Statistically, the values of total TGF-β1 in aqueous humor of the patients with POAG were considerably higher in relation to the values of aqueous humor inpatients with senile cataract ($p < 0.0001$). The values of TGF-β1 in the aqueous humor of the patients with POAG statistically were considerably lower than the values in the aqueous humor of the patients with PEX Sy ($p < 0.05$).

The patients of different groups with different ophthalmological diseases had different – statistically significant – values of MMP-2 in aqueous humor ($p < 0.0001$).

MMP-2 was detectable in aqueous humor of all the patients. The values of MMP-2 in the aqueous humor of the patients with PEX Gl were statistically significantly higher in comparison with the values in the patients of senile cataract ($p < 0.0001$), while that difference in comparison with the values of this proenzyme in aqueous humor of the patients with POAG was also significant ($p < 0.001$).

The MMP-2 values in aqueous humor of the patients with PEX Gl were not significantly higher in comparison with the values of this proenzyme in aqueous humor of the patients with PEX Sy ($p > 0.05$), while the difference in the values of this proenzyme in the aqueous humor of the patients with PEX Sy in comparison with the senile cataract and POAG groups, respectively, was ($p < 0.05$). The TIMP-2 values ranged from 19,947 pg/mL to 43,521 pg/mL. A significant increase in TIMP-2 in aqueous humor of the patients both with PEX Gl and PEX Sy was noticed in comparison with the values measured in the patients both with POAG and cataract ($p < 0.001$).

In their study, Schlotzer-Schrehard et al. [16] examined whether they could detect latent and active TGF-β1 i TGF-β2 in aqueous humor using the ELISA method. Both latent and active ones could be detected in aqueous humor and serum of the patients with the PEX eye. The level of total and active TGF-β1 respectively was statistically significantly higher in patients both with PEX Sy and PEX Gl in comparison with the group with cataract and open-angle glaucoma respectively, while the difference was not noticed between the groups with PEX changes. These authors also found that the TGF-β1 values in serum statistically were not significantly different among the examined groups.

Koliakos et al. [13] also found increased levels of TGF-β1 in the patients with PEX Sy ranging from 6.1 to 54.6 (median value 17.06 ± 11.02) pg/mL, which statistically was a significant rise in comparison with the group with cataract.

Slotzer-Schrehard et al. [14] measured a total and active quantity of MMPs and TIMPs in patients with PEX Gl, PEX Sy and POAG, using the Western Blot, elektrophoresis and the ELISA method. MMP-2 (both as proenzyme and in its complex form) was found in considerable quantity ranging from 18.6 to 232.4 ng/mL. Despite this high varibility, the total quantity of MMP-2 statistically was considerably elevated in aqueous humor of the patients with PEX Sy with or without glaucoma, respectively, in comparison with aqueous humor of the patients with POAG and cataract, respectively. Free, unbound MMP-2 made 22–24% of the total quantity in aqueous humor and was signifigantly increased in the patients with PEX Sy. The concentrations of TIMPs in aqueous humor were six to seven times as high as the concentrations of MMPs, and they had the predominant role in the activation of MMPs. MMP-2 and TIMP-2 should be balanced and any imbalance can affect the biological activity of the cell. It was noticed that the concentrations of MMPs and TIMPs in aqueous humor were considerably higher in patients with pseudoexfoliation with or withour glaucoma, respectively, in comparison with the patients with primary open-angle glaucoma, especially MMP-2, -3, TIMP-1, -2 [17-25].

Konstas et al. [26] in their study found a statistically considerable decrease in the quantity of total TGF-β1 in samples

from patients who had PEX Gl and used the prostaglandin, latanoprost (0.005% eye drops) monotherapy in comparison with the patients who had PEX Gl and used beta blockers in the form of timolol maleate, (0.5% eye drops). These authors believed that TGF-β1 increased the TIMP-2 and MMP-2 expressions in the eyes with pseudoexfoliation, and that latanoprost interrupted the positive feedback mechanism of TGF-β1 accumulation. However, the reduction mechanism of TGF-β1, MMP-2 i TIMP-2 by latanoprost required furthur clarification.

Patients with PEX Gl had a statistically significantly higher degree of pseudoexfoliative changes in comparison with patients with PEX Sy ($p < 0.0001$). The greatest number of POAG patients had I^o chamber angle pigmentation according to Scheie (96.7%). In the PEX Gl group, the goneoscopic findings mostly showed II^o or III^o chamber angle pigmentation (86.7%). The observed difference in chamber angle pigmantation degree between these two groups was statistically highly significant ($p < 0.0001$).

In the PEX Gl group, it was confirmed that TGF β1 was positively correlated with MMP-2 ($c = 0.51$; $p < 0.01$), and a positive correlation between MMP-2 and its tissue inhibitor TIMP-2 was also noticed ($c = 0.54$; $p < 0.01$).

Statistically, a significant correlation between the levels of TGF β1, MMP-2, TIMP-2 in aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, positive correlations between TGF β1 concentration in aqueous humor and the presence of pseudoexfoliation ($c = 0.47$; $p < 0.01$), on the one hand, and between TIMP-2 level and the presence of pseudoexfoliation ($c = 0.46$, $p < 0.05$), on the other, were reported.

In this study the relation of TGF β1 and MMP-2 levels, and the degree of chamber angle pigmentation was established, but that connection was not statistically significant in the PEX Sy group ($p > 0.05$), while a statistically significant positive correlation of TGF β1 and MMP-2, and the degree of chamber angle pigmentation in the PEX Gl group was confirmed ($c = 0.312$; $p < 0.05$). In the POAG group, the TIMP-2 values were in a negative correlation with the degree of pigmentation ($c = -0.48$, $p < 0.05$), and the IOP value ($c = 0.36$; $p < 0.05$).

At the same time, the MMP-2 values, on one hand, and the presence of exfoliation PEX, on the other, did not show a statistically significant connection in the PEX Gl patients and PEX Sy patients.

Conclusion

Concentrations of TGF β1 and MMP-2 in the aqueous humor of patients with pseudoexfoliative changes are considerably elevated, and TGF β1 and MMP-2 affect the degree of chamber angle pigmentation and the degree of pseudoexfoliation presence in patients with pseudoexfoliative glaucoma.

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Effects of a short-term differently dosed aerobic exercise on maximum aerobic capacity in breast cancer survivors: a pilot study

Uticaj kratkotrajnog aerobnog vežbanja različitog intenziteta na maksimalni aerobni kapacitet preživelih od karcinoma dojke

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Abstract

Background/Aim. Regular physical activity and exercise improves quality of life and possibly reduces risk of disease relapse and prolongs survival in breast cancer survivors. The aim of this study was to evaluate the impact of a 3-week moderate intensity aerobic training, on aerobic capacity (VO_2max) in breast cancer survivors. **Methods**. A prospective, randomized clinical study included 18 female breast cancer survivors in stage I-IIIA, in which the primary treatment was accomplished at least 3 months before the study inclusion. In all the patients VO_2max was estimated using the Astrand's protocol on a bicycle-ergometer (before and after 3 weeks of training), while subjective assessment of exertion during training were estimated by the Category-Ratio RPE Scale. Each workout lasted 21 minutes: 3 minutes for warm-up and cool-down each and 15 min of full training, 2 times a week. The workload in the group E1 was predefined at the level of 45% to 65% of individual VO_2max, and in the group E2 it was based on subjective evaluation of exertion, at the level marked 4–6. Data on the subjective feeling of exertion were collected after each training course in both groups. **Results.** We recorded a statistically significant improvement in VO_2max in both groups (E1 – 11.86%; E2 – 17.72%), with no significant differences between the groups. The workload level, determined by the percent of VO_2max, was different between the groups E1 and E2 (50.47 ± 7.02% *vs* 55.58 ± 9.58%), as well as subjective perception of exertion (in the groups E1 and E2, 11.6% and 41.6% of training, respectively, was graded in the mark 6). **Conclusion.** In our group of breast cancer survivors, a 3-week moderate intensity aerobic training significantly improved the level of VO_2max.

Key words:
breast neoplasms; physical fitness; exercise.

Apstrakt

Uvod/Cilj. Redovna fizička aktivnost može značajno uticati na kontrolu neželjenih efekata terapije kod žena obolelih od karcinoma dojke, na kvalitet života posle završenog lečenja, pa čak i na smanjivanje rizika od ponovne pojave bolesti. Cilj ovog rada bio je da se provere efekti tronedeljnog aerobnog treninga, doziranog na dva načina, na maksimalni aerobni kapacitet (VO_2max) bolesnica koje su završile lečenje karcinoma dojke. **Metod.** Prospektivno, randomno kliničko istraživanje uključilo je 18 žena u I-IIIA stadijumu karcinoma dojke, čije je lečenje završeno najmenje tri meseca pre uključivanja u studiju. Maksimalni aerobni kapacitet određen je Astrandovim testom na bicikl-ergometru (na početku i posle tri nedelje treninga), a procena stepena uloženog napora kroz modifikovanu skalu subjektivne procene napora (*Category-Ratio* RPE *Scale*). Svaki trening trajao je 21 minut: po 3 min za zagrevanje i hlađenje i 15 min punog treninga, dva puta nedeljno. Opterećenje u grupi E1 određeno je na nivou 45–65% individualnog VO_2max, a u grupi E2 na osnovu subjektivne procene napora, na nivou ocene 4–6. Podaci o subjektivnom osećaju napora prikupljeni su u obe grupe, posle svakog treninga. **Rezultati.** Registrovana je statistički značajna promena VO_2max unutar obe grupe (E1 – 11,86%; E2 – 17,72%), bez značajne razlike između grupa. Nivo opterećenja određen preko % VO_2max razlikovao se između grupa (50,47 ± 7,02% *vs* 55,58 ± 9,58%), kao i osećaj napora tokom treninga (ocenu 6 dobilo je 11,6% treninga u grupi E1, a 41,6% treninga u grupi E2). **Zaključak.** U našoj grupi ispitanica 3-nedeljni aerobni trening umerenog intenziteta značajno je povećao nivo VO_2max, bez obzira na način određivanja opterećenja.

Ključne reči:
dojka, neoplazme; sposobnost, fizička; vežbanje.

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Introduction

Breast cancer is the most common female cancer and the second leading cause of death from malignancy in women [1, 2]. The treatment of early breast cancer usually involves a combination of surgery, chemo- and radiotherapy, often with a prolonged hormonal and biological therapy. Besides the problems of acute and chronic adverse effects of treatment, these women also are challenged with other diseases common for their age. Their rehabilitation is a complex process and requires multidisciplinary team cooperation [3]. Previous studies have shown that physical activity and exercise are associated with a lower sense of fatigue during and after the treatment, improve muscle status, physical strength, aerobic fitness and have a positive effect on confidence and quality of life [4–8]. In addition, it is possible that regular physical activity can reduce the risk of disease relapse and prolong survival [9].

The largest number of studies that investigate physical activity of patients with malignant disease are related to the aerobic, cardiovascular training [10]. Among all patients with malignant diseases, breast cancer patients are the most common studied [11–20]. However, there are still no standardized protocols with regards neither to the exercise modalities, nor the intensity and frequency of exercise.

The most common aerobic activities investigated are walking, whether home-based [21] or supervised, in the laboratory, on a treadmill [22], or bicycle-ergometer [23]. Duration and frequencies of the training also varies (usually 3–5 times a week, 10 to 30 minutes). The intensity was determined in different ways. Some are based on VO_2max [21, 23], some on maximum heart rate (MHR) [14, 15, 24] or heart rate reserve (RHR) [12] and some on subjective evaluation of efforts, by using the rate percieved exertion (RPE) scale [25, 26]. Maximum aerobic capacity was measured directly, through a progressive maximal tests [23] or estimated from the results of submaximal tests (Modified Canadian Aerobic Fitness Test [21], Astrand-Rhimings protocol [25]. The karvonen formula was the most commonly used to determine the MHR [27]. Exercise program in most studies lasts between 5 weeks and 6 months [28, 29], and they show that a regular physical activity improves aerobic capacity and quality of life (QOL) of these patients and alleviates many side effects of the treatment (nausea, fatigue, depression and anxiety), as well [10, 28]. Burnham and Wilcox [30] showed the positive effects of a 10-week of lasting aerobic training on aerobic capacity, body fat percentage and QOL in cancer survivors, regardless of loading during exercise – small (23%–35% HRR) *vs* moderately high (40%–50% HRR).

However, to our best knowledge there is no study which compares the effects of a controlled aerobic training of relatively short duration and dosed in two ways – objectively (based on measured values of VO_2max) and subjectively (based on subjective feelings of fatigue, estimated through RPE or Category–Ratio RPE Scale).

The aim of this study was to evaluate the impact of a 3-week moderate intensity aerobic training on aerobic capacity in breast cancer survivors, regardless of the method for determining the workload (objectively, based on measured values of VO_2max, or subjectively, based on the subjective feeling of exertion, measured through the Category-Ratio RPE scale).

Methods

Participants, recruitment strategies, and eligibility

Inclusion criteria were: female breast cancer survivors without disease relapse, diagnosed in stage I-IIIA, in which the primary treatment (radical surgery and/or postoperative radiotherapy and/or adjuvant systemic therapy) was accomplished at least 3 months before the investigation. The recruitment strategy included the treating oncologist who identified potentially eligible patients during a regular clinical control. Exclusion criteria were: disseminated breast cancer, cardiorespiratory disease (uncontrolled hypertension, heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease and pulmonary fibrosis) and age over 65 years.

Patients were informed about the goals and methods of research, and after written consent, they were randomly divided into two experimental groups: the group E1 (10 woman), whose workload level was determined by the examiner based on the measured values of VO_2max and the group E2 (8 woman), in which the participants self-determined the workload level according to a subjective feeling of the exertion. The Military Medical Academy Belgrade Ethics Committee provided the approval for this study.

Procedures

The program consisted of three weeks of aerobic training on a bicycle-ergometer (ERG Bosh 550), two times a week. Each workout lasted 21 minutes, and the structure of the training was as follows: 3 min of warming-up and cooling-down period each and 15 min training period. All the participants were introduced with the Category-Ratio RPE Scale. The intensity of the workload, expressed in Watts (W), was determined in two ways. In the group E1 it was determined on the basis of the estimated values of VO_2max as follows: 30%–35% VO_2max for the period of warming, 45-65% VO_2max for training period and 40%–45% VO_2max for the period of cooling. The conversion of the workload was done based on the measured values of VO_2max and the known energy expenditure of different intensities of the bicycle-ergometer [31], according to the formula:

$$\text{Workload (W)} = 0.08333 \times VO_2\text{max (mL/min)} - 25.$$

In the group E2, after being informed about the structure of the training and the Category-Ratio RPE scale, the patients themselves determined workload level. The recommended level of exertion was rating between 4 and 6. The participants were asked not to change their habits of regular physical engagement nor the nutrition habits during the research period.

Colecting data and measurement

General information was collected at the beginning of the study using a questionnaire that the patients filled in themselves. Body weight and VO_2max were determined at

baseline and after a 3-week training period. Subjective assessment of exertion with the Category-Ratio RPE Scale was performed after each training course, in both groups.

Height and weight were measured on the standing balance (TTM Zagreb), and the values of BMI were calculated. Heart rate during testing and training was continuously monitored and recorded using a Polar Cycling Computer S725X Pro Team, while the measurement of arterial blood pressure was done using a manometer with a cuff (Dosh Heidelberg).

For the estimation of VO_2max in all participants, we used the Astrand's protocol on a bicycle-ergometer. It is a progressive, continuous exercise test during which a patient is encumbered to submaximal levels (to reach steady state). Each level of the workload lasted 6 minutes. Levels of workload for women 50W–125W, with the progression of 25 W between the levels. Steady-state reached when the heart rate was between 120 and 170 beats per minute (bpm), and the difference between the 5th and 6th minutes no more than 5 bpm. The value of VO_2max was determined by a table data, based on the reached pulse value of a certain load levels and patient's age. The participants were divided according to VO_2max levels using the classification aerobic fitness World Health Organization (low, fair, average, very good, high), that was mathematically modified to improve accuracy [32].

For subjective assessment of exertion during training we used the Category-Ratio RPE Scale [33, 34]. This is a 10-level scale for subjective assessment of exertion, where the grade 0 means "absolutely no exertion" and the grade 10 "maximal exertion that one can still submit a short time". It is shown that the level of grade 4 (moderate) is the level of lactate threshold for most people [35]. Exercising below this level is not strong enough to increase cardiorespiratory endurance. The recommended level of subjective feeling of effort for our participants was moderate, "somewhat strong" degree (grade 4 to 6).

The primary objective was to investigate the differences in the VO_2max expressed in mL/kg/min after a 3-week aerobic training in the whole group, in the groups E1 and E2 as well as between the groups E1 and E2. A secondary goal was to test changes in VO_2max level categories, and changes in BMI.

The statistical package GraphPad Prism 5th was used for statistical analysis. For parametric categories of the observation we calculated the mean ± SD, median and range, and for nonparametric categories the distributions of frequency were calculated. To test the significance of differences between initial and posttraining values within groups, we used the paired *t*-test for parametric and Fisher's exact test and χ^2 test for nonparametric categories. Significant difference between groups was tested by unpaired *t*-test and χ^2test. Statistical significance was accepted at the level of $p < 0.05$ [36].

Results

There were no significant differences between the groups according to age and time from the end of breast cancer treatment, but there were differences according to the type of therapy: all the participants in the group E1 were treated with adjuvant chemotherapy (100%) while in the group E2 adjuvant chemotherapy received only 3/8 (37.5%) patients. Basic characteristics of patients prior entering the study are shown in Table 1.

Table 1

Basic parameters of the participants before starting the study

Parameter	Patient's groups					
	E1 (n = 10)			E2 (n = 8)		
	$\bar{x}_{av}$ ± SD	median	min–max	$\bar{x}_{av}$ ± SD	median	min–max
Age (year)	51.60 ± 7.47	49	43–63	52.75 ± 7.42	52	42–63
Time after finishig treatment (year)	5.10 ± 4.45	3.5	0.5–12	3.43 ± 2.57	3	1–7
Surgery [n (%)]		10 (100)			8 (100)	
Chemotherapy [n (%)]		10 (100)			3 (37.5)	$p = 0.001$
Radiotherapy [n (%)]		8 (80)			5 (62.5)	
Hormonal therapy [n (%)]		5 (50)			4 (50)	

There were no statistically significant differences between the groups in the VO_2max expressed in mL/kg/min before starting the training. According to the WHO classification level of aerobic fitness, 10 woman (55.55%) had fair levels of VO_2max (6/10 in the the group E1 and 4/8 in the group E2), while 8/18 woman (44.45%) had an average level of VO_2max (4 women in each group). The groups did not differ in the size of the workload expressed in Wats (W) but the significant differences were noted with the workload expressed in percent of VO_2max (Table 2). The groups also differed in the subjective perception of exertion by percent of Category-Ratio RPE scale: 76% of training in the group E1 was marked by 4, compared to 27% in the group E2. On the other hand, only 11.6% of training in the group E1 was marked 6 or higher, while this percentage in the group E2 was 41.6% (Figure 1).

After 3 weeks of training, the value of VO_2max significantly increased (14.46%) in both groups (Figure 2). Percentages of increasing in VO_2max for the groups E1 and E2 were 11.86% and 17.72%, respectively. The values of VO_2max between the groups still did not differ significantly (Table 2).

According to WHO categories of aerobic capacity, 3/18 patients remained in the fair category (2/10 in the group E1 and 1/8 in the E2 group), 12/18 were classified as average (8/10 in the E1 and 4/8 in the group E2), and 3/8 patients in the group E2 had entered into the very good category level of VO_2max. Although category changes in each group were not statistically significant, the overall change was statistically significant (Figure 3).

Table 2

Maximum aerobic capacity (VO_2max), loading and BMI in both groups, before and after a 3-week treaning

Parameters	Patient's groups		*p*
	E1 (n = 10)	E2 (n = 8)	
	$\bar{x}_{av} \pm SD$	$\bar{x}_{av} \pm SD$	
VO_{2max} (mL/kg/min) before training	20.47 ± 2.28	21.66 ± 4.39	
VO_{2max} (mL/kg/min) after a 3-week training	22.85 ± 2.26	24.90 ± 5.26	
Workload (W)	50.65 ± 9.11	53.05 ± 7.87	
Workload (% VO_2max)	50.47 ± 7.02	55.58 ± 9.58	0.002
BMI (kg/m^2) before training	26.73 ± 2.11	26.19 ± 4.87	
BMI (kg/m^2) after a 3-week treaning	26.77 ± 2.32	26.14 ± 4.72	

BMI – body mass index

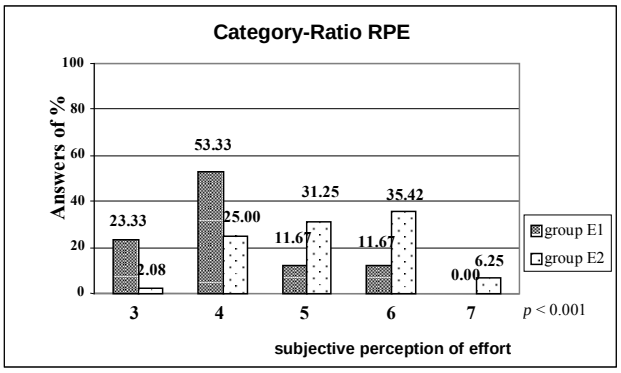

Fig. 1 – Subjective perception of exertion according to the Category-Ratio RPE scale in both groups

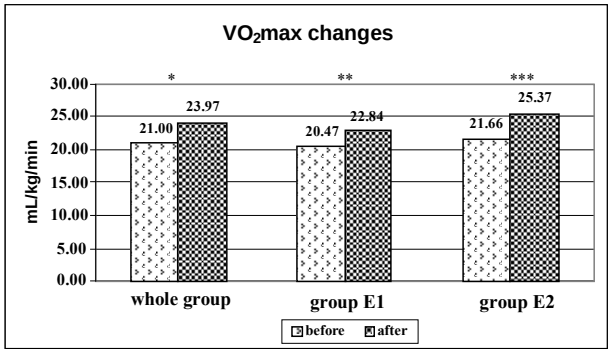

Fig. 2 – Maximum aerobic cepacity (VO_2max) changes after a 3-week training
***p* = 0.0001; ***p* = 0.0002; **p* = 0.014**

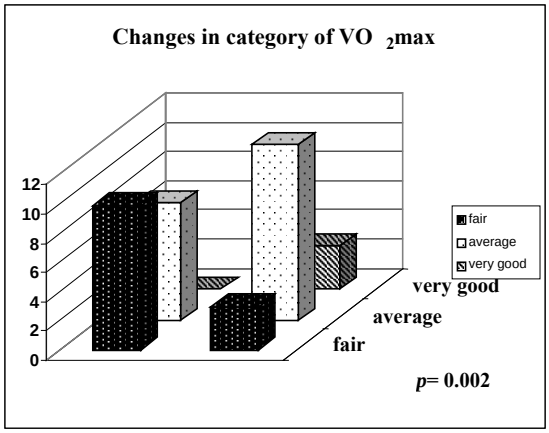

Fig. 3 – Changes in category of maximum aerobic cepacity (VO_2max) in the whole group of participants

There were no differences in BMI, both within each group and between the groups, as well (Table 2).

Discussion

Epidemiological studies in the second half of the 20th century confirmed a dose dependent link between physical activity and physical fitness [37–40]. The greatest difference in mortality due to cardiovascular disease and some types of cancer recorded between categories of sedentary (little or no physically active persons) and the first following categories of physically active, or when sedentary people become moderately physically active [39]. To improve overall health status it is enough to reach and maintain the average level of aerobic capacity [32]. Any physical engagement of the appropriate intensity causes an acute adaptive response (change in arterial pressure, heart rate, stroke volume and cardiac output, blood distribution, ventilation). One of the latest researches suggests that it may also influence the level of anxiety [41]. If done regularly, physical training leads to chronic adaptability reactions (central and peripheral). The size of chronic adaptation to regular physical training depends on the frequency, intensity and duration of training, types of activities and previous physical status. Some of cardiorespiratory and metabolic responses to workload develop relatively quickly during exercise (VO_2max), while others require more time (*e.g.* changes in capillary density) [42, 43]. Cardiorespiratory intensive training of young healthy subjects (6 days a week, 40 min–60 min a day, the intensity of 70% to 90% VO_2max) during the first 3 weeks significantly improved VO_2max, submaximal frequency of heart rate, ventilation and lactate production [43]. It is shown that middle-aged and elderly people, obese patients and those with low aerobic capacity, over several months of regular aerobic training may, with the loss of weight, dramatically improve their cardiorespiratory fitness [42, 43] and reduce the risk of illness even when they practice at the level lower than the American College of Sports Medicine (ACSM) recommended (less than 50% VO_2max) [40, 44].

Healthy female breast cancer survivors do not differ much than the average sedentary population [45], so the mechanisms by which regular physical activity (exercise) improves aerobic capacity are identical. In our country women treated from breast cancer are generally of low physical activity and often unprepared to cope with any serious physical chal-

lenge. Although all our participants indicated that they occasionally practiced exercise at home or go for a walk, the majority of them (55.5%) did not have enough physical activity to reach the average level of baseline aerobic capacity. Guided by this, and bearing in mind the potential cardiotoxicity of the applied antineoplastic therapy [46, 47], we decided to lower the levels and shorten the duration of training workload compared to general recommendations [44, 48].

The work of Pinto et al. [24] shows that regular home-based aerobic exercise (fast walking, biking, swimming or exercise at home) of moderate intensity (55% to 65% HRmax) lasting 12 weeks, has positive effects on psychological well-being, level of fatigue and physical ability of female breast cancer survivor. The frequency of the training was initially 2 times per week, with progressive increase to 5 times per week, and physical ability was assessed through one-mile walk test. Corneya et al. [23] showed that aerobic training intensity of 70%–75% VO_2max three times a week for 15 weeks, significantly improved VO_2max and QOL. Peak oxygen consumption was assessed by a graded exercise test using gas exchange analysis at the beginning and at the end of training period [23].

Our research shows that training involvement two times a week with moderate intensity (45% to 65% VO2max or 4–6 on Category-Ratio RPE Scale) for 15 minutes (plus 3 minutes for warm-up and cool-down each) is enough to achieve some improvements in aerobic capacity (2.97 mL/kg/min, 14.46%). The subjects in the group E2, who determined the workload by themself, set it at a higher level, which became evident when the level of workload was expressed in the percentage of VO_2max (E2 – 55.58 ± 9.58% *vs* E1 – 50.47 ± 7.02% of VO_2max). Change in categories of aerobic capacity levels in the group E2 is also indicative (3/8 patients were switched to the category of very good). When people with low level of physical activity become active, they fairly quickly can achieve very impressive results [40], but in order to improve good results they need more time for exercise and, in particular, a larger workload.

It is possible that self-determination of exercise intensity within recommended limits results in more active participation in training. This is supported by the research of Nyikos et al. [49], who showed that moderate physical activity may have beneficial effects on some of the components of physical and mental health and pain relief in cancer survivors treated with aromatase inhibitors. The program lasted 12 weeks, with the recommendation of at least 30 minutes of moderate physical training two times a week. Similar to our participants, the woman in that study, by its own sense, opted for the greater workload (137.9 ± 67.6 min moderate, and 52.5 ± 43.6 min vigorous exercise weekly). A similar result was reported by Segal et al. [21] in a group with a self-determined load of physical activity at home which achieved better results in physical status than the group that practiced under supervision. The work of Korstjens et al. [50], points that self-defining level of physical involvement has beneficial effects on QOL with no other intervention. They examined the effects of a 12-week self-determined physical activity of breast cancer survivors, comparing a group that had only two times physical training a week and a group that, in addition to physical training, also had once a cognitive-behavioral training week. At the end of the training period, there were no significant differences between those two groups.

Our results show that for the improvement of aerobic metabolism of breast cancer survivors it is sufficient to start with relatively little exertion, and that they are ready for greater exertion if they are responsible for their training. Improvement that is achieved in this way can be very supportive in terms of changes in habits related to physical activity over long period of time.

Our results obtained in this study are encouraging. However, there are several caveats of this investigation that we consider important. First, the number of patients included was relatively small. Second, the groups were not well balanced in regard to adjuvant chemotherapy received, although there was enough time elapsed between the completion of adjuvant chemotherapy and study beginning (months to years) in all the included patients.

Conclusion

In our group of patients, the VO_2max determined using the Astrand's test on a bicycle-ergometer was significantly improved after only three weeks of moderate aerobic exercise, regardless of whether the workload is given on the basis of objective parameters (size of VO_2max) or self-determined on the basis of the Category-Ratio RPE Scale.

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Vitamin D and parathyroid hormone in relation to bone mineral density in postmenopausal women

Vitamin D i paratireoidni hormon i povezanost sa mineralnom gustinom kostiju kod žena u postmenopauzi

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Abstract

Background/Aim. Despite vitamin D insufficiency being widely reported, in Serbia the epidemiological data lack information regarding vitamin D status in the sera of postmenopausal women. The aim of this study was to establish the prevalence of inadequate serum 25-hydroxyvitamin D [25(OH)D] concentrations in postmenopausal Serbian women with seasonal variations of 25(OH)D, in relation to parathyroid hormone (PTH) and bone mineral density (BMD). **Methods.** A total of 95 postmenopausal women, mean age 65.1 ± 9.08 years, were examined. Measurements of 25(OH)D and PTH were performed both in the winter and the summer period, using electrochemiluminiscence immunoassays. BMD (g/cm2) was measured by the dual-energy x-Ray absortimetry (DXA) method on the spine and hip areas. **Results.** A decreased value of vitamin D (< 75 nmol/L) in 88.4% of postmenopausal women and an elevated level of PTH (> 65 pg/mL) in 25.3% of the cases were found. Elevated PTH varied individually, but was mostly increased if 25(OH)D was equal or lower than 37.6 nmol/L. 25(OH)D insufficiency was found in winter in 94.5% and in summer in 80% of the cases ($p < 0.01$). The mean of the PTH was higher ($p < 0.05$) in winter than in summer. A significant negative correlation between 25(OH)D and PTH ($p < 0.001$) was proved. Correlation between 25(OH)D and PTH with BMD at lumbar spine was established in the whole group, but at the femoral neck in women aged over 65 years ($p < 0.05$). **Conclusion.** Our results showed a high prevalence of vitamin D insufficiency (88.4%) among postmenopausal women. The levels of 25(OH)D and PTH changed significantly according to the season.

Key words:
vitamin d; parathyroid hormone; bone density; postmenopause.

Apstrakt

Uvod/Cilj. Iako u svetu postoje brojne studije o insuficijenciji vitamina D, u Srbiji nema dovoljno epidemioloških podataka o statusu vitamina D u serumu postmenopauzalnih žena. Cilj ovog istraživanja bio je da se ispita učestalost sniženih koncentracija 25-hidroksi vitamina D [(25OHD)] u serumu postmenopauzalnih žena u Srbiji, sezonska varijacija 25(OH)D i povezanost sa nivoom paratireoidnog hormona (PTH) i sa mineralnom koštanom gustinom (BMD). **Metode.** Ispitano je 95 postmenopauzalnih žena, prosečne starosti 65,1 ± 9,08 godina. Za određivanje 25(OH)D i PTH u zimskom i letnjem periodu korišćeni su imunološki testovi zasnovani na metodi elektrohemiluminiscencije. Mineralna koštana gustina (g/cm2) merena je metodom DXA u predelu kičme i kuka. **Rezultati.** Snižene vrednosti vitamina D (< 75 nmol/L) ustanovljene su kod 88,4% postmenopauzalnih žena, a povišene vrednosti PTH (> 65 pg/mL) kod 25,3%. Povećanje PTH variralo je individualno, ali je bilo najčešće kada je 25(OH)D bio jednak ili niži od 37,6 nmol/L. Insuficijencija 25(OH)D u zimskom perodu nađena je kod 94,5%, a u letnjem kod 80% ($p < 0,01$) ispitanika. Srednja vrednost PTH bila je viša ($p < 0,05$) u zimskom nego u letnjem periodu. Značajna negativna korelacija je dobijena između 25(OH)D i PTH ($p < 0,001$). Takođe, 25(OH)D i PTH značajno su korelisali sa BMD u predelu kičme u celoj grupi, a sa vratom femura kod žena starijih od 65 godina ($p < 0,05$). **Zaključak**. Rezultati ukazuju na visoku zastupljenost insuficijencije vitamina D (88,4%) kod postmenopauzalnih žena. Vrednosti 25(OH)D i PTH statistički se značajno menjaju u zavisnosti od godišnjeg doba.

Ključne reči:
vitamin d; paratireoidni hormoni; kost, gustina; postmenopauza.

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Introduction

The incidence of osteoporosis increases with age and occurs most frequently in postmenopausal women because the decrease in ovarian oestrogen associated with the menopause accelerates bone loss and increases bone remodeling [1, 2]. The evidence of vitamin D inadequacy in postmenopausal women is shown in worldwide studies [3–9].

In a study of 8,532 postmenopausal, osteoporotic European women, 79.6% were found to have vitamin D insufficiency where the serum 25-hydroxy vitamin D [25(OH)D] threshold was considered to be 80 nmol/L, and 32.1% if the threshold was set at 50 nmol/L [1].

In a Belgian study, of 1,195 postmenopausal women the prevalence of 25(OH)D inadequacy was 91.3%, 87.5%, 43.1% and 15.9% when considering cut-offs of 80, 75, 50 and 30 nmol/L, respectively [9].

Vitamin D plays an important role as one of a number of calcium regulating hormones in the pathogenesis of osteoporosis. The two most important forms of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is produced in human skin from 7-dehydrocholesterol as a result of sun exposure, and may also be acquired from dietary sources, but vitamin D is rarely found in foods. More than 90% of the vitamin D requirement for most people comes from casual exposure to sunlight [10–12].

Cholecalciferol from the skin, together with dietary cholecalciferol and ergocalciferol, are transported to the liver, bound to vitamin-D binding protein where hydroxylation occurs to 25(OH)D. Calcidiol [25(OH)D] is the main circulating form of vitamin D. Further hydroxylation into biologically active 1,25 dihydroxyvitamin D [1,25-$(OH)_2$D] occurs primarily in the kidney by renal 1α-hydroxylase. Hydroxylation in the kidney is stimulated by parathyroid hormone (PTH) and suppressed by phosphate. Calcitriol or 1,25-(OH)2D is the most active metabolite stimulating the absorption of calcium and phosphate from the gut. The free serum 1,25-$(OH)_2$D concentration is very low, as 1,25-$(OH)_2$D is more than 99% bound to vitamin D binding protein (DBP) and albumin with levels approximately 1000-fold less than circulating 25(OH)D. The half-life of 1,25-(OH)2D is only 4–6 h [12, 13].

The active metabolite 1,25-(OH)2D acts through the vitamin D receptor which is present in the intestine, bone, kidney and parathyroid gland. In addition to the classic target organs, vitamin D receptor are also present in tissues and organs that are not directly involved in the regulation of calcium homeostasis, such as the brain, breast, immune cells, muscle tissue, cardiomyocytes, vascular endothelial and vascular smooth muscle cells, endothelial cells of colon mucosae, as well as malignant colon cells [6, 10]. This suggests the possibility of a broad range of functions of vitamin D, as seen in hypertension, immunoregulation, embryogenesis and tumorigenesis [14, 15].

Circulating 25(OH)D should be measured in the blood to determine the overall status of vitamin D, because it is the major storage form of vitamin D in the human body [10]. This primary circulating form of vitamin D is biologically inactive. The half life of 25(OH)D is at least 2–3 weeks [10, 12].

Vitamin D deficiency leads to a decrease in calcium absorption and secondary hyperparathyroidism resulting in bone loss, mineralization defect and increasing fracture risk [10, 16].

For a full understanding of the dynamic of secretion, should first be appreciated the bifunctional relationship between PTH and serum calcium, because the serum calcium concentration controls PTH secretion while simultaneously PTH regulates serum calcium concentrations [17]. Serum calcium concentration is maintained at a very constant level, which is supersaturating with respect to bone mineral.

The suppression of PTH by hypercalcemia acts to restore serum calcium to normal by increasing renal excretion of calcium through both the effect of reduced PTH values and activation of the calcium-sensing receptor in the loop of Henle. A reduced PTH value also decreases calcium efflux from bone, renal phosphorus excretion, and calcitriol production, all of which act to restore the serum calcium concentration to normal. Conversely, when hypocalcemia develops, the resulting increase in PTH restores the serum calcium value to normal by increasing calcium efflux from bone, serum calcitriol production, renal reabsorption of calcium, and renal phosphorus excretion. The effect of the last is mediated through the reduction of the serum phosphorus concentration.

Despite the fact that vitamin D insufficiency is widely reported, in Serbia we do not have the epidemiological data considering vitamin D status in the sera of postmenopausal women. The aim of this study was to establish the prevalence of inadequate serum 25(OH) D concentrations in postmenopausal Serbian women with seasonal variations of 25(OH)D, in relation to PTH and axial bone mineral density (BMD).

Also, we evaluated serum and urinary calcium, ionized calcium, serum and urinary phosphate.

Methods

The study was approved by the Ethics Committee of the Institute for Rehabilitation, Belgrade.

A total of 95 postmenopausal women with low BMD were recruited for this study, from November 2008 to March 2010. The patients were divided into the winter group (n = 55) and the summer group (n = 40). Summer was defined as May through October, winter as November through April. No women had received vitamin D supplements before the study.

Following an overnight fast, all the patients brought a 24 h urine collection and gave a blood sample for biochemical analyses. Biochemical measurements were performed in daily routine assays. 25(OH)D and PTH were measured using electrochemiluminiscence immunoassays (Roche Diagnostics, Elecsys 2010). Ionized calcium was determined by ion-selective electrode (ILyte, Instrumentation Laboratory), while serum and 24 h urinary calcium and phosphate were measured by colorimetric assays (Cobas Integra 400, Roche Diagnostic). BMD was measured by dual-energy x-ray absorptiometry (DXA) at the lumbar spine – LS (L1-L4) and the hip. We assessed the lowest two vertebra BMD and the lower value on the hip (femoral neck or total hip). A spine

phantom was scanned each morning as a quality control and instrument calibration.

The values were expressed as mean ± standard deviation. Statistical tests were performed by the statistical package Statistic for Windows (Stat for Windows, R. 7.0) choosing the parametric or nonparametric methods in accordance to coefficient of variability. The difference between groups was determined by the Mann-Whitney U-test or Student's t-test for independent samples. The correlation was analyzed by the Pearson linear regression test or Spearman nonparametric correlation test. Values of $p < 0.05$ were taken as statistically significant [18].

Results

Participants were aged 65.1 ± 9.08 years (43–86 years) with years since menopause 15.15 ± 10.0. The mean serum concentration of 25(OH)D, PTH, ionized calcium, serum calcium, urinary calcium, serum and urinary phosphate as well as descriptive characteristics were shown in Table 1.

A serum level of 25(OH)D ≤ 50 nmol/L was recorded in 51 (53.7%) patients and 20 (39.2 %) of them had elevated PTH. Also a serum level of 25(OH)D ≤ 30 nmol/L was found in 11 (11.6%) patients and 6 (54.5%) of them had increased value of PTH.

The mean of 25(OH)D in the winter period was lower ($p < 0.01$), than in the summer one (44.32 ± 16.8 nmol/L *vs* 60.12 ± 24.48 nmol/L). Conversely, the mean of the PTH was higher ($p < 0.05$) in winter than in summer (65.03±32.24 pg/mL, *vs* 49.36 ± 20.62 pg/mL). In addition, 25(OH)D insufficiency was found in the winter period in 94.5% and in the summer in 80% of the cases. In Tables 2A and 2B seasonal variations of PTH in regard to 25(OH)D insufficiency were presented.

Moreover, the mean of the serum calcium, ionized calcium and serum phosphate, urinary calcium and urinary phosphate were in accordance with the reference values (Table 1). It should be noted that the ionized calcium was above the upper reference limit in 1 (1.1%) and below the lower limit in 5 (5.3%) of investigated patients. Also, serum calcium and serum phosphate were above the upper limit in 2 (2.1%) and in 3 (3.2%), respectively, and below in 4 (4.2%) and in 3 (3.2%) patients, respectively. The value of urinary calcium was above the upper limit in 8 (8.4%) cases.

Table 1

Descriptive characteristics of the study group

Characteristics	whole (n = 95)	Groups of women with decreased 25(OH)D (n = 84)	with increased PTH (n = 24)
Age (year)	65.1 ± 9.08	65.5 ± 9.22	65.2 ± 9.63
Years since menopause	15.15 ± 10.00	15.66 ± 10.12	13.33 ± 7.85
T-score LS (SD)	-2.61 ± 0.973	-2.62 ± 0.981	-2.84 ± 0.888
BMD LS (g/cm^2)	0.821 ± 0.117	0.822 ± 0.118	0.784 ± 0.125
T-score hip (SD)	-1.86 ± 0.785	-1.88 ± 0.812	-1.94 ± 0.704
BMD hip (g/cm^2)	0.757 ± 0.106	0.756 ± 0.109	0.753 ± 0.107
T-score neck (SD)	-1.94 ± 0.803	-1.94 ± 0.840	-1.99 ± 0.643
BMD neck(g/cm^2)	0.713 ± 0.119	0.714 ± 0.122	0.701 ± 0.118
25(OH) D (nmol/L)	50.97 ± 21.55	45.65 ± 14.4	37.6 ± 11.6
PTH (pg/mL)	58.8 ± 29.1	62.3 ± 29.1	91.7 ± 28.5
Ionized-Ca (mmol/L)	1.18 ± 0.063	1.18 ± 0.069	1.15 ± 0.079
Serum-Ca (mmol/L)	2.40 ± 0.11	2.40 ± 0.11	2.39 ± 0.13
Urinary-Ca (mmol/24h)	4.30 ± 2.36	4.12 ± 2.30	3.80 ± 2.26
Serum-P (mmol/L)	1.15 ± 0.15	1.15 ± 0.15	1.11 ± 0.13
Urinary-P (mmol/24h)	20.53 ± 6.56	19.77 ± 6.26	20.85 ± 7.32

Results are given as mean ± standard deviation
25(OH)D – 25-hydroxyvitamin D; PTH – parathyroid hormone; LS – lumbar spine; BMD – bone mineral density; Ca – calcium; P – phosphate

A decreased value of 25(OH)D (< 75 nmol/L) was found in 84 (88.4%) of postmenopausal women (45.65 ± 14.4 nmol/L). An elevated level of PTH (> 65 pg/mL) was found in 24 (25.3%) of all investigated cases (91.7 ± 28.5 pg/mL). In the group with increased PTH, the mean level of 25(OH)D was 37.6 ± 11.6 nmol/L (Table 1).

The insufficiency of 25(OH)D in the subgroup aged ≥ 65 years was found in 49 (92.5%) women. Also, this number represents 58.3% of all cases with a low level of 25(OH)D (46.3 ± 15.19 nmol/L; min.19.55 nmol/L; max.71.6 nmol/L). In this subgroup, elevated PTH was found in 13 (54.2%) pg/mL (91.52 ± 16.3 pg/mL; min 67.8 pg/mL; max 128.7 pg/mL) of all the patients with elevated PTH levels.

In addition, the T-score at the level of osteoporosis (< -2.5 SD) at the lumbar spine was 59 (61.7%), total hip in 23 (25.3%), and femoral neck in 24 (25.0%). Osteopenia was found in 27 (30.3%), 59 (61.7%) and 60 (63.2%) of the patients, respectively. The T-score (> -1SD), within reference values, was at the lumbar spine in 4 (4.5%), total hip in 11 (11.6%), and at the femoral neck in 10 (10.8%) of the patients (Table 3).

Table 2A

Concentration of parathyroid hormone (PTH) in regard to 25-hydroxyvitamin D [25(OH)D] insufficiency in the winter period

25(OH)D values (nmol/L)	Women (n)	PTH (pg/mL) $\overline{X}$ ± SD	Women (n)	25(OH)D (nmol/L) $\overline{X}$ ± SD
< 75	42	67.31 ± 32.1	52	42.22 ± 13.98
< 50	28	76.28 ± 34.4	36	34.63 ± 8.66
< 30	10	85.43 ± 39.6	10	22.92 ± 3.08

Table 2B

Concentration of paratyroid hormone (PTH) in regard to 25-hydroxyvitamin D [25(OH)D] insufficiency in the summer period

25(OH)D values (nmol/L)	Women (n)	PTH (pg/mL) $\overline{X}$ ± SD	Women (n)	25(OH)D (nmol/L) $\overline{X}$ ± SD
< 75	22	54.69 ± 21.5	32	51.23 ± 13.5
< 50	10	59.07 ± 24.1	15	38.83 ± 5.42
< 30	–	–	1	29.5 ± 0

Table 3

Results of bone mineral density measurements

T score	Lumbar spine (L1- L4) $\overline{X}$ ± SD (n)	Total hip $\overline{X}$ ± SD (n)	Femoral neck $\overline{X}$ ± SD (n)
< -2.5 SD	-3.12 ± 0.582 (59)	-2.85 ± 0.369 (23)	-2.87 ± 0.316 (24)
< -1.0 and > -2.5 SD	-1.92 ± 0.340 (27)	-1.70 ± 0.40 (59)	-1.82 ± 0.390 (60)
> -1.0 SD	0.125 ± 1.158 (4)	-0.554 ± 0.326 (11)	-0.561 ± 0.745 (10)

n – number of women

A strong negative linear correlation between 25(OH)D and PTH (r = -0.508, $p < 0.001$) was found (Figure 1). Serum levels of 25(OH)D were significantly correlated to T score at the lumbar spine (r = 0.227, $p < 0.05$), but not at the total hip and femoral neck (r = 0.093, $p = 0.373$; r = 0.110, $p = 0.290$) in the whole group. In addition, PTH correlated only to BMD at lumbar spine (r = -0.258, $p < 0.05$). It was noticed that in the subgroup aged ≥ 65 years, correlations between 25(OH)D and T score LS (r = 0.315, $p < 0.05$), BMD of at the neck (r = 0.321, $p < 0.05$), and PTH with BMD of the neck (r = -0.352, $p < 0.05$) were found. (Figures 2 and 3).

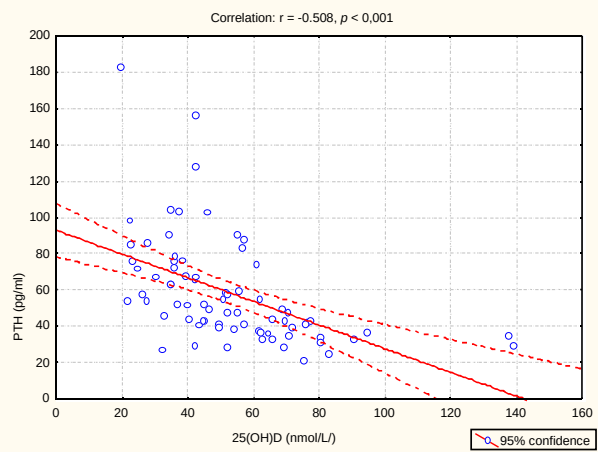

Fig. 1 – Correlation between 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) in the whole group

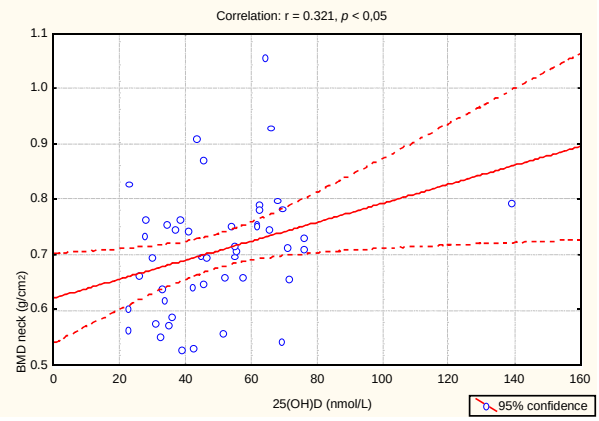

Fig. 2 – Correlation between 25-hydroxyvitamin D [25(OH)D] and bone mineral density (BMD) of the femoral neck in the age of ≥ 65 years

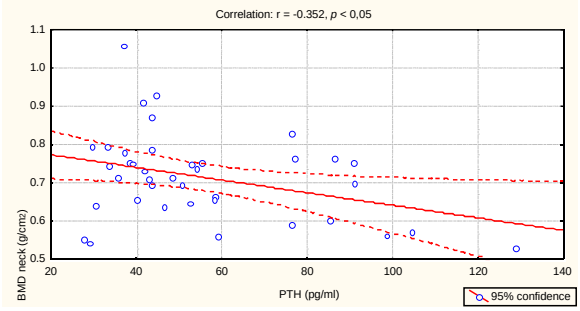

Fig. 3 – Correlation between parathyroid hormone (PTH) and bone mineral density (BMD) of the femoral neck in the age of ≥ 65 years

Discussion

Recent publications suggest that for bone and overall health desirable 25(OH)D concentration should be up to 75 nmol/L [6, 7, 19]. In accordance with other authors [3–9, 16] we found a high prevalence of vitamin D insufficiency in postmenopausal women (88.4%).

Given that sunshine exposure is the most important source of vitamin D, one should expect that vitamin D status depends on geographic location and seasonal variation. In addition, time spent outdoors, clothing habits, skin type and pigmentation, as well as diet, may influence differences in vitamin D status among countries [3, 4, 16]. Our results of seasonal variation among postmenopausal women in Belgrade (45 degree latitude North) confirmed significant difference in 25(OH)D and PTH levels [9, 20]. Vitamin D insufficiency is often associated with secondary hyperparathyroidism [9, 16]. In our study, in accordance with other investigators, we found secondary hyperparathyroidism in 25.3% of all investigated patients. Consequently, the prevalence of secondary hyperparathyroidism was higher (28.6%) among subjects with vitamin D insufficiency [9, 16, 21, 22]. Consistent with_other reports, a significant inverse correlation between serum 25(OH)D and PTH was shown [9, 22–26]. In the group with 25(OH)D ≤ 30.0 nmol/L, 54.5% had elevated values of PTH. But, it should be noted that in patients with vitamin D insufficiency, PTH is not always high. Despite of increases of serum PTH associated with vitamin D insufficiency, PTH values were usually within the normal reference ranges [4].

It should be noted that the prevalence of elevated PTH (54.2%) in women aged ≥ 65 years is similar to those with severe 25(OH)D insufficiency (55.5%). Literature data confirmed that PTH rises with age [25], but we have not found relationship between PTH and age ($p > 0.05$) In addition, many studies have reported that PTH values are higher in older than in younger adults [9, 17, 25]. Contributing to the higher PTH values in the elderly are several factors that are intrinsic to aging, such as decreased renal function, age related changes in the dermis which diminish the capacity for cutaneous synthesis of vitamin D, less efficient intestinal absorption of calcium, resistance to the calcemic action of PTH, a greater prevalence of vitamin D insufficiency, and perhaps the acidotic tendency of old age [1, 11, 17].

In the group of patients with elevated PTH, the mean of vitamin D was 37.6 nmol/L. This practically means it is a cut point value below which appears elevated PTH. This result was similar or equal with other authors [4, 25–27]. The modifying factor of the relationship between serum 25(OH)D and PTH is the calcium intake. The 24 h pattern of PTH secretion decreases markedly after an increase in calcium intake [28, 29].

Our study shows that vitamin D insufficiency is a common risk factor for osteoporosis in ambulatory postmenopausal women.

It is of relevance, in the elderly population, that chronic vitamin D insufficiency leads to osteoporosis or gradual loss of bone, which results in the impaired structural integrity of trabecular bones, with thinner and more porous cortical bones, thereby making the bones weaker and more likely to fracture [14].

A statistical analysis confirmed a significant correlation between 25(OH)D insufficiency and low BMD at lumbar spine in the whole group, and at femoral neck in the subgroup aged over 65 years. The pathogenic role of vitamin D insufficiency in decreased bone mass is shown by the significant correlation between 25(OH)D and T-score at lumbar spine. Vitamin D status appeared to be less related to proximal femur than to lumbar spine BMD. This may be caused by the fact that other mechanical factors (i.e., physical activity and weight) could influence proximal femur BMD to a higher extent. Moreover, the sex hormone deficiency makes lumbar spine bone more susceptible to vitamin D insufficiency. As suggested previously, oestrogen deficiency potentiates the effect of PTH excess because of vitamin D insufficiency [16]. Furthermore, hyperparathyroidism predisposes to cortical rather than cancellous bone loss, which would be more obvious at femoral neck compared with lumbar spine and, also may explain why PTH was a significant predictor of BMD at femoral neck as confirmed by our results [9, 26].

Conclusion

Our results showed a high prevalence of 25(OH)D insufficiency among postmenopausal women (88.4%) with seasonal variation in serum levels of 25(OH)D and PTH. Secondary hyperparathyroidism appeared in 25.3% of the patients. A very significant inverse correlation between 25(OH)D and PTH was established by BMD at lumbar spine in the whole group, and femoral neck in the subgroup of postmenopausal women aged more than 65 years. In patients with 25(OH)D insufficiencies, elevated PTH varied individually, but it was most often increased if 25(OH)D was equal or lower than 37.6 nmol/L.

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Evaluation of the patients with Grave's ophthalmopathy after the corticosteroids treatment

Ocena bolesnika sa Grejvsovom oftalmopatijom posle lečenja kortikosteroidima

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Abstract

Background/Aim. Graves' ophthalmopthy is one of the most common causes of exophthalmos as well as the most common manifestation of Graves' disease. The treatment of Graves' ophthalmopathy includes ophthalmological and endocrinological therapy. The aim of this study was to clinically evaluate the patients with Graves' ophthalmopathy treated with corticosteroids. **Methods.** Evaluation of 21 patients was performed in the Ophthalmology Clinic and Endocrinology Clinic, Clinical Centre Kragujevac, in the period from 2009 to 2010. They were treated with pulse doses of intravenous corticosteroids. They were referred to ophthalmologist by endocrinologist in euthyroid condition in the active phase of Graves' ophthalmopathy (ultrasonography of orbit findings and positive findings of antithyroid stimulating hormone receptor antibody – anti-TSH R Ab). The clinical activity score (CAS) and NO SPECS classification for evaluation of disease severity were used. Ophthalmological examination includes: best corrected visual acuity, slit-lamp exam, Hertels' test, direct ophthalmoscopy and ultrasonography of the orbit. **Results.** According to our results 76.19% of the patients were female; mean age of the patients was 35.2 ± 5.6 years. According to CAS classification after 6 months of the treatment recovery was shown in 23.81% of the patients, partial amelioration in 47.62% and no clinical amelioration in 28.57% of the patients. We achieved better results with male, young patients with high clinical activity score. Good results were observed after the first dose of corticosteroids, much better CAS after the third dose, which maintained until 6 months after the first treatment. **Conclusion.** Our results signify that intravenous pulse dose of corticosteroids treatment of the patients with Graves' ophthalmopthy is safe, comfortable, clinically justified and accessible for the clinicians and patients. Positive results are achieved after the first dose with increasing trend up to the third dose, which was maintained for the next three months.

Key words:
graves ophthalmopathy; thyrotropin; antibodies; severity of illness index; classification; adrenal cortex hormones; convalescence.

Apstrakt

Uvod/Cilj. Grejvsova oftalmopatija najčešći je uzrok egzoftalmusa i najčešća ekstratireoidna manifestacija bolesti. Za lečenje aktivne faze bolesti koriste se kortikosteroidi. Cilj rada bio je evaluacija lečenja bolesnika sa Grejvsovom oftalmopatijom tretiranih kortikosteroidnom terapijom. **Metode.** Ispitivan je 21 bolesnik u aktivnoj fazi bolesti, koji su u eutireoidnom statusu tretirani pulsnim dozama intravenskih (*iv*) kortikosteroida u Klinici za oftalmologiju i Klinici za endokrinologiju Kliničkog Centra Kragujevac, od 01. 01. 2009. do 31. 12. 2010. Aktivnost Grejvsove oftalmopatije potvrđena je ultrazvučnim pregledom orbite (oftalmolog) i određivanjem koncentracije antitela na receptore tireostimulišućeg hormona (TSH) ab (endokrinolog). Procena aktivnosti bolesti određivana je skorom kliničke aktivnosti (*Clinical Activity Score* – CAS), a stepen težine bolesti NO SPECS klasifikacijom koja određuje kliničke aspekte ispitivanja i praćenja oftalmopatije. Klinički pregled oftalmologa obuhvatao je: određivanje vidne oštrine, biomikroskopski pregled, direktnu oftalmoskopiju, egzoftalmometriju i ultrazvučni pregled orbite. **Rezultati.** Među ispitanicima bilo je 76,19% pripadnika ženskog pola. Prosečna starost bolesnika bila je 35,2 ± 5,6 godina. Analiza podataka prema CAS klasifikaciji, posle šest meseci pokazala je: potpuni oporavak kod 23,81% bolesnika, a kod 47,62% parcijalni oporavak, dok kod 28,57% bolesnika nije bilo kliničkog poboljšanja. Bolji terapijski rezultati postignuti su kod pripadnika muškog pola, mlađih, sa većom kliničkom aktivnošću bolesti. Prvi pozitivni rezulati postižu se nakon prve doze kortikosteroida, bolji posle treće doze, a održavaju se na nivou, šest meseci posle prve doze lečenja. **Zaključak.** Naši rezultati ukazuju na visoku efikasnost lečenja bolesnika sa Grejvsovom oftalmopatijom primenom *iv* pulsnih doza kortikosteroida. Ovakav tretman je bezbedan i komforan i za lekara i za bolesnika. Pozitivni rezutlati vidljivi su već posle prve doze kortikosteroida uz tendenciju poboljšanja posle treće doze, što se održava tokom sledeća tri meseca.

Ključne reči:
gušavost, egzoftalmička; tireotropin; antitela; bolest, indeks težine; klasifikacioni indeksi; kortikosteroidni hormoni; oporavak.

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Introduction

Graves' ophthalmopathy (GO) is one of the most common causes of exophthalmos and the most common cause of morbidity and discomfort in patients with Graves' disease [1]. The first document about Graves' disease was found in 1786 by Perry, but a complete clinical manifestation was described in 1835 by Basedow [2]. Ophthalmopathy is a manifestation of autoimmune process with the expressed extraocular myositis, glicosaminoglican production, orbital congestion and mononuclear orbital infiltration. The main causes of GO are genetic (positive findings of HLA-A8, HLA-DR3) and the influence of surroundings (stress, smoking cigarettes, infection) [3]. The disease is more frequent in female patients, with the ratio 3–10 : 1, and the mean age is 41 years, 2.5 years after the beginning of the disease. The more difficult form of the disease is described in male patients, at the age of 50 [3]. Clinical manifestation of the disease is typical and self-limited with active (progressive exacerbation) and inactive phase (regression and stagnation). Werner et al. [4] classified clinical signs of the disease in NO SPECS system, and classification was modified in 1981 to RELIEF classification. The clinical activity score (CAS) is based on 4 of the 5 classical signs of inflammation and has 10 well-known items. For each item, one point can be given. The sum of these points is CAS (range 0–10) [5, 6]. The diagnosis can be proved by endocrinologist and ophthalmologist. Computerized tomography (CT) and nuclear magnetic resonance (NMR) are reserved for unclear clinical manifestations of the disease [7]. Intravenous (*iv*) pulse doses of corticosteroids are used for the treatment of the active phase GO. Their action is mediated by inhibition of polymorphonuclear migration [8]. Side effects of corticosteroid treatment are rarely reported. Some of them like weight gain, hypertension, diabetes mellitus induction, pyloric ulcer, osteoporosis and the most difficult of them – fatal autoimmune hepatitis, can be notified [9]. Indications for this treatment are: euthyroid condition of patients, positive findings of anti thyroid stimulating hormone receptor anti-body (anti-TSH R Ab), extraocular muscle hypertrophy without fibrosing.

The aim of our study was to evaluate the patients with GO treated with corticosteroids *iv* pulse doses of.

Methods

We examined 21 patients with the active phase of GO in euthyroid condition, treated with *iv* pulse doses of corticosteroid therapy in the Ophthalmology Clinic and Endocrinology Clinic, Clinical Centre Kragujevac, from January 1, 2009 until December 31, 2010. The active phase of GO was confirmed by orbital ultrasonography, positive finding of anti-TSH R Ab and clinical activity was classified by CAS and disease degree was classified by NO SPECS classification (Tables 1, 2). Ophthalmological examination included: best corrected visual acuity (Snellen table), slit-lamp examination, direct ophthalmoscopy, Hertels' exophtalmometry and orbital ultrasonography. The patients were referred to ophthalmologist by endocrinologist with a detailed endocrinological status. All the patients were classified according to the duration of the disease into 3 groups: 1 – duration less than 1 year, 2 – duration from 1 to 2 years and 3 – duration for more than 2 years. The patients with active phase GO were treated with *iv* pulse doses of corticosteroids with Ethical Committee approval. We used *iv* pulse doses of corticosteroids (methylpredisolone 1 g/24 h for 3 days) followed by corticosteroides *per os*, 40 mg/24 h seven days, with a decreasing dose for 10 mg every week to the next pulse dose. Our patients were treated with 3 cycles of pulse dose every fourth week. Before the treatment the patients were examined for the clinical parameters: arterial pressure, glycemia and the serum liver enzymes level, as well as basic blood examination. During the treatment, there were no complications related to the corticosteroid therapy. The patients were ophthalmologically examined after 4 weeks, 3 and 6 months. We evaluated CAS and NO SPECS signs values in our patients analyzed by SPSS, version 13.

Table 1

NO SPECS (underlined first letter) and RELIEF (bolded first letter) categorization of Graves'ophthalmopathy

Classification	Signs and symptoms
0	No signs and symptoms
1	Only signs are upper eyelid retraction
2	Softe tissue signs and symptoms
	Resistance to retropulsation
	Edema of conjunctiva or caruncula
	Lacrimal gland enlargement
	Injection over the horizontal rectus muscle insertion
	Edema of eyelid
	Fullness of the eyelid
3	Proptosis
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loss

Table 2

Clinical Activity Score

Symptoms/Signs	Description
Pain	1 – Painfull, oppresive feeling on or behind the globe, during the last
	2 – Pain or attempted up, side or down gaze, during the last 4 weeks
Redness	3 – Redness of the eyelid(s)
Swelling	4 – Diffuse redness of the conjunctiva, covering at least one quadrant
	5 – Swelling of the eyelid
	6 – Chemosis
	7 – Swollen caruncle
	8 – Increase of proptosis of ≥ 2 mm during 1–3 minutes
Impaired function	9 – Decrease of eye movements in any direction ≥ 5°, 1–3 months
	10 – Decrease of visual acuity of ≥ 1 line on Snellen chart (using pinhole), 1–3 months

Results

According to our results, 16/21 (76.19%) of the patients were female, with a clinically significant manifestation of the disease ($\chi^2 = 5.762$, $p = 0.016$). The mean age of the patients was 35.2 ± 5.6 years. Clinical activity measured by CAS was ≥ 4 in 80.95%. According to NO SPECS classification, 71.43% of the patients had class 2 of the disease with a significant differences ($\chi^2 = 14$, $p = 0.001$). There were 14.28% of the patients in the third class and 19.04% patients in the first class. There were no patients in the lower class of the NO SPECS classification. After 4 weeks of the treatment there were no statistically significant differences about the distribution of patients by NO SPECS classification (in the class 0 – 19.04%, class 1 – 42.86%, class 2 – 33.33%, class > 3 – 4.76%; $\chi^2 = 7.0$, $p = 0.072$). After the third *iv* pulse dose of corticosteroids, a great number of the patients was in the class 1 – 38.10%, then in the class 2 – 33.33% with increasing number of patients in the class 0 – 28.57%, but with no statistically significant differences ($\chi^2 = 0.286$, $p = 867$). After 6 months, a great number of the patients was in the class 1 – 47.62%, in the class 2 – 23.81%, but without patients in the hardest class 3, with no statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$) (Table 3). According to our results classified in CAS, best results were reached after 6 months – complete remission in 23.81%, partial remission in 47.62%, without remission in 28.57% of the patients, without statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). The results after 4 weeks were: complete remission in 19.04%, partial remission in 42.86%, without remission in 38.10% of the patients, with no statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). After 3 months we achieved complete remission in 23.81%, incomplete remission in 42.86%, no remission in 28.57%, without statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). It means that many clinical signs decreased in their manifestation after corticosteroid treatment. After 4 weeks of the beginning of the treatment we summarized the number of patients with a complete and incomplete remission, when we reached no statistically significant differences ($\chi^2 = 5.762$, $p = 0.275$), but after 3 and 6 months we got statistically significant differences in the number of patients with complete and incomplete remission ($\chi^2 = 3.857$, $p = 0.005$). There were no statistically significant differences in these analysis, but we were able to notify great changes in the variables during the examination, with a significantly better clinical status of the patients after the first dose of the *iv* pulse dose of corticosteroids, with increasing trend after the second and the third dose maintained until 6 months after the beginning of the treatment. A complete and incomplete remission was achieved in male patients. A complete remission was achieved in 19.04% of females, incomplete remission in 28.57%, without remission in 28.57%. According to these results we can notify that at the very beginning of the corticosteroid treatment a great number of patients had incomplete remission with trend for increasing effectiveness of the therapy. A complete remission was achieved in 14.28% of all patients younger than 40 years, followed by 33.33% with incomplete remission. All the patients without remission were older than 40 years. There was a significant difference related to the age of the patients and the results of the therapy. The group of the younger patients (< 40 years) had better results ($\chi^2 = 12.095$, $p = 0.02$). A complete recovery was noted in the group with CAS > 4, incomplete in 33.33 % of the patients with CAS > 4 and in 14.28% of patients with CAS ≤ 4, but all the patients without recovery had CAS ≤ 4 (Table 4). There were no significant differences between the duration of the disease and the results of the therapy. In the group of patients with the duration of the disease less than 2 years, complete recovery was achieved in 9.52%, incomplete in 19.05% and without recovery in 2 patients. In the group of patients with the disease

Table 3

Distribution of patients according to NO SPECS classification, after 4 weeks, 3 and 6 months

Duration of drug therapy	NO SPECS classification*			
	0	1	2	≥ 3
Before treatment		4	15	2
After 4 weeks	4	9	7	1
After 3 months	6	8	7	
After 6 months	5	10	6	

***see Table 1**

Table 4

Effects of the therapy according to the CAS classification, sex, age and disease degree

Parameters	Recovery (number of patients)			
	complete	incomplete	partial	no recovery
Duration of drug treatment				
after 4 weeks		4	9	8
after 3 months		5	9	7
after 6 months		5	10	6
Sex				
male	4		1	0
female	4		6	6
Age (years)				
> 40	2		3	5
< 40	3		7	1
CAS*				
≤ 4			3	6
< 4	5		7	

***see Table 2**

duration of one to two years, complete recovery was achieved in 9.52%, incomplete in 14.28% and without recovery in 9.52% of the patients. In the group of patients with the disease duration more than 2 years, complete recovery was noted in 4.76%, incomplete in 14.28% and without recovery in 2 patients.

Before the treatment all the patients were examined (arterial pressure, blood examination, liver enzimes). All the patients were treated with gastroprotective therapy. Cushingoid syndrome was detected in 18 (85.71%) patients, but after the treatment it was regulated. During the treatment transitorial hypertension was notified in 2 patients, but arterial preassure was regulated at the end of the treatment. We notified weight gain in all the patients, but after 3 months of the treatment it was also regulated. There were no elevation of the serum liver enzimes values.

Discussion

Rundle at all. [10] notified that Graves' ophthalmopathy has two phases, interrupted with a "plate" phase: initial phase with high activity after 6–24 months from the beginning of the disease and the phase of incomplete regression. Early symptoms are a consequence of autoimmune process and inflammation. The later ones are a consequence of the fibrosing process. Some earlier studies indicated that there is no correlation between the disease duration and the treatment effects as well as in our study [6]. The active phase of GO can be treated with corticosteroids and the late one can be treated with radiation and surgical therapies [11]. Peroral steroids were used for the treatment of the active phase of GO, but better results were achieved with intravenous steroids [11]. There are some data about using rituximab (anti-CD20), etancerot (anti-TNF), octreotide, somatostatin, plasmapheresis, etc. [3, 12]. Corticosteroid therapy in our opinion has many advantages, such as lower costs and lower number of side effects and contraindications [11]. Very important predictive factor for the efficiency of corticosteroid therapy are CAS values. Good results were noted in the group of patients with CAS > 4 and bad results in the group with CAS ≤ 4. In this fashion our results are similar to other records [13]. The majority of the patients were younger female patients (< 40 years). The best results were noted in younger male patients (< 40 years). The efficacy of the therapy in the female group was 66.66%. Incomplete recovery was noted in 76.19% of the patients with lower CAS values, according to other investigations [13]. The younger patients had better effects of the corticosteroid therapy. Euthyroid status of the patient was of great importance during the whole therapy in our investigation.

Conclusion

Our results signify that intravenous pulse dose of corticosteroids treatment of the patients with Graves' ophthalmopthy is safe, comfortable, clinically justified and accessible for the clinicians and patients. Positive results are achieved after the first dose with increasing trend up to the third dose, which was maintained for the next three months.

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Urodynamic characteristics of the modified orthotopic ileal neobladder

Urodinamske karakteristike modifikovane ortotopne ilealne neobešike

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Abstract

Background/Aim. Radical cystectomy is the method of choice in management of muscle invasive, organ-confined tumors of the bladder (T2-T4, N0-Nx). The most frequent continent orthotopic urinary diversion after radical cystectomy is the ileal neobladder. A modified technique consists of using a shorter segment of the terminal ileum than the standard technique, around 30 cm. The aim of this study was to determine the urodynamic characteristics of the orthotopic ileal neobladder created by a modified technique. **Methods.** In this prospective clinical study we analyzed the urodynamic parameters of 24 patients who had underwent radical cystectomy with orthotopic urinary diversion by ileal neobladder created using a modified technique. In all the patients we performed invasive and noninvasive urodynamic investigations 12 months after the operation. The urethral pressure profile parameters analyzed were maximal urethral pressure, maximal urethral closure pressure and the functional urethral profile length. **Results.** The average age of the patients was 63 (49–73) years, 90% were males and 10% were females. The median length of the shorter segment of the terminal ileum was 28 (range 22–35) cm. Prior to enterocystometry and uroflowmetry postvoid residual (PVR) urine was measured by a urethral catheter. The median PVR was 16.7 (0–140) mL. The median enterocystometric capacity was 396 (range 372–532) mL. The median end filling pouch pressure was 27.6 (range 20–70) cmH_20. The median maximal flow of urine was 22.1 (range 9.7–39.5) mL/s and the average flow of urine was 9.61 (range 3.6–17.6) mL/s. Flow time in the analyzed group was 47.5 (range 22–119) s. The median maximal urethral pressure was 54 (range 12–101) cmH_2O, maximal urethral closure pressure 36.6 (range 6–91) cmH_2O. Functional urethral profile length was 14.9 (range 4–37) mm. **Conclusion.** An ileal orthotopic pouch created by a modified technique using a shorter segment of the terminal ileum after 12 months presents with urodynamic characteristics similar to the native bladder.

Key words:
urinary bladder neoplasms; cystectomy; urologic surgical procedures; ileum; treatment outcome.

Apstrakt

Uvod/Cilj. Radikalna cistektomija predstavlja metodu izbora u lečenju mišićnoinvazivnog organ-ograničenog tumora mokraćne bešike (T2-T4, N0-Nx). Radikalna cistektomija zahteva da se obezbedi derivacija urina. Ilealna neobešika je najčešća kontinentna ortotopna derivacija urina. Modifikovana tehnika podrazumeva upotrebu kraćeg segmenta terminalnog ileuma u dužini od oko 30 cm. Cilj rada bio je da se utvrde urodinamske karakteristike ortotopne ilealne neobešike kreirane modifikovanom tehnikom. **Metode.** U prospektivnoj kliničkoj studiji mereni su urodinamski parametri 24 bolesnika kod kojih je učinjena radikalna cistektomija sa ortotopnom derivacijom urina formiranjem ilealne neobešike modifikovanom tehnikom. Kod svih bolesnika sprovedeni su invazivni i neinvazivni urodinamski pregledi 12 meseci nakon operativnog lečenja. Profilometrijom uretralnih pritisaka određivan je maksimalni uretralni pritisak, maksimalni pritisak zatvaranja uretre i funkcionalna dužina uretre. **Rezultati.** Životno doba bolesnika bilo je 63 (49–73) godine. Muškaraca je bilo 90%, a žena 10%. Dužina segmenta terminalnog ileuma bila je 28 (22–35) cm. Pre enterocistometrije, kao i nakon uroprotoka, kod svih bolesnika meren je rezidualni volumen urina (PVR) uretralnim kateterom. Vrednosti PVR bile su 16,7 (0–140) mL, a maksimalni enterocistometrijski kapacitet 396 (372–532) mL. Pritisak unutar neobešike pri maksimalnom enterocistometrijskom kapacitetu iznosio je 27,6 (20–70) cmH_20. Maksimalni protok urina iznosio je 22,1 (9,7–39,5) mL/s. Vrednost prosečnog protoka urina pri mokrenju iznosila je 9,61 (3,6–17,6) mL/s,

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a vreme mokrenja bilo je 47,5 (22–119) s. Vrednosti maksimalnog pritiska uretre bile su 54 (12–101) cmH_2O, dok je maksimalni pritisak zatvaranja uretre iznosio 36,6 (6–91) cmH_2O. Funkcionalna dužina uretre u posmatranoj grupi bila je 14,9 (4–37) mm. **Zaključak.** Ilealna ortotopna neobešika, kreirana modifikovanom tehnikom korišćenjem kraćeg segmenta terminalnog ileuma, nakon godinu dana poseduje urodinamske karakteristike slične nativnoj bešici.

Ključne reči:
mokraćna bešika, neoplazme; cistektomija; hirurgija, urološka, procedure; ileum; lečenje, ishod.

Introduction

Radical cystectomy is the method of choice in management of muscle invasive, organ-confined tumors of the bladder (T2-T4, N0-Nx) [1]. Radical cystectomy demands urinary diversion. Continent urinary diversion consists of creating a urinary reservoir that will enable urinary continence and voiding. They can be heterotopic (continent cutaneous urinary diversion) and orthotopic (pouch, neobladder) [2,3]. The modified technique consists of using a segment of the ileum around 30 cm in length, shorter than standard technique [3–7].

Urodynamic investigations are functional and diagnostic procedures that are used to evaluate the function of the lower urinary tract. The orthotopic ileal neobladder "imitates" the native bladder and the same functional and diagnostic procedures can be used to evaluate the ileal neobladder [8].

Methods

The prospective clinical study included 24 patients who underwent radical cystectomy with orthotopic ileal neobladder urinary diversion. In all the patients we performed invasive and noninvasive urodynamic investigations 12 months following the operation. Uroflowmetry was used as a noninvasive urodynamic procedure. Enterocystometry, urethral pressure profile (UPP) and measurement of postvoid residual (PVR) urine by catheter are invasive urodynamic procedures that were used. The urodynamic investigations were performed using the Medtronic Duet Encompass (Medtronic, Minneapolis, USA). Enterocystometry was performed using a cystometric transurethral filling catheter CH 8 by which the intraluminal pressure was measured during filling of the neobladder, a catheter for measurement of intraabdominal pressure CH 12, sterile NaCl 0.9% solution and transducers for intravesical and intraabdominal pressure were used. UPP was performed using a transurethral filling catheter CH 8, pullera – a device that pulls the catheter in a constant speed of 2 mm/s, and tranducers for intravesical pressure and urethral pressure profile. The change of pressure in the catheters are transferred to the transducer, that converts it into an electric signal and after that computer analyzes and presents the graphic and numeric results of measurements.

We determined the following urodynamic parameters: enterocystometric capacity of the neobladder, maximal neobladder pressure (pressure at enterocystometric capacity), the average flow rate, maximal flow rate, flow time, maximal urethral pressure, maximal uretharal closure pressure, functional length of the urethra and PVR.

All procedures were performed in accordance with the principles of sterility. The patients were informed in detail about the examination and they signed the consent form. The procedures were conducted in a standardized manner with the patient in a sitting position. In invasive urodynamic procedures antibiotic prophylaxis was conducted (ciprofloxacin 500 mg, one hour prior to the examination). The examinations were performed in accordance with the guidelines and terminology of the International Continence Society (ICS) [9].

Results

In the monitored group of patients who underwent radical cystectomy because of muscle-invasive bladder cancer, urinary diversion was performed by orthotopic neobladder created using a shorter segment of the terminal ileum in the average length of 28 (22–35) cm. The demographic data, and results of invasive and noninvasive urodynamic investigations are presented in Table 1. The results of UPP are presented in Table 2.

Table 1
Demographic data of patients and urodynamic parameters of the neobladder

Patients data / Parameter	Mean value (range)
Age (years)	63 (49–73)
Gender (male/female)	22/2
Length of terminal ileum (cm)	28 (22–35)
Postvoid residual (mL)	16.7 (0–140)
Enterocystometric capacity (mL)	396 (372–532)
Pressure at enterocystometric capacity (cmH_2O)	27.6 (20–70)
Maximal flow rate (mL/s)	22.1 (9.7–39.5)
Average flow rate (mL/s)	9.61 (3.6–17.6)
Flow time (s)	47.5 (22–119)

Table 2
Urethral pressure profile

Parameter	Mean value (range)
Maximal urethral pressure (cmH_2O)	54 (12–101)
Maximal closure urethral pressure (cmH_2O)	36.6 (6–91)
Functional length of the urethra (mm)	14.9 (4–37)

Discussion

The role of a neobladder is to replace the bladder both in place and function. A neobladder that imitates the native bladder should have satisfying capacity, low intraluminal pressure and to enable physiological voiding frequency and urinary continence.

Searching through the Medline and Pubmed database and professional literature up to December 2010, there are nine published papers which consider neobladders created of an ileal segment shorter than by the standard technique [4–7, 10–14]. There are 7 papers that have been published which evaluated urodynamic characteristics of neobladders created by modified technique [4–7, 10–14].

Based on the available published data for neobladders created by the standard technique there are no standard values for urodynamic parameters. Although the data obtained by urodynamic investigations are objective, precise and comparable, this evaluation is not standard procedure in a follow-up period after radical cystectomy. There is limited number of published papers that consider urodynamic evaluation of neobladders compared to the large number of variations of ileal orthotopic neobladders (49 papers).

The length of the segment of terminal ileum is limited with the possibilities of creating the vascular pedicle, so the average length of the segment was 28 cm in our patient group. Two studies analyzed neobladder created from 40 cm of the terminal ileum, while Constantinides et al. [5] used 36 cm of the terminal ileum [4, 6]. In our previously published study we presented the use of a shorter segment of ileum than in other published papers and in this study as an upgrade of the previous one we evaluated the urodynamic characteristics of the neobladder created by a modified technique [7].

In our study PVR was 16.7 mL (0–140), compared to 40 (0–150) mL and 30 mL presented in two other studies [4, 5]. The median maximal flow rate in our group was 22.1 mL/s (9.7–39.5) and in Sevin´s [4] study 17.5 mL/s (11–30) [4]. The difference is significant and expected. It is a known fact that the neobladder enlarges in volume in the first year following the operation up to four times so will the capacity of the neobladder in our study [15]. This occurs only if they are frequently filled otherwise neobladder volume decreases in time if they are nonfunctional. The enlargement of the neobladder leads to creating a larger contact and resorptive surface of the neobladder that may cause an increase in metabolic and electrolyte abnormalities and may also lead to problems in voiding and an increase in PVR. Beside neobladder capacity many factors can have an influence on maximal flow rate: strength of the abdominal wall, position and shape of the neobladder, sphincteric mechanisam, possible stenosis of entero-urethral anastomosis and voiding position of the patient. Using a shorter segment of the terminal ileum decreases the capacity of the neobladder that leads to a smaller PVR [7].

Enterocystometry is an invasive urodynamic procedure by which the pressure/volume relationship of the intestinal reservoir is measured. The prerequisite for creating a neobladder is intestinal detubularization [3]. Intestinal detubularization is needed to avoid the peristaltic activity of the small bowel and also by folding the bowel the circumference is doubled, thus doubling the volume [3]. Intestinal detubularization not only decreases intraluminal presssure, but also by change of shape changes the capacity and pressure on the wall of the small bowel. The clinical significance of Laplace´s law is that by creating a spheric reservoir of an intestinal segment we achieve that the capacity of the reservoir increases by r^2 (r – radius of the bowel). By increasing the radius of the reservoir the intraluminal pressure decreases. Increasing the intraluminal pressure increases the pressure on the wall of the reservoir and with a larger capacity the influence of peristaltic activity on the increase of intraluminal presure decreases.There are some difficulties in conducting the examination and interpretation of the results of enterocystometry. First of all, this relates to the sensitivity of the neobladder as a subjective part of the examination and also to determine the enterocystometric capacity of the neobladder. Compared to the native bladder to determine the sensitivity of the neobladder is very difficult because patients have impaired feeling for the need to void but instead feel pressure in the place of the neobladder. Enterocystometric capacity is determined by a strong desire to void or when it is absent with onset of leakage beside the cystometric catheter [16]. In our study the average enterocystometric capacity was lower compared to the Sevin group where it was 550 (310–720) mL [4]. Enterocystometric pressures at enterocystometric capacity are approximately the same and comparable to the Sevin group 26.4 (11–48) cmH_20 [4]. We can conclude that the capacity of the neobladder created by modified technique in our group is similar to the native bladder with an unsignificant difference in pressure at enterocystometric capacity.

The measurement of the UPP is not only to determine if the patient is continent or the level of incontinence, but to understand the mechanism of urethral closure and appropriate urodynamic parameters [16]. In our group we considered the average maximal urethral pressure and maximal urethral closure pressure. In the study of Kakizaki et al. [14] the average maximal urethral closure pressure was 49.9 cmH_20. The patient is continent till the moment when the maximal urethral closure pressure exceeds the intraluminal pressure of the native bladder or the neobladder [8]. The values of the maximal urethral closure pressure and maximal urethral pressure can have influence on nocturnal continence especially if the maximal urethral closure pressure is < $45cmH_2O$ [17]. In our study the maximal urethral closure pressure is lower than in the Kakizaki study and can have influence on continence (day and night) but that cannot be analyzed isolated from other urodynamic parameters (enterocystometric pressure, capacity and PVR).

Conclusion

Analyzing the urodynamic parameters of invasive and noninvasive urodynamic procedures we can conclude that the neobladder created by the modified technique using a shorter segment of the terminal ileum compared to the standard neobladder has functional characteristics similar to the native bladder. Adequate capacity, small PVR, good maximal flow rate, low enterocystometric pressure and satisfying UPP decreases the possibility of functional and metabolic abnormalities of the upper urinary tract and can influence quality of life. Prospective studies with larger numbers of patients included and a longer follow-up period are needed to determine all advantages of the modified technique over the standard technique.

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CURRENT TOPIC

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Quality of life in childhood and adolescence: from concept to practice

Kvalitet života u detinjstvu i adolescenciji: od koncepta do prakse

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Key words:
quality of life; child; adolescent; health; health promotion; questionnaires.

Ključne reči:
kvalitet života; deca; adolescenti; zdravlje; zdravstvo, unapređenje; upitinici.

The concept of quality of life

The definiton of quality of life

Quality of life (QOL) is an extensive and broad ranging concept with the important position in the studies of psychology, economy, and medicine. QOL is an interdisciplinary conceptresulting from numerous social, economical, health and environmental factors that cumulatively and, often in unknown ways, can interact to affect both human and social development at the level of the individual or society [1]. However, this definition of QOL provides only the framework for genesis and participants, but does not describe the core of concept. The essence is determined to refer to the primary focus for forming the QOL conceptual models: a) economical with „not how much, but how good; not with the quantity of goods, but with the quality of lives"; b) sociological with „social utility and preference" and c) psychological with „happiness and satisfaction" [2].

Refer to health related QOL concept, the World Health Organization defined the QOL in 1991 as "the individual perception of his or her position in life, within the cultural context and value system he or she lives in, and relation to his or her goals, expectations, parameters and social relations. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment".

The subjective nature of QOL ("the individual perception" is crucial for understanding this concept) [3, 4]. QOL is open, self–esteem concept.

At the same time, the subjective nature of QOL causes various difficulties in QOL assessment and evaluation.

Health-related QOL concepts summarize those aspects of life quality or function which are impacted by one's health status (i.e. the impact of a person's health on his/her ability to lead full life, and "well-being" with or after the treatment) [5].

The QOL concept is much broader and encompasses both medical and non medical aspects.

The QOL concept is complex, multidimensional construct and actually is the holistic approach to a person.

Historical view

Is quality of life a new expression for old ideas [3]? Yes, although the expression was introduced for the first time in 1975 as a key term in medical indexes. Despite the fact that similar theoretical (philosophical) discussions had been taking place even in ancient time (including some scientific studies), quality of life in today's sense became a topic for research only in 1980's. So to say, that is an old-new concept with the same essence "well-being" – for persons and their environment, but presented by a new, subjective view for the person whose QOL is evaluated.

The oncologist were the first physicians that have been confronted with the dilemma: "Should we add years to life or life to years ?" [4].

Since then, QOL has become a relevant factor in clinical research and patient treatment QOL is relevant how the patient feels, if she/he is satisfied with the treatment, it is import what the patient can actually expect from the treatment. At this time QOL is characterized by different approaches, thus it could be said that in a medical work term QOL does not have a single and/or distinct meaning. It ranges from a wide holistic approach to the quality of life, to more specific meaning relative to the way how the level of health of an individual would affect his/her level of life comfort. Sometimes, the term QOL is substituted with other terms such as health or functional status or simply a sum of all these as-

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pects of QOL or function that affect human health. However, the widespread attitude is that: "QOL concept is much broader and encompasses both medical and non medical aspects, including physical, psychological and social functioning and also the perception of own health status, pain and, in the first place, satisfaction or dissatisfaction with the areas of life that are important to him/her" (Figure 1) [2, 4].

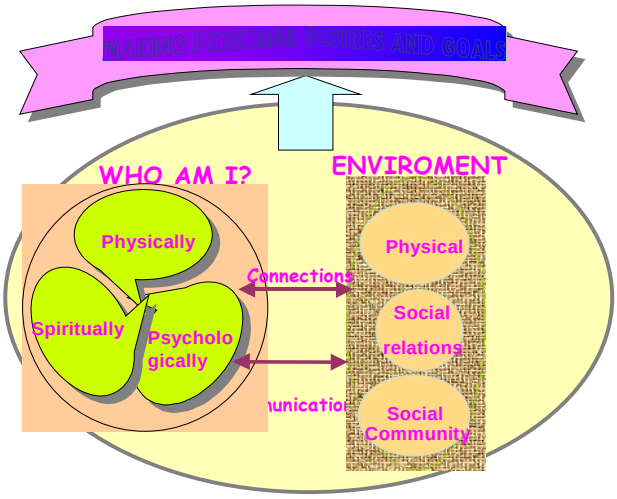

Fig. 1 – Quality of life concept: basic dilemmas and problems

Basic dilemmas and problems

The basic problem of QOL conceptualization (before all the health-related QOL) is not very clear distinction between classic medical and contemporary mediational model of QOL in practice [4].

In medical model – QOL is mostly the product of symptoms and side effects of medication [4].

A mediational model introduces a "mediator" between QOL and the symptoms/side effects. Mediator are person's characteristics which have big input in the way one perceives his/her quality of life. These are well-known facts coming from the practical work which show that two patients with the same diseases, at the same level of symptoms and therapy reaction, have different levels of QOL (patients characteristics can indeed mediate between quality of life and symptoms/side effects).

The second problem is related to the core of QOL concept and actually is pseudo-dilemma: subjective (self related) *vs* objective (clinician related) [1, 4].

The question is: is and how much, the personal subjective assess really more realistic presentation of the own QOL level related to physicians objective assessment? The key for understanding and solving this pseudo-dilemma depends on the focus of the scope.

Patients personal sense of well-being is their main point of reference. Patients assess the outcome of treatment according to whether they feel more comfortable or can participate again in everyday activities in a satisfactory way.

Clinicians base their assessment on the extent to which the disease process has been halted, i.e. their main point of reference is a disease.

It is very important to understand a matter of fact that the patients QOL assessment is more closely related to the fact how these patients feel their conditions have impacted on their lives, rather than to the presence of symptomatology.

Based on this, we could discuss additional benefits of the patient's subjective value of its QOL to the physicians as well: it can help in prioritizing the problems, it can improve communication, provide better compliance, assist in recognizing patient's preferences, indentify the differences, etc.

Assessment of quality of life measurement issues

The holistic orientation of the concept in practice suffers from various problems; within them the assessment and the measuring are prominent. Despite these facts there are numerous useful instruments (scales, inventories, questionnaires) in practice for assessment of different areas of life functioning (health, psychological, social, pleasure, satisfaction, etc.).

Scales

a) Relative to the population that is targeted, scales could be generic or oriented to the specific diseases. There are two different scales for assessment QOL: generic scales (developed for research and comparison between different diseases) *vs* disease-specific scales (developed for those individuals with particular disease or condition)
Generic scales are so-called "general scales" developed for research focused on differences between diseases and states and, in certain circumstances, for research on QOL in healthy population. These scales are the main topics in all studies.
Scales which have been developed specifically for certain diseases are much more "sensitive" and productive when come to the discovery of the problems specific for these disorders or conditions. However, they can be used only to "differentiate" relevant from irrelevant integers within one disorder or condition. It is nearly impossible to compare two disorders or conditions using these scales, therefore they are recommended only as an addition to the generic scale.

b) Relative to the estimation of capabilities and needs they can be functionalist-approach scales and needs-based approach scales.
Functionalist approach scales (i.e. individuals being able to perform roles that are deemed "normal" – physical mobility, socialization, employment) *vs* needs-based approach scales (individuals being able to satisfy their physical needs, psychological needs such as self-respect, autonomy, pleasure, socialization...)

Based on their orientation, scales could be: (so-called) functionalistic scales (one that refer to the level of function-ability/independent movement...) or on-need-bases scales (which are more accurate data and fulfill basic goal which is auto-estimate). For QOL estimating at functionalistic scales

the most important factor is if the disease or disorder has influence on the motor conditions (e.g. moving, working, etc.), on-need-bases scales offer more complex QOL estimating. These estimates target personal ability and capacity to fulfill its own needs (physical, as well as sociological, such as self-integrity, independence, social relations and content) [5, 6].

Commonly used instruments in pediatric practice are: Pediatric Quality of Life Inventory (PEDSQOL) [7], and Child Health Questionnaire (CHQ) [8]. CHQ besides "typical" items, estimates family activities as well, family relationship, as well as behavioral dimensions, quality of life questionnaire for children and adolescents (KINDL) [9].

Additional sources for estimating which could be used (are used) are estimating QOL in children by parents (parents asked as proxies about QOL of children) and physicians (which are mostly aimed towards "objective" increased of conditions – by symptoms and results) [10, 11].

Quality of life in practice research and implementation

Developmental age and quality of life assessment

Youth and their well-being are in the first place in all national strategies.

Research on youth and especially on childhood is not easy, not only because of methodological issues, but also because of developmental specifics. This brings out most dilemmas and questions. Some interesting are the ethical questions, i.e. children rights (to understand problems, consent for participation in a research...).

The basic question for all researches on childhood is the ability for self-assessment. What is the appropriate age when children can provide realistic and valid information about their QOL?

Most interesting for QOL research on childhood and youth are the "groups at risk". In everyday practice these groups, or more precisely the areas of research on childhood and adolescence are: children and adolescents in social welfare system, children and adolescents with disabilities or special needs and their families [10], and children and adolescents with different chronic health conditions and their families [12–15].

Research is an intermediate step between concept and real practice. In practice, QOL assessment is the basis for development, implementation and evaluation of "focus-oriented" programs and actions (QOL–related services). It is a multidisciplinary activity assembled to create better life in child and youth. The real practice is evaluation and implementation of research results in different areas of life – for improvement QOL.

Conclusion

The core of QOL concept is understanding of a human being and its needs, from different perspectives, keeping in mind that a human being is in constant interaction with the surroundings, according to the holistic-ecological approach.

In practice, the goal is to create a patient more comfortable (psychological, physical and social) environment from a holistic-ecological perspective.

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Conceptual framework for communicating health and illness across cultures

Konceptualni okvir za interkulturalnu zdravstvenu komunikaciju

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Key words:
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Ključne reči:
komunikacija; kultura, kompetencije; edukacija, medicinska; lekar-bolesnik odnosi.

Introduction

The formal study of intercultural communication is generally associated with the publication of Edward Hall's "The Silent Language" in 1959, where the author showed how culture is critical to understanding intercultural communication. After millennia of research, intercultural communication challenges today are global and by that it is meant that intercultural communication is present in every segment of life and in every profession. Correspondingly, the significance of health communication is very important because if people are to interculturally interact with other people, it is important to understand how socio-cultural factors shape the well-being of others. Owing to that, effective health care delivery relies on clear and effective communication which is an essential element in every form of medicine and health care between all of the individuals who are involved: patients, physicians, and other health care professionals. If, in any way, communication between health care providers and patients is not clear, the entire medical treatment process can be problematic and clear communication may be hindered when the participants come from diverse cultural backgrounds. Thus, it is exactly the health care provider who is responsible for communicating effectively with people from diverse cultural backgrounds meaning that a fundamental understanding of the relationships among health care providers, culture and communication is a prerequisite for everyone involved in the health care professions. Furthermore, culturally competent communication appropriates sophisticated and contextually suitable communication behaviors designed to foster maximum physician sensitivity to cultural differences in patients and concomitantly serve as bedrock of the physician-communication competence in interacting with patients.

Diverse health care belief systems

Cultures all over the world have beliefs about illness and health that derive from the way they perceive the world. Generally speaking, people are taught well what to value or devalue, appreciate or denigrate, love or hate with regard to the healing process [1–4]. Therefore, culture and ethnicity create unique patterns of beliefs and perceptions about health and illness. In turn, these patterns influence how illness is recognized, to what it is attributed, how it is interpreted and how and when health services are sought [1–4]. To this end, health care providers should not approach health care from a single cultural perspective and must learn to treat patients from other cultures in a culturally competent manner because cultural barriers can greatly influence the healing process [5]. Granting all this, health belief systems are divided into three major categories: occult, holistic and scientific traditions, each with its own corresponding system of related beliefs [1, 2].

The occult health care tradition comes from a belief system in which the world is perceived as an arena where supernatural forces predominate. Followers of this tradition hold strong beliefs about the existence of sorcery, magic and evil spirits. In this tradition, the fate of the world and all of those in it depends upon God, gods or other supernatural forces of good or evil. Here, illness is attributed to spiritual forces and results from the possession of the body by evil spirits or from casting evil spells. The ill person is considered a victim of punishment rendered by the occult being or power. In the supernatural tradition, treatment involves achieving a positive association with spirits, deities and the like where treatment is carried out by healer-practitioners recognized by their communities as shamans (Siberian word for spirit healer) who have supernatural powers and strength

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to ward off the evil spirits or entities that possess and torture the body and soul of the ill person [1–4].

This tradition is characteristic of some parts of Southeast Asia, Vietnamese, the Caribbean and some Latino countries. Also some of the oldest and most widespread superstitions regarding the cause of illness is the evil eye, which is the belief that someone can inflict harm by gazing or staring at another person. Belief in the power of the evil eye still exists in many parts of the world as well such as Southern Europe, the Middle East and North America.

The holistic tradition is based on the principle that a whole is made up of interdependent, interacting parts. In the same view, an individual is a whole made up of interdependent parts which are known as physical, mental, emotional and spiritual. Therefore, if one part is not functioning at its best, it affects all of the other parts of that person because all parts are in constant interaction with everything in the surrounding environment [1, 2].

Interestingly enough, holistic health is an approach to life as well. The goal is to achieve maximum well-being, where everything is functioning in the best way possible – the mind, the body and the soul. With holistic approach to health, people accept responsibility for their own level of well-being and everyday choices are used to take change of one's own health. This approach is embraced by Asian people (Filipinos, Koreans, Japanese and Southeast Asians), Africans, Haitians and Jamaicans [1–4].

Holistic treatment of illness is found in some Chinese and Japanese medical practices as well. It includes ingesting thousand-year-old eggs, strict rules of food combinations or a Japanese tradition of drinking turtle blood which is considered a youth and health elixir. Traditional cures also include acupuncture (applying needles to the body to cure diseases or relieve pain), moxibustion (therapy based on the value of heat), herbal remedies, such as ginseng as well as exercising programs such as *tai chi* (an internal Chinese martial art practiced for both its defense training and its health benefits).

The scientific tradition focuses on the objective diagnosis and scientific explanation of disease. It is an evidence-based approach to illness and other bodily disorders and relies on procedures such as laboratory tests to verify the presence and diagnosis of disease. Since it is based on rational thinking it very often ignores psychosocial aspects of illness such as cultural norms, coping abilities and life events that may interact with physical problems.

The scientific tradition understands health in terms of physical and chemical processes and most doctors in the world are trained in this tradition. This health care system rejects the metaphysical and usually ignores holistic approaches to medicine as well. Such a strong and shared belief in the scientific health care approach is inclined to become in some cases the Western biomedical ethnocentrism [1, 2] which can be a serious barrier to effective health care communication and oftentimes results in an undermining response to a patient's use of or interest in alternative supernatural or holistic health practices. For the firm supporters of scientific tradition, these practices are perceived to lie outside accepted medical practices and will be tolerated only if they do not interfere with the widely accepted treatment plan of scientific tradition. Consequently, treatments in this approach seek to destroy or remove the causative agent of disease or illness and seek to return the body to its normal state. The treatments include: surgery, medications and other therapeutic interventions such as antibiotics, nutritional supplements, vitamins and minerals.

As seen from the above, diverse cultural beliefs regarding the causes and treatments of illness have led to a variety of methods to deal with the prevention of illness. Many cultures incorporate a combination of supernatural, holistic and scientific approaches to prevent illness. For example, in the United States and other highly technological cultures such as Germany or Japan, good health is based on regular annual physical examinations, immunizations at specified times, exercise and good nutrition. Additionally, many people also follow preventive health regimens such as anti-stress massage and meditation, yoga, ingestion of probiotic bacteria, a variety of natural herbs to prevent and/or reduce memory loss, promote energy and seek preventive treatment from chiropractors, chiropodists, acupuncturists and colonic irrigationists. In contrast, many Muslims rely on the Koran to protect them from illness. Latino and Asian cultures, on the other hand, believe that illness may be prevented by maintaining a "hot-cold" balance. Many members of Mexican and Puerto Rican cultures believe that health may be the result of good luck or reward from God for good behavior. The Chinese prepare amulets (especially jade charms) to ward off evil spirits and to protect their health [1–4]. An eloquent Serbian adage "good thoughts are half of health" implies that the act of thinking good thoughts wards off illness.

So far, the point of this discussion indicates that what patient believes can strongly affect the treatment process. But even so, each health care provider should bear in mind that health care delivery anywhere in the world can be impeded by cultural diversity, lack of knowledge about diversity and an inability to communicate effectively that altogether lead to false diagnosis. Conjointly, in order to achieve an objective of optimal health care for all people, health care providers and institutions must be culturally competent.

Intercultural health care competence

As indicated before, intercultural competence is generally defined as the knowledge, motivation and skills to interact effectively and appropriately with members of different cultures [1–4, 6–11]. Overtly, five attributes of intercultural competence that are a must in health care are: 1) cultural awareness, 2) cultural knowledge, 3) cultural understanding, 4) cultural sensitivity, and 5) cultural skill [1–3, 5, 7–11]. Still and all, when applied in health care settings such as a physician's office, clinic or hospital, intercultural competence must include tailor-made attributes of the intercultural healthcare competence (Table 1). In other words, healthcare providers must take a proactive attitude and develop sensitivity to the role culture plays in health care. It is essential, therefore, that health care providers not only learn about other cultures but their own beliefs respectively, only to realize how they affect

Table 1

Attributes of Intercultural Healthcare Competence [1]

A culturally diverse staff that reflects the cultures served
Health care providers or interpreters who speak patients` language(s)
Training for health care providers about the culture and language of the people they serve
Signage and instructional literature in the patients` language(s) that is consistent with their cultural norms
Culturally specific health care settings

their ability to look at, understand and appreciate other belief systems [2, 3, 5, 6]. The more health care professionals know about someone's health care beliefs or practices, the better their care and treatment plans can take into account a patient's worldview that in most cases might be completely different from their own. Owing to that, health care in a multicultural environment can enhance medical providers' ability to communicate with patients from other cultures. At the same time, it must focus on the cultural beliefs and lifestyles of diverse groups and apply this knowledge to achieve culturally appropriate patient care. Still and all, in multicultural health care situations, health care providers must respect and, in more difficult cases, even explore patient's beliefs within the context of the patient's religion and culture rather than dismiss traditional practices (occult or holistic medical traditions and belief systems) that affect patients' acceptance of, and compliance with, treatment protocols [1, 2]. Moreover, beliefs of both provider and patient are influenced by social and cultural factors which are a huge challenge, and if not handled correctly, will adversely affect the clinical interaction [3–5]. Thus, when working in a multicultural environment, the first step is to understand the beliefs of the patient and his/her family, towards treatment goals. The next step is to identify a treatment plan that is acceptable to the patient, the family and the health care team [1, 2, 12]. Concern about the family is important because in many cultures health care decisions are not made solely by the patient but by the family as a team (Greece and Latin American countries). Furthermore, the delivery of satisfying health care to culturally diverse patients requires that their beliefs concerning the causes of illness, how illness should be treated and how it can be prevented in the future must be acknowledged and the best way to address cultural differences is through an open and balanced intercultural communication [1, 2].

Health care communication strategies

A communication strategy is a model or guide a health care provider can follow to help create effective messages for specific purposes [1]. To this end, health care communication strategies offer advice and/or suggestions about gaining insight into a patient's background, health care beliefs and help overcome barriers to effective communication between caregivers and patients. Conversely, there are eight barriers to effective communication in the health care setting: 1) lack of knowledge about the patient's background and beliefs, 2) patient fear and distrust of caregivers, 3) racism, 4) bias and ethnocentrism on the part of both caregivers and recipients, 5) mutual stereotyping, 6) ritualistic behavior, 7) differences in perceptions and expectations, and 8) language differences [1, 2, 4, 6]. Furthermore, the role of medical English can in many instances affect health care communication. Albeit it is obvious that language differences can complicate medical interactions, the use of medical jargon can also complicate health care instructions. For example, the use of words like "rhinitis" rather than hay fever, "anosmia" instead of loss of smell and "dementia" rather than memory loss can be rather confusing not only to native speakers of English, but to speakers of many other languages.

As a rule of thumb, conducting medical interviews is a primary technique used by physicians and other caregivers to elicit information about the patient necessary to make a diagnosis, determine what tests might be necessary and to ultimately treat an illness [2–4, 13, 14]. Nevertheless, every health care provider should bear in mind that when communicating with patients from different cultures during an intercultural medical interview, the care provider should ask the patient a series of questions that will elicit the information necessary to provide effective treatment. There are no strict rules to how to conduct the intercultural medical interview with the patient and the interview does not require a particular style but it actually encourages the individual physician to develop his/her own approach. What is important, however, is that, at the end of the interview, it is necessary to establish that both the doctor and the patient understand what occurred and what the plan for treatment is going to be. The easiest way to do this is to summarize the encounter for the patient and to get their agreement of the doctor's summary [3, 12–14].

The doctor also has to make sure that all of the patient's questions and concerns have been addressed. On the part of the patient it is important that intercultural rapport has been established because the patient needs to be able to depend on the fact that the doctor will be there in the future for them should they need him/her. Therefore, the doctor should discuss with the patient the next steps in his/her care, user-friendly and patient-centered compliance instructions, determine follow-up for a specific reason or at the very least reassure the patient that they are welcome to come back to see him/her again [12–15]. To this end, ten general strategies have been singled out for every health care provider to follow during the intercultural medical interview that will help in overcoming possible intercultural barriers [1–5, 12, 14, 15].

1. Do not treat the patient in the same manner in which you, as a health care provider, would want to be treated because each culture has a set of rules for polite, caring behavior that will, in the end of the day, determine the patient's concept of a satisfactory rapport.

2. Begin an interaction by being more formal with patients who were born in another culture because in many international cultures, there is a greater social distance between

caregiver and patient. This means that it is best to address the patient by his/her last name and maintain this formal relationship until the patient signals a different approach is appropriate: "Good afternoon Ms X. My name is Dr Y, specialist in hematology."

3. Allow patients to be open and honest because in most cases the patients are reluctant to tell caregivers that they are visiting a folk healer or are taking alternative medication concurrently with prescription drugs. A doctor should start with more relaxing questions. This will enable to create common ground: "Tell me Ms X, what is your present occupation? …How long have you been working there? …What exactly are your duties?" Once the doctor has established rapport with the patient together with the necessary introduction he/she can ask the patient to explain why they are there and let the patient tell their story in their own words: "Ms X, could you please tell me what sort of problems have you been experiencing?"

4. Do not disregard the possible effects of beliefs in the supernatural on the patient's health because if patients believe that their illness was caused by bewitchment, the evil eye or God's punishment they will not take responsibility for their cure. The following questions should suffice: "What do you call the illness? What do you think has caused the illness? Why do you believe the illness started when it did? How severe is the illness? What kind of treatment do you think is necessary? What are the most important results you hope to receive from this treatment? What are the main problems the illness has caused you? What do you fear most about the illness? Are you visiting a shaman or a holistic healer alongside?"

5. Inquire indirectly about the patient's belief in or use of nontraditional remedies and consequently ask the patient does he/she do too: "What treatments, if any, are you receiving and are you using folk medicines? What obstacles/factors would prevent you from being able to comply with the proposed treatment plan?" This may lead to negotiation with the patient to arrive at a mutually acceptable course of action.

6. Never try to force change or demand compliance from patients because a caregiver should be prepared to negotiate with the patient about the instructions he/she must follow on less critical health issues: "Ms. X, I believe that somewhere down that road we will have to take a turn, which means that you should start with antibiotics instead of the holistic medication you have been taking in order to make sure that the bacteria causing your illness is completely destroyed. This is the only way to avoid further deterioration of your health condition."

7. Always employ empathy in constructing messages because in most cases patients visit healthcare providers at a very vulnerable time in their lives when a patient has exhausted all attempts to care for him/herself at home. This is the point when a caregiver must show vulnerability, offer compassion and determine patients' views and beliefs in order to accurately decode verbal messages: "I am really worried about this lump. It is completely natural for you to have concern, and if you let me, I would like to ask you some questions so as to figure out what is going on." When the patient does reveal such information, the doctor should take a moment to explore what they have revealed i.e: "You mentioned you feel overwhelmed. Can you tell me more about that? You seem quite nervous. Can you tell me why you might be a bit anxious?"

More importantly, as the patient's health care provider, the doctor must put aside his/her own beliefs and values and refrain from projecting them onto the patient. The medical problem or issue is not about you, but about the patient and his/her belief system and the doctor needs to understand it from their perspective. Avoid judgmental language or nonverbal behaviors that the patient may interpret as disapproving (for instance making faces, frowning, nodding as a sign of disapproving). Encouragement is another key trait that also strengthens the intercultural patient-doctor rapport. The doctor should reinforce the patient's positive behaviors by offering them praise for the steps he/she has taken up to that point e.g: – It sounds like cutting back on smoking has been difficult for you, but I am glad to hear you have not given up trying. Have you tried nicotine patches?

8. Be careful in relating bad news. This means, that a health care provider must determine how much are patients able to deal with when their diagnosis is concerned and not abide by an American trait that the patient needs to know everything: "I feel a lump under your arm pit. What we need to do, in order to be sure that it is harmless, is run some tests and wait for the lab results. After they come out, we will determine the diagnosis and set up the appropriate type of treatment. Meanwhile, you can go home and continue with your daily activities."

9. Follow the patient's lead in communication style which means that if a health care provider is unaware of the patient's cultural rules in communication, he/she should observe how the patient communicates and follow suit. Thus, there are five verbal and nonverbal techniques that will help every health care provider to follow the patient's lead [1, 4, 5, 16]:

If the patient does not look you in the eyes when speaking, do not look the patient in the eyes but direct your gaze to whatever the patient is looking; Speak in the same manner as the patient which means if he/she speaks slowly and softly, speak the same way; Mirror the patient's handshake and apply the same pressure, rather than firmly squeezing his/her hand; If a patient allows a family member answer questions, refer to the family member and permit him/her to answer the questions; Observe the patient's physical comfort zone for interpersonal communication meaning that if the patient moves closer to you while engaged in conversation, do not back away and move out of his/her comfort zone.

10. Use the **LEARN** model (Table 2) as a comprehensive guide to interactions with patients coming from a different culture.

As a point of note, a health care provider should keep in mind that the above mentioned key points in an intercultural medical interwiew are by no means definitive, but should prove effective in the majority of communication situations in any culture.

Table 2

The LEARN Model [10]

Listen and ask questions to assess which words the patient uses to describe his/her illness, as well as what the patient believes is causing the illness.
Explain (using simple not medical language) what the patient needs to understand about his/her illness and the reasons for any required interventions.
Acknowledge that the patient's views may differ from your own and try not to devalue the patient's views.
Recommend what the patient should do. For instance, help him/her practice drawing insulin or changing a dressing.
Negotiate with the patient and adapt recommendations to the patient's views and daily patterns over aspects of the therapeutic plan

Conclusion

Living in a multicultural world not only opens a new world of opportunities but also brings myriad of challenges for all individuals. The cultural challenges especially, can be of significance for the individuals working in the health care setting as they often collect sensitive personal and private information about patients. In most cases, such information is subjected to culture specific behavior and rules of disclosure. Overtly, living in a multicultural world requires different sets of skills for a health care professional in order to competently and effectively maneuver intercultural interactions with patients. Accordingly, intercultural communication competence plays a significant role in preparing the health care professional to be an effective communicator in intercultural interactions. Pertaining to this, communicating health and illness across cultures is not an easy task. Until a health care provider actually overcomes cultural, and oftentimes, language barriers, the treatment and cure of the patient may be seriously hampered. Simply stated, an understanding of different cultural health belief systems, communication styles and individual beliefs will assist health care providers in becoming more attuned to the culturally based health expectations held by people whose cultural background is different from their own. Nevertheless, it is noteworthy to observe that people in all cultures go about their daily lives enacting health practices and values that are deeply rooted in their cultural experiences. Knowing how to approach a person from a different culture will enhance a health care provider with understanding of what happens to cultural knowledge when it crosses intercultural boarders. After all, effective communication between doctors and patients coming from different cultures is a central clinical objective and one of the first steps in building a successful intercultural rapport. Finally, building a successful intercultural rapport largely depends upon the effectiveness of communication between patients and doctors, the validity of the patient expectations and the ability of the doctor to fulfill them.

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SEMINAR PRAKTIČNOG LEKARA

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Najvažnije promene u Preporukama za kardiopulmonalnu resuscitaciju Evropskog resustitacionog saveta za 2010. u oblasti osnovne i napredne podrške života kod odraslih

Major changes in the European Resuscitation Council Guidelines for Cardiopulmonary Resuscitation 2010 in the field of Adult Basic and Advanced Life Support

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Key words:
resuscitation; guidelines as topic; monitoring, physiologic; heart arrest; electric countershock; drug therapy.

Uvod

Preporuke za kardiopulmonalnu reanimaciju 2010. god. rezultat su analize i sistematizacije objavljene literature iz oblasti resustitacione medicine u poslednjih pet godina. Ocenu i sintezu objavljenih podataka uradila je grupa eksperata, članova *International Liaison Commitetee on Resuscitation* (ILCOR) iz Evrope, Amerike, Kanade, Australije i Novog Zelanda, Afrike i Azije. Time je nastavljen petogodišnji ciklus ažuriranja i promene kliničkih vodiča kardiopulmonalne reanimacije (KPR), čime se sprovodioci kardiopulmonalne reanimacije obaveštavaju o terapijskim postupcima koji mogu uticati na ishod KPR. Naučni simpozijum ILCOR i završna debata i diskusija, održan je u Dalasu februara 2010, a zaključci i preporuke ovog sastanka bili su osnova za Preporuke Evropskog resustitacionog saveta, koje su objavljene u časopisu *Resuscitation* [1].

U ovom članku date su glavne promene u oblasti osnovne i napredne životne potpore odraslih, navedene u Preporukama za KPR iz 2010. u odnosu na Preporuke iz 2005, uz analizu razloga i očekivanih efekata ovih promena. Najznačajniji izazov u 2010. bio je da se pojednostave Preporuke za KPR, kako bi ih što više potencijalnih sprovodilaca oživljavanja, uključujući i laike, usvojilo i primenjivalo, čime se nastavlja tendencija Preporuka iz 2005. Naglašen je značaj osnovne životne potpore kao najbitnije za povećanje preživljavanja nakon iznenadnog srčanog zastoja.

Osnovna životna potpora kod odraslih

Algoritam postupaka pružanja osnovne životne potpore isti je kao i u Preporukama iz 2005. godine. Najvažnije novine u Preporukama iz 2010. godine su u sledećim oblastima:

Preporuka za dispečere hitnih medicinskih službi

Dispečeri bi trebalo da budu obučeni da ispituju pozivaoce po strogim protokolima, radi dobijanja informacija koje se odnose pre svega na reagovanje bolesnika (stanje svesti) i kvalitet disanja. Naglašena je važnost prepoznavanja agonalnog disanja (hvatanje vazduha), koje se javlja kod 40% bolesnika u prvim minutima nakon srčanog zastoja, kao indikacije za započinjanje KPR [1].

Preživljavanje nakon iznenadnog srčanog zastoja moglo bi biti udvostručeno ili utrostručeno ukoliko bi očevici srčanog zastoja pružili kvalitetnu KPR. Verovatnoća da će očevici pružiti efektivnu KPR veća je ako postoje jasne telefonske instrukcije zdravstvenih radnika za način vršenja kompresije grudnog koša i disanja usta na usta [2].

Naglašen značaj kompresija grudnog koša; Kardiopulmonalna reanimacija samo kompresijama

Svi spasioci, obučeni ili ne, trebalo bi da započnu kompresije grudnog koša kod unesrećenog koji ne reaguje i ne diše normalno. Naglašena je važnost pružanja kvalitetnih kompresija. Neophodno je da dubina kompresija bude naj-

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manje 5 cm (ali ne preko 6 cm), frekvencija najmanje 100/min (ali ne više od 120), da se nakon kompresije dozvoli kompletno vraćanje grudnog koša i da se prekidanje kompresija svede na minimum. Obučeni spasioci bi trebalo da primene i ventilacije, u odnosu kompresija : ventilacija – 30 : 2. Samo kompresije tokom KPR, uz telefonsko navođenje, prihvatljive su i trebalo bi da ih primenjuju neobučeni spasioci [1].

U novim preporukama još više se naglašava važnost kvalitetnih kompresija, koje bi trebalo što duže izvoditi u kontinuitetu. Previše spore ili plitke kompresije neće proizvesti dovoljan protok krvi u vitalnim organima (mozak, srce) [2]. Kada se kompresije ne vrše, nema ni protoka krvi. Merenja su pokazala da su po ponovnom započinjanju ciklusa kompresija, prvih nekoliko kompresija daleko manje efikasne od ostalih kompresija. Što ima više prekida u kompresijama, odnosno što je manji protok krvi ka vitalnim organima, to će ishod srčanog zastoja biti lošiji. Važno je da se dozvoli vraćanje grudnog koša u početni položaj nakon svake kompresije, jer to omogućava da krv ponovo napuni srce, što Preporuke iz 2010. posebno naglašavaju. Ako se ne dozvoli reekspanzija grudnog koša nakon svake kompresije, količina krvi koja puni srce neće biti adekvatna i protok krvi tokom naredne kompresije će biti manji.

Kardiopulmonalna reanimacija samo kompresijama prihvatljiva je ukoliko spasioci nisu obučeni ili nisu voljni da vrše ventilaciju metodom usta na usta. Studije na životinjama pokazale su da je i KPR bez ventilacija podjednako efikasna kao KPR sa ventilacijama u prvih nekoliko minuta, ukoliko uzrok srčanog zastoja nije bila asfiksija. Pasivno pomeranje grudnog koša tokom kompresija obezbeđuje određenu gasnu razmenu, ali ovo može rezultovati i ventilacijom mrtvog prostora. Studije na životinjama i studije matematičkog modela KPR samo sa kompresijama pokazale su da se zalihe arterijskog kiseonika iscrpe nakon 2–4 min. Ishod srčanog zastoja kada se radi KPR samo kompresijama znatno je bolji nego kada se KPR uopšte ne radi. Podaci studija govore da KPR samo kompresijama nije tako efikasna kao klasična KPR, kada srčani zastoj nije srčanog porekla (npr. utopljenje ili gušenje) [2]. Stoga, kombinacija kompresija i ventilacija ostaje metoda izbora kada KPR pružaju medicinski profesionalci ili obučeni laici. Laike treba ohrabriti da pružaju KPR samo kompresijama ukoliko nisu osposobljeni ili ne žele da rade ventilacije.

Poboljšanje efikasnosti i kvaliteta kardiopulmonalne reanimacije

Preporučuje se upotreba uređaja za KPR koji odmah daju povratnu informaciju o kvalitetu KPR [1].

Studije pokazuju da i zdravstveni radnici ne rade dovoljno brze i duboke kompresije, kao i da prave nepotrebno duge pauze u kompresijama grudnog koša, tokom pružanja osnovne životne potpore. Upotreba aparata za reanimaciju kojima se prati kvalitet KPR i informacije o tome čuvaju u memoriji, omogućila bi kasniju analizu rada zdravstvenih radnika i poboljšanje kvaliteta rada. Uređaji sa navođenjem i mogućnost kasnije analize pomažu u usvajanju i poboljšavanju veština KPR i treba ih koristititi i tokom obuka i vežbe na lutkama [2].

Napredno održavanje života kod odraslih

U preporukama iz 2010. najvažnije promene su u oblastima prevencije srčanog zastoja.

Naglašena je važnost primene *track and trigger* (pratititi i reagovati) sistema, kako bi se na vreme prepoznalo pogoršanje kod bolesnika i primenio tretman koji bi sprečio srčani zastoj kod hospitalizovanog bolesnika [1].

Za svakog bolesnika trebalo bi napisati plan praćenja vitalnih parametara u odnosu na ozbiljnost njegovog stanja. Mogu se koristiti skorovi za rano prepoznavanje ugroženih bolesnika – *early warning scores* (EWS), kao kriterijumi za pojačano praćenje, lečenje ili poziv za stručnu pomoć. Ukoliko je bolesnik u kritičnom stanju potrebno je da reaguju posebni timovi koji se formiraju u okviru bolnice, a u njihov sastav ulazi osoblje obučeno za reanimaciju (npr. osoblje Jedinice za intenzivnu terapiju). Prevencija intrahospitalnog srčanog zastoja zahteva edukaciju osoblja, praćenje bolesnika, ustanovljen sistem poziva pomoći i efikasan odgovor [3].

Povećana opreznost kod prisustva znakova koji upozoravaju na mogući iznenadni srčani zastoj van bolnice

Većina žrtava iznenadne srčane smrti ima od ranije poznato srčano oboljenje i znake upozorenja, najčešće bol u grudima, sat vremena pre srčanog zastoja. Podaci istraživanja pokazuju da ove simptome, uz palpitacije ili sinkopu, imaju i naizgled zdrave, mlađe žrtve srčanog zastoja. Ovi znaci moraju se prepoznati na vreme i pozvati pomoć stručnjaka [3].

Kompresija grudnog koša

Pri primeni kompresija grudnog koša naglašena je važnost minimalnog prekidanja visokokvalitetnih kompresija grudnog koša prilikom sprovođenja bilo kojih intervencija za napredno održavanje života (*advanced life support* – ALS): kompresije se prekidaju samo nakratko kako bi se omogućila neka intervencija [3].

Defibrilacija

Kompresije se sprovode i tokom punjenja defibrilatora – ovo skraćuje pauzu u kompresijama pre isporuke šoka [4].

Kratka pauza u kompresijama sprovodi se samo tokom analize ritma i tokom primene šoka. Nakon primenjenog šoka odmah se nastavlja KPR koja započinje kompresijama u trajanju od 2 min, a potom se vrši analiza ritma, odnosno efekata defibrilacije [4]. Ako je pokušaj defibrilacije bio uspešan i uspostavljen perfuzioni ritam, potrebno je vreme da se uspostavi i cirkulacija. Zato ne treba gubiti vreme na proveru pulsa neposredno posle primene šoka. Ako šok nije eliminisao ventrikularnu fibrilaciju/ventrikularnu tahikardiju (VF/VT), kompresije će obezbediti perfuziju miokarda i povećati šanse da naredni šok bude uspešan.

Preporučuje se primena tri uzastopna šoka pri pojavi ventrikularne fibrilacije/tahikardije tokom kateterizacije srca ili tokom ranog postoperativnog perioda nakon operacija na srcu [4].

Preporuke iz 2005, takođe, ne predviđaju primenu tri vezana šoka, jer je masovnom primenom bifazičnih defibrilatora porastao procenat uspešnosti prvog šoka [5, 6]. Kod primene šoka monofaznim defibrilatorom koji su ranije bili u upotrebi, prvi šok je često bio neuspešan. Vezana, brza isporuka tri šoka smanjuje transtorakalnu impendancu, pa su izgledi za eliminisanje VF znatno veći, i zbog toga su preporuke iz 2000. savetovale primenu tri vezana šoka. Novo je da preporuke iz 2010. ponovo predviđaju primenu tri uzastopna šoka, ali samo pri pojavi ventrikularne fibrilacije/tahikardije tokom kateterizacije srca ili tokom ranog postoperativnog perioda nakon operacija na srcu [4]. Iako nema dokaza za ovakav stav, pretpostavlja se da je malo verovatno da će kompresije grudnog koša dodatno poboljšati već velike šanse za povratak spontane cirkulacije (ROSC) kada se defibrilacija radi u ranoj električnoj fazi, odmah nakon pojave fibrilacije što je slučaj kod ovih praćenih bolesnika, pa stoga ih ne treba ni raditi. Osim toga, u ranoj postoperativnoj fazi kompresije mogu pokidati šavove na krvnim sudovima [4].

Više ne važe preporuke za određeni period KPR (2 min) pre defibrilacije, kod bolesnika sa produženim kolapsom (> 5 min) [1].

Ova preporuka najčešće se odnosila na nastanak srčanog zastoja van bolnice, kada je prošlo više od 4 do 5 min od poziva (nastanka srčanog zastoja) do stizanja hitne ekipe [6]. Nedavna randomizovana kontrolisana ispitivanja pokazala su da period od 1,5 do 3 min KPR pre defibrilacije ne povećava izglede za ROSC ili preživljavanje i otpuštanje iz bolnice, kao ni jednogodišnje preživljavanje kod srčanog zastoja sa VF/VT. Ostavlja se mogućnost da se sa ovom praksom nastavi zbog nedostatka podataka koji ili podržavaju, ili odbacuju ovu strategiju [4].

Prekordijalni udar

Značaj prekardijalnog udara u novim preporukama nije naglašen [1]. Spasilac bi trebalo da ga primenjuje samo ukoliko je svedok nastanka srčanog zastoja uzrokovanog aritmijom ili tahikardijom, a defibrilator nije odmah dostupan [3].

Disajni put i ventilacija

U novim preporukama umanjena je važnost rane intubacije, osim ako je mogu izvesti veoma stručna lica, uz minimalan prekid kompresija grudnog koša [1].

Tokom laringoskopije kompresije se ne prekidaju. Kratka pauza može se napraviti tokom plasiranja tubusa između glasnih žica. Postoje dokazi da je izvođenje endotrahealne intubacije, od strane nedovoljno iskusnog osoblja praćeno brojnim komplikacijama i u velikom procentu neuspešno. Tokom brojnih pokušaja prave se veliki prekidi u kompresijama grudnog koša. Plasiranje supraglotičnih sredstava može se izvesti bez prekidanja kompresija [3].

Naglašena je važnost primene kapnografa kako bi se potvrdio i pratio položaj tubusa u traheji, kvalitet KPR i kako bi se uočili rani indikatori povratka spontane cirkulacije (ROSC) [1].

U preporukama iz 2005. akcenat je bio na primarnoj, kliničkoj potvrdi ispravnog položaja tubusa, a primena kapnografa smatrana je dodatnom potvrdom kliničke procene.[5] Međutim, istraživanja pokazuju da klinička procena (posmatranje podizanja grudnog koša, auskultacija grudnog koša obostrano u aksilama i iznad epigastrijuma) nije sasvim pouzdana [3].

Primena lekova

Davanje lekova preko endotrahealnog tubusa se više ne preporučuje; ukoliko se ne može obezbediti intravenski put, lekove treba davati intraosealnim putem [1].

Kanulacija perifernih vena tokom KPR je brža, jednostavnija i sigurnija od kanulacije centralnih vena. Ukoliko je nemoguće obezbediti intravenski put, lekove treba davati intraosealnim putem, jer se adekvatna koncentracija leka u plazmi postiže za vreme slično onom kada se lek primeni centralnim venskim putem. Za razliku od preporuka iz 2005. koje su ostavljale mogućnost davanja lekova endotrahealno [5], u vodičima za KPR iz 2010. ovaj način se izričito ne preporučuje, jer su brzina apsorpcije, kao i potrebne endotrahealne doze za dostizanje potrebne koncentracije leka u plazmi nepoznate. Danas je, takođe, široko dostupna komercijalna oprema koja znatno olakšava intraosealni pristup [3].

Kada se tretira srčani zastoj uzrokovan VF/VT, adrenalin 1 mg daje se nakon trećeg šoka kada se nastave kompresije, a potom svakih 3–5 min (tokom ciklusa KPR). Amjodaron 300 mg daje se takođe, nakon trećeg šoka [1].

Nijedna od sprovedenih kliničkih studija nije dokazala da primena bilo kog vazopresora tokom KPR povećava stopu dugoročnog preživljavanja i oporavka bez neuroloških posledica nakon srčanog zastoja. Za razliku od preporuka iz 2005. koje su savetovale primenu adrenalina nakon drugog ili čak nakon prvog šoka [5], preporuke iz 2010. predviđaju davanje adrenalina nakon trećeg šoka po započinjanju kompresija grudnog koša. Ako je nakon šoka uspostavljena spontana cirkulacija, bolus adrenalina može izazvati tahikardiju i hipertenziju i precipitirati ponovnu pojavu VF. Međutim, ako ROSC nije uspostavljen nakon trećeg šoka, adrenalin će popraviti miokardni krvni protok i povećati izglede za uspešnom defibrilacijom u narednim pokušajima. Vazopresin nije uključen u algoritam iz 2010. za razliku od preporuka iz 2005. kojima se navodi da se jedna doza adrenalina može zameniti vazopresinom. Ne treba prekidati kompresije grudnog koša radi davanja lekova. Amjodaron se, takođe, daje nakon trećeg šoka u slučaju perzistentne, refraktarne VF/VT, u dozi od 300 mg, intavenski. U slučaju rekurentne VF/VT može se primeniti još jedna doza od 150 mg, a nakon toga 900 mg, tokom 24 h, u kontinuiranoj infuziji [3].

Atropin se više ne preporučuje za rutinsku primenu kod asistolije ili bezpulsne električne aktivnosti (PEA) [1].

Asistolija tokom srčanog zastoja primarno je uzrokovana oboljenjem miokarda, a ne ekscesivnim nadražajem vagusa. Rezultati nedavnih studija, takođe, ne pokazuju korist od primene atropina tokom srčanog zastoja [3].

Potencijalno reverzibilni uzroci srčanog zastoja

Utvrđen je potencijalni značaj ultrazvučnog snimanja tokom ALS. Tokom srčanog zastoja i sprovođenja KPR mora se tragati za reverzibilnim uzrocima srčanog zastoja i oni se bez odlaganja moraju tretirati. Kada je dostupan ultrazvu-

čni aparat i postoji obučeno osoblje za njegovu primenu, ehokardiografija je izuzetno korisna metoda za dijagnozu reverzibilnih uzroka srčanog zastoja: tamponade miokarda, plućne embolije, disekcije aorte, hipovolemije, pneumotoraksa [3].

Postresustitaciono lečenje

Sindrom nakon srčanog zastoja uključuje postreanimaciono oštećenje mozga, postreanimacionu miokardnu disfunkciju i sistemski odgovor organizma na ishemiju/reperfuziju, kada se aktiviraju imunološke i koagulacione kaskade, što može dovesti do multiple organske disfunkcije. Težina ovog sindroma zavisi od uzroka i trajanja srčanog zastoja. Nove preporuke naglašavaju značaj lečenja i prevencije faktora koji dovode do daljeg oštećenja organa nakon uspostavljanja ROSC [3].

Utvrđeno je da implementacija sveobuhvatnog, strukturisanog protokola postreanimacionog lečenja može povećati stopu preživljavanja žrtava srčanog zastoja nakon ROSC [1].

Naglašen je značaj primene primarnih perkutanih koronarnih intervencija kod odgovarajućih bolesnika sa ROSC nakon srčanog zastoja (uključujući i komatozne) [1].

Nekoliko studija pokazalo je superiornost koronarne angioplastike kod bolesnika sa STEMI u odnosu na fibrinolizu (praćeni su mortalitet i reinfarkcija). Osim toga fibrinoliza je efikasna ukoliko se primeni 2–3 h od nastanka simptoma. Efektivnost perkutanih koronarnih intervencija manje zavisi od vremena [3].

Izmenjena je i preporuka za kontrolu glikemije: kod odraslih sa postignutim ROSC nakon srčanog zastoja glikemiju preko 10 mmol/L treba lečiti, ali se hipoglikemija mora izbeći.

Visoka vrednost glikemije nakon reanimacije udružena je sa lošim neurološkim oporavkom nakon srčanog zastoja. Međutim, istraživanja su dokazala veći mortalitet bolesnika kod kojih je glikemija striktno kontrolisana (4,5–6 mmol/L) u odnosu na one kod kojih je primenjen konvencionalni režim kontrole glikemije (10 mmol/L ili manje) [3].

Utvrđena je i potencijalna štetnost hiperoksemije nakon postizanja ROSC. Kada se vrati spontana cirkulacija i kada se saturacija arterijske krvi (SaO_2) može pouzdano meriti, inspiratornu koncentraciju kiseonika treba titrirati tako da se postigne SaO_2 od 94 do 98%.

Nekoliko studija na životinjama ukazuju da hiperoksemija izaziva oksidativni stres, što u postishemičnoj fazi može izazvati dalje oštećenje neurona. Nema podataka koji parcijalni pritisak CO_2 bi bilo najbolje održavati nakon postizanja ROSC, ali se čini najlogičnijim da treba održavati normokarbiju [3].

Primena terapijske hipotermije kod komatoznih bolesnika uključuje kako one koji su inicijalno imali „šokabilni" ritam, tako i one sa inicijalno „nešokabilnim ritmom". Priznat je manjak dokaza za njenu primenu nakon srčanog zastoja sa „nešokabilnim" ritmom [3].

Istraživanja na životinjama i ljudima dokazuju da blaga hipotermija ima neuroprotektivni efekat, smanjuje cerebralnu metaboličku potrošnju kiseonika, smanjuje oslobađanje ekscitatornih amino-kiselina i slobodnih radikala i smanjuje inflamatorni odgovor organizma nakon srčanog zastoja [7]. Zato se, za razliku od preporuka iz 2005, savetuje hlađenje bolesnika i nakon srčanog zastoja sa „nešokabilnim" ritmom.

Utvrđeno je da su mnogi od prihvaćenih prediktora lošeg ishoda kod preživelih bolesnik u komi nakon srčanog zastoja nepouzdani, naročito ako je bolesnik bio tretiran terapijskom hipotermijom [3].

U vremenskom periodu kraćem od 24 h nakon srčanog zastoja nijedan od kliničkih neuroloških znakova nije pouzdani prediktor lošeg ishoda. Odsustvo kornealnog refleksa i odsustvo pupilarne reakcije na svetlost nakon 72 h smatra se pouzdanim prediktorom lošeg ishoda. Međutim, odsustvo motorne reakcije na bol nakon tri dana od srčanog zastoja, kao i odsustvo vestibulookularnog refleksa, više se ne smatraju pouzdanim prediktorima lošeg ishoda. Bilateralno odsustvo kortikalnog odgovora nakon evociranih somatosenzornih potencijala *n. medianusa*, 72 h nakon srčanog zastoja, pouzdan je prediktor lošeg ishoda [8].

Zaključak

Preporuke za kardiopulmonalnu reanimaciju iz 2010. ukazuju na značaj ranog prepoznavanja vitalno ugroženih bolesnika i mogućnost prevencije srčanog zastoja od strane urgentnih, obučenih timova. Ističe se uloga osnovne životne potpore u povećanju stope preživljavanja žrtava iznenadnog srčanog zastoja. Spasilac mora primeniti kompresije grudnog koša adekvatne dubine i frekvencije i dozvoliti potpuno vraćanje grudnog koša nakon svake kompresije. Veoma je važno svesti na minimum prekide u kompresijama grudnog koša, kako u fazi pre i posle primene šoka, tako i tokom drugih intervencija tokom KPR. Povratak spontane cirkulacije samo je prvi korak ka potpunom oporavku bolesnika nakon srčanog zastoja. Lečenje postresustitacionog sindroma i drugih precipitirajućih faktora neophodna je karika u lancu dobrog ishoda iznenadnog srčanog zastoja.

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K A Z U I S T I K A

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Uticaj lokalizacije miksoma srca na klinički tok i ishod bolesti

Impact of heart myxoma localization upon its clinical course and outcome

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Apstrakt

Uvod. Primarni tumori srca su retki. Mogu biti benigni i maligni. Benigni tumori čine oko dve trećine svih tumora srca i benigni su samo po svojim biološkim karakteristikama, ali su potencijalno maligni. Oko tri četvrtine benignih tumora su miksomi. Rast miksoma obično je spor i može ostati dugo bez simptoma, naročito ako ne kompromituje vitalne funkcionalne delove srca. Miksomi rastu u pretkomorama, uglavnom levoj, a veoma retko i u komorama. **Prikaz bolesnika.** Prikazane su dve bolesnice sa miksomima leve, odnosno desne pretkomore koji predstavljaju reprezentativne uzorke za najčešće lokalizacije miksoma u srcu, uz poređenje dosadašnjih saznanja o ovim tumorima. Analiza kliničkog toka kod obe bolesnice pokazala je opšte karakteristike kliničkog toka miksoma srca. Bolesnice su bile bez karakterističnih tegoba u dužem vremenskom periodu, a standardnim pregledima nisu dobijeni nalazi koji su pobuđivali sumnju na tumor srca. Kod jedne bolesnice je plućna, a kod druge kardijalna simptomatologija, u periodu kada je tumor ispunjavao gotovo celu pretkomoru, navela na kardiološko ispitivanje. Kod obe bolesnice indikacija za operaciju data je nakon ehokardiografije, kompjuterizovane tomografije grudnog koša i angiografije srca sa ventrikulografijom. Veličina izvađenih tumora iz pretkomora i njihova lokalizacija objašnjavale su deo smetnji koje su bolesnice imale, ali izazivale su i čuđenje da smetnje nisu bile veće. Operacija, kao jedini vid lečenja, bila je uspešna kod obe bolesnice, sa trajnim efektom. U višegodišnjim kontrolama nije zapažen recidiv tumora, a smetnje koje su se mogle vezati za miksom povukle su se. **Zaključak.** Bolesnici sa miksomom srca obično prolaze kroz asimptomatsku ili oligosimptomatsku fazu, a kada smetnje postanu izražene ne razlikuju se mnogo od smetnji izazvanih drugim uzrocima. To je razlog što se ovaj tumor otkriva tek kada nastanu komplikacije uzrokovane njegovim položajem i rastom. Savremena kardiološka dijagnostika, prvenstveno neinvazivna ehokardiografska, omogućavaju da se miksom srca na vreme otkrije i odstrani jer tek tada može da nosi pravi naziv – benigni tumor.

Ključne reči:
miksom; srce, pretkomora; srce, komora; dijagnostičke tehnike i procedure; dijagnoza, diferencijalna; hirurgija, kardijalna, procedure.

Abstract

Introduction. Primary heart tumors are very rare. They can be benign and malignant. Benign ones make about two thirds of all heart tumors. However, they are benign only by their biologic characteristics, but potentially malignant by their localization. About three forths of benign tumors are myxomas. Their growth is usually slow and they can be for a long time silent, particularly if they do not compromise vital functional parts of the heart. Myxomas grow in the atria, mostly in the left one and very rarely in the ventricles. **Case report.** We presented two patients with myxomas in the left, and, in the right atrium which are representative samples of the most common localization of heart myxoma considering previous knowledge of these tumors. Analysis of the clinical course in the two presented patients with characteristic localizations showed general characteristics of the clinical course of heart myxoma. The patients did not have characteristic symptoms for a rather long period of time and the findings obtained by standard examinations did not raise suspicion of heart tumor. Pulmonary symptomatology in one patient and cardial in the other, when tumor had already occupied almost the entire atrium, suggested necessity of cardiologic examination. Indication for operation was in both patients confirmed after performed echocardiography, computed tomography of the thorax and angiography with ventriculography. The size of the removed atrial tumors and their localization explained some of the patients' troubles, but it was also amazing that they had not caused more serious problems. Operation as the only

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method of treatment was successful in both female patients and its effect was permanent. At annual controls neither recurrence of the tumor nor troubles possibly associated with it were observed. **Conclusion.** Patients with heart myxoma usually pass through asymptomatic or oligosymptomatic phase, but when troubles become manifested, they do not much differ from those due to other causes. For this reason this tumor can be diagnosed just when complications caused by its localization and growth develop. Modern cardiologic diagnostics, primarily preventive non-invasive echocardiography, enables timely diagnosis and removal of the tumor because only then it may take a name benign tumor.

Key words:
myxoma; heart atria; heart ventricles; diagnostic techniques and procedures; diagnosis, differential; cardiac surgical procedures.

Uvod

Tumori srca mogu biti benigni i maligni, primarni i sekundarni. Benigni tumori srca uvek su primarni i dva puta su češći od primarnih malignih tumora. I jedni i drugi su veoma retki [1]. S druge strane, sekundarni maligni tumori srca veoma su česti: gotovo da svaki četvrti maligni tumor iz organizma daje metastaze i u srce, najčešće u svojoj terminalnoj evoluciji [2].

Benigni tumori srca su, međutim, dobroćudni samo po svojim biološkim karakteristikama, ali su po svojoj lokalizaciji potencijalno maligni. Najčešći benigni tumori srca su miksomi koji čine oko tri četvrtine svih benignih tumora u srcu [2–4]. Najčešće preko 90% javljaju se u srednjem životnom dobu (30–60 godina) [5, 6]. Rast miksoma obično je spor i može ostati dugo bez simptoma, naročito ako ne kompromituje vitalne funkcionalne delove srca.

Prvi opis tumora u srčanoj šupljini koji je podsećao na miksom dao je Colombo, još 1559. godine. Pri obdukciji našao je veliki viseći tumor u levom srcu, veličine kokošijeg jajeta. Stotinak godina kasnije Piscini opisuje tumor u srcu koji naziva polip srca, a koji bi po opisu mogao odgovarati miksomu. Tek Lorne, 1869. godine, sličan polip u srcu naziva miksomatozni polip. Razlikovao ga je od tromba u srcu nalaženog pri obdukciji. Od tada raste interesovanje patologa za ove izrasline u srcu koje su nalazili na autopsijama, a koje su opisivali sa različitih aspekata. Do prve polovine XX veka miksom nije za života otkrivan, tj. isključivo je otkrivan na autopsijama.

Prvi miksom za života bolesnika dijagnostikovali su Goldberg i sar. 1952. godine [7]. Dve godine kasnije urađena je i prva uspešna operacija miksoma od strane Crafoorda [8]. Godine 1961. Papo i sar. [9] uradili su prvu uspešnu operaciju miksoma u našoj zemlji. Operacija miksoma srca u to vreme postaje rutinska metoda lečenja. U Vojnomedicinskoj akademiji u Beogradu, u periodu od 1961. do 2009. godine operisan je 61 bolesnik sa miksomom srca [10].

Većinu autora miksom srca podsećao je na organizovani tromb. Teorija da je to organizovani tromb koji je nastao na lediranom delu endokarda, sa alteracijom ćelija u njemu stara je preko 100 godina i još uvek je aktuelna u nekim izveštajima [11, 12].

Miksomi najčešće rastu u levoj pretkomori, znatno ređe u desnoj, a veoma retko u komorama [3, 10, 13, 14]. Simptomatologija je različita i zavisi od lokalizacije, veličine i brzine rasta tumora. Može proći više godina dok se ne ispolji.

Cilj rada bio je da se prikaže klinički tok kod dva naša bolesnika sa lokalizacijom miksoma u levoj, odnosno desnoj pretkomori (gde inače najčešće izrastaju) i da se analizira njihov klinički tok pre i posle operacije, a nalazi uporede sa dosadašnjim saznanjima o ovom tumoru.

Prikaz bolesnika

Iz analize bolesnika koji su dijagnostikovani i lečeni u našoj ustanovi proteklih oko 5 decenija, u periodu od 1961. do 2009. godine, odabrana su dva bolesnika kod kojih je klinički tok bio nekarakterističan za proces kakav je tumor u srcu, što inače odlikuje miksome srca. Operacijom miksoma, koja se danas izvodi gotovo bez rizika, otklanjaju se sve tegobe koje se inače mogu vezati za sam tumor, a kasnije kontrole uglavnom služe za otkrivanje eventualnog recidiva, čemu su skloni ovi tumori. Kod dva opisana bolesnika operacijom su odstranjeni miksomi što je dovelo do postepenog povlačenja kardioloških smetnji do kojih su oni doveli.

Odabrane su dve bolesnice, sličnog životnog doba, jedna sa miksomom leve, a druga desne pretkomore. Kada su se pojavile smetnje koje je uzrokovao miksom, kod jedne se javila pulmonalna, a kod druge dominantno kardiološka simptomatologija. Dijagnostička procedura bila je karakteristična za ispitivanje tumora u srcu. Rađeni su radiografija pluća, ehokardiografija, kompjuterizovana tomografija grudnog koša i selektivna angiografija srca sa ventrukolografijom, a posle operacije i histopatološko ispitivanje.

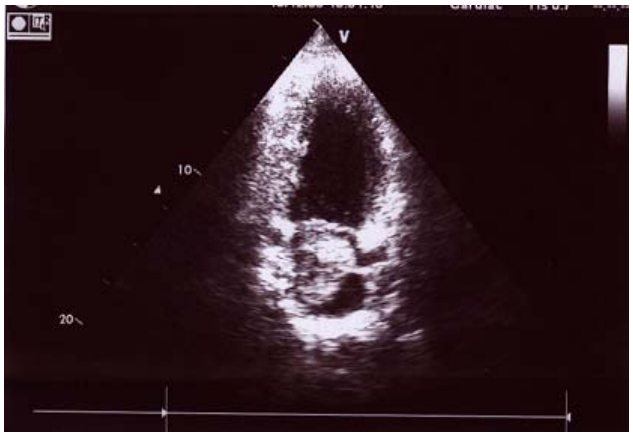
Prva bolesnica, stara 58 godina u vreme dijagnostikovanja miksoma leve pretkomore, nije imala većih tegoba koje bi karakterisale ovaj tumor u srcu sve do nekoliko meseci pre dijagnostikovanja. Kardiološko ispitivanje usledilo je aprila meseca 2001. godine nakon učestalih prekordijalnih bolova koji su imali karakter angine pektoris. Sve češće je imala produktivan kašalj koji je pri naprezanju bio sukrvičav. Kako je bila dugogodišnji pušač, posumnjalo se na tumor pluća zbog čega je započeto kliničko ispitivanje.

U fizikalnom nalazu bio je izražen aspekt anemijskog sindroma, opšte stanje bilo je dobro, *Karnofsky* skor iznosio je 90/100. Nije bilo znakova kardiorespiratorne insuficijencije u miru. Auskultatorno, na plućima imala je difuznobronhitične šušnjeve. Akcija srca bila je ritmična sa ređim ekstrasistolama (ES), blag sistolni šum nad mitralnim ušćem, nešto tiših tonova. Jetra se palpirala za 1 cm ispod rebarnog luka. Arterijski pritisak 150/80 mmHg.

Na elektrokardiografiji (EKG) sem registrovanih ventrikularnih ekstrasistola (VES) nije bilo drugih promena. Radiografija pluća i srca pokazala je pojačan bronhovaskularni

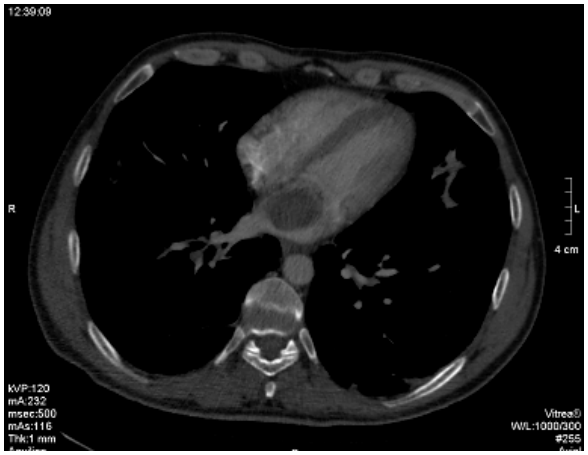
crtež sa voluminoznijim desnim hilusom i srce miopatske konfiguracije.

Ehokardiografija je pokazala vidljiv tumor u levoj pretkomori sa insercijom uz fosu ovalis, promera 41 × 30 mm (slika 1). Sistolna funkcija srca bila je dobra (ejekciona frakcija – EF 60%).

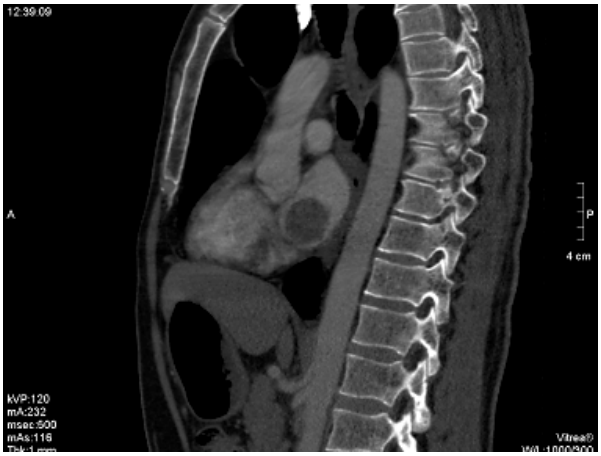


Sl. 1 – Ehokardiografija: miksom u levoj pretkomori kod prve bolesnice

Na kompjuterizovanoj tomografiji (KT) viđen je tumor koji je ispunjavao levu pretkomoru (slike 2 a i b).



a)



b)

Sl. 2, a i b – Kompjuterizovana tomografija miksoma u levoj pretkomori kod prve bolesnice

Selektivna koronarografija sa ventrikulografijom pokazala je vidljiv tumor u levoj pretkomori osobina kao na ehokardiografiji, koji se uskom peteljkom pripajao za endokard. Uočena je i značajna redukcija lumena.

Urađena bronhoskopija zbog sumnje i na bronhopulmonalni infiltrativni proces nije ukazivala na maligni proces.

U biohemizmu krvi sedimentacija (SE) je bila 17 u prvom satu, hemoglobin (Hb) 119 g/L, eritrociti (Er) 3,9 × 10^{12}/L, MCV (*mesu cell volume*) 92 FL 9, trombociti (Tr) 202 × 10^{9}/L, glikemija 6,9 mmol/L, holesterol 3,6 mmol/L, trigliceridi 2,8 mmol/L.

Urađena je hirurška intervencija sa uspešnim odstranjenjem miksoma iz leve pretkomore koji je skoro ispunjavao pretkomoru. Tumor je bio vezan za endokard u širini pripoja oko 1,2 cm. Tumor je bio elastičan, na preseku beličast, bez mikrocističnih formacija. Histološki nađene su karakteristične miksomske ćelije sa zvezdastim produžecima koji su se mestimično spajali. Prokrvljenost tumora bila je slaba.

Posle operacije stanje bolesnice se normalizovalo. Na kontrolnim ehokardiografijama nije uočavan recidiv miksoma. Kontrolisana je oko osam godina nakon operacije miksoma.

Druga bolesnica, stara 46 godina u vreme dijagnostikovanja miksoma desne pretkomore decembra meseca 2008. godine, oko dve godine osećala je povremeno brže zamaranje koje je nije ometalo u normalnoj fizičkoj aktivnosti. Stanje se potom postepeno pogoršavalo sa otežanim disanjem i gušenjem pri većem a kasnije i manjim naporima. Kašalj je bio suv, nadražajan. U ovim stanjima primećivala je da ima modrije usne. Sve češće imala je osećaj lupanja srca sa stezanjem u sredogrudju, što se sve spontano smirivalo nakon odmora. Ovi „napadi“ sve više su je uznemirivali, ali se duže vreme nije obraćala lekaru. Kada je započeto ispitivanje nije imala većih tegoba, ali je pri pregledu bila naznačena laka cijanoza akralnih delova. Bile su vidljive pulsacije perifernih arterija, posebno na vratu. Na plućima je auskultatorni nalaz bio normalan. Srce je bilo u sinusnom ritmu sa pojedinačnim VES, uz slabije čujne tonove i povremeno čujan III ton. Nije imala organomegaliju ni periferne edeme.

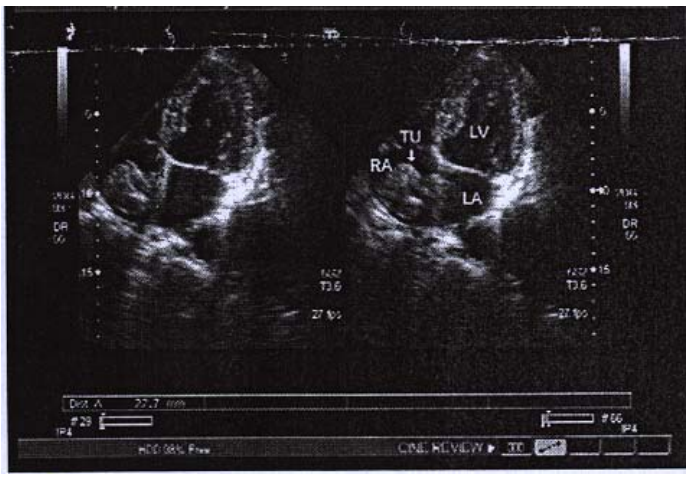
Na EKG-u registrovan je sinusni ritam, niži QRS kompleks, P talas proširen, bifazičan. Laboratorijski nalazi bili su normalni, sem lako ubrzane sedimentacije (SE – 32 u prvom satu. Radiografija pluća i srca nije pokazivala patološke promene.

Na ehokardiografiji viđen je veliki tumor u desnoj pretkomori (slika 3).

Na kompjuterizovanoj tomografiji viđen je tumor koji je ispunjavao veći deo desne pretkomore.

Angiografijom srca sa ventrikulografijom potvrđen je tumor u desnoj pretkomori promera oko 5 cm koji je ispunjavao gotovo celu pretkomoru.

Operisana je uspešno pri čemu je izvađen miksom iz desne pretkomore koji je bio širom peteljkom urastao u endokard, blizu fose ovalis. Nakon operacije vremenom su se



Sl. 3 – Ehokardiografija: miksom u desnoj pretkomori kod druge bolesnice

povukle sve tegobe vezane za tumor, a fizikalni nalaz se normalizovao. U desetomesečnom praćenju postoperativnog toka ehokardiografskim pregledima na tri meseca, nije utvrđen recidiv.

Makroskopski izgled izvađenih miksoma kod naših bolesnica bio je karakterističan: bledobeličaste boje, nepravilnog oblika, glatke površine sa prekidom na mestu pripajanja, meke konzistencije.

Mikroskopski nalaz miksoma, takođe, bio je karakterističan: nisu nađene druge ćelije sem miksomskih, a želatinozni matriks nije bio mnogo zastupljen (kao što se obično nalazi). Viđene su male poligonalne, okruglaste, vretenaste i zvezdaste ćelije, međusobno mestimično povezane.

Diskusija

Prikazane bolesnice imale su karakterističnu lokalizaciju miksoma srca u levoj, odnosno desnoj pretkomori, sa smetnjama koje su mogle ukazivati na poremećaj u srcu, ali su smetnje bile promenljive, a na tumor se nije mislilo.

Slična lokalizacija ovih tumora nalažena je kod velike većine lečenih od miksoma u Vojnomedicinskoj akademiji, prema analizi iz perioda od 1961. do 2009. godine. Od 61 bolesnika sa miksomom srca čak 98,4% imalo je miksome u pretkomorama. Zapravo, samo jedna bolesnica imala je miksom u levoj komori. Izrastanje miksoma sa međupretkomorske pregrade u samu pretkomoru bilo je karakteristično kod naših bolesnica, kao i kod većine lečenih bolesnika sa miksomom.

I naše bolesnice, kao i većina bolesnika iz ove hirurške serije, imale su miksom sa rastom blizu fose ovalis, što se i inače najčešće sreće. Veza miksoma za endokard je kod naših bolesnica bila u obliku polipoidne peteljke, koja se i inače sreće u ovim lokalizacijama miksoma. Miksom se najčešće veže uskom trakom za međupretkomorsku pregradu, bilo sa leve ili desne strane, zavisno od šupljine u kojoj raste. Kada je miksom na širokoj osnovi, svojom veličinom ometa funkciju, a kad je na tanjoj peteljci može se ponašati kao čep koji po ventilnom sistemu delimično zatvara srčano ušće ispred koga se tumor formira. Kod naših bolesnica taj fenomen nije zapažen, iako je kod jedne od njih miksom gotovo u potpunosti ispunio pretkomoru.

Miksom je dobio naziv po mukopolisaharidnom matriksu u svom tkivu. Još uvek nije dovoljno poznata njegova histogeneza. Obično raste iz endokarda, uglavnom u pretkomorama, najčešće blizu fose ovalis. Hromozomske abnormalnosti nalažene su u miksomima [15].

U svom izvornom ćelijskom sastavu potiče od ćelija sluzavog tkiva koje postoji samo u razvojnoj fazi fetusa. Pravog sluzavog tkiva nema kod odraslih ljudi, pa je teško reći otkud tumor sluzavog vezivnog tkiva kod odrasle osobe, na šta asocira miksom svojom vanćelijskom arhitekturom (*myxa* – sluz). Sam tumor nastao je od multipotentne izvorne vezivne ćelije opredeljene za sluzavo vezivno tkivo [16].

U miksomima se može naći želatinozna acelularna masa nalik na tromb. Kada tumor potekne iz veće dubine mogu se u njemu naći i glatke mišićne ćelije. Ako ima više vezivnih ćelija tkivo ovog tumora asocira na fibrom [15].

Iz navedene serije lečenih miksoma u VMA, samo jedna bolesnik (1,6%) imao je biatrijalni rast, tj. rastao je sa obe strane interatrijalnog septuma. Ova pojava nije tako česta i nalazi se kod najviše 5% bolesika sa miksomima [3, 10, 14]. Najčešće su, pojedinačni, ređe multiple lokalizacije. Kad su multipli obično ne rastu uz fosu ovalis.

Čest je nalaz tromba na površini miksoma, što nije zapaženo kod naših bolesnica. Takođe, nije zapažena znatnija vaskularizacija tumora niti kalcifikacija miksoma, što se inače nalazi u ovim tumorima. Vaskularni splet može biti dosta vulnerabilan i doprineti nepovoljnijem kliničkom toku. Kalcifikacija i osifikacija miksoma ređe su pojave.

Miksomi najčešće sporo rastu. Potrebno je više godina da bi prominencija ovog tumora, posebno u srcu, izazvala prepoznatljive smetnje. Sličan tok imali su miksomi kod naših bolesnica. Kada se simptomatologija ispolji, može biti veoma različita i uslovljena je najviše lokalizacijom, a zatim brzinom rasta i veličinom miksoma. Različitost ispoljavanja koje je često netipično naveli su neke autore da ovaj tumor nazovu „veliki maskirant“. Obično treba više vremena od početka rasta miksoma do pojave karakterističnih smetnji. I kod naših bolesnica rast tumora duže vremena nije dao prepoznatljive smetnje.

Miksom vremenom izaziva poremećaje koji su najviše uslovljeni mestom izrastanja tumora. Miksom koji zatvara

mitralno ušće postepeno se ispoljava posledicama, sve do manifestne plućne hipertenzije koja se klinički ispoljava dispnejom, ortopnejom i progredijentnim umorom. Moguće su i iznenadne smrti kod ove lokalizacije miksoma, jer fragmenti miksoma mogu otići u koronarnu arteriju ili iznenada zatvoriti mitralno ušće. Veći miksomi znatno utiču na minutni volumen srca i na opštu hemodinamiku.

Osnovni klinički poremećaji u miksomima su posledica opstrukcije protoka, okluzije ušća i embolizacije tkivom miksoma ili nadodatim trombom.

Opstrukcija protoka nastaje kod značajnijeg rasta miksoma u srčanoj šupljini iz koje je izrastao. Posle asimptomatskog i/ili oligosimptomatskog perioda bolesnik sa miksomom može imati dispneju, kašalj, retrosternalni bol, opštu slabost i malaksalost, osećaj umora, palpitacije, aritmije i hemoptizije. Kod miksoma u levoj pretkomori mogu postojati znaci zastoja u plućima, sa razvojem edema pluća i indikacijom za urgentnom ekstirpacijom [17], a kad je miksom u desnoj pretkomori znaci zastoja u velikim venama i jetri. Miksom može dovesti do kardiomegalije i srčane dekompenzacije.

Okluzija mitralnog ili trikuspidnog ušća daje simptome koji su slični drugim uzrocima. Okluzija ušća češća je kada je miksom na dužoj peteljci, a smetnje nastaju samo u pojedinim položajima tela kada se i tumor u srcu pomera. Smetnje su u vidu paroksizama i traju dok se pomeranjem tela miksom, odvajanjem od ušća, ne vrati u pređašnji položaj. Bolesnik vremenom nauči da izbegava položaj u kome mu nastaju ove smetnje.

Pri pregledu bolesnika ovaj fenomen se najbolje otkriva auskultacijom, kada se nalaz na srcu menja pri određenom položaju bolesnika ili pri novim pregledima, ako ova pojava ranije nije zapažena. Kvalitet i intenzitet šuma menja se pri položaju tela, u toku auskultacije srca. Može se, češće, čuti i treći ton, ritam galopa. Kod labavijeg tumora može se čuti udar na početku dijastole. Ređe se čuje zvuk otvaranja atrioventrikularnih zalistaka, koji je više karakterističan za reumatsku etiologiju oštećenja zalistaka.

Najčešće smetnje zbog okluzije srčanih ušća ispoljavaju se kao ponavljane sinkope, paroksizmi dispneje i paroksizmi aritmija.

Miksomi lokalizovani u levom i desnom srcu daju različite simptome i poremećaje, što je od dijagnostičkog značaja.

Miksom leve pretkomore može dovesti do delimične ili znatnije opstrukcije mitralnog ušća izazivajući smetnje karakteristične za mitralnu stenozu. Slične smetnje karakterišu hroničnu reumatsku mitralnu valvularnu bolest. Oštećenje same valvule uzrokuje mitralnu regurgitaciju [5, 13, 18, 19].

Rast u trikuspidno ušće dovodi do smetnji karakterističnih za njegovu stenozu. Ređe može da dođe do poremećaja srčanog ritma, koji može ići čak do fibrilacije pretkomora, zavisno od lokalizacije miksoma. Bolesnici sa miksomom u levoj pretkomori mogu imati supraventrikularne tahikardije, a ponekad i flater ili fibrilaciju pretkomora. Čak je moguće da se ovi tumori otkriju slučajno u toku etiološkog razjašnjenja poremećaja srčanog ritma.

U miksomu leve pretkomore EKG promene mogu biti slične kao u mitralnoj stenozi (P-mitrale, devijacija QRS kompleksa udesno, znaci hipertrofije desne komore). Kod miksoma desne pretkomore može se naći P- pulmonale.

Embolijske komplikacije u arterijama malog i velikog krvotoka česte su kod miksoma. Može se odvojiti deo miksoma ili tromb koji se stvara na miksomu koji ulazi u cirkulaciju, što može dovesti do embolizacije u arterijama bilo kog dela tela. Miksom iz leve pretkomore daje najčešće embolije u slezini, mozgu, retini, ekstremitetima, bubrezima i drugim perifernim organima. Miksom iz desne pretkomore daje embolije u plućnim arterijama. Opisan je miksom u levoj pretkomori koji se klinički ispoljio kao akutni infarkt miokarda [20]. Koliko je ovo česta pojava govori to da se miksom često dijagnostikuje u toku etiološkog razjašnjenja perifernih embolija. Dijagnoza miksoma bila je postavljana posle embolektomija i analize embolusa. Ranije je bilo teže dijagnostički razlučiti tromb u pretkomorama od miksoma, pa je analizom odstranjenog „tromba“ nalažen miksom kod pojedinih bolesnika.

Miksom obično nije biološki aktivan i ne daje biohumoralne promene po kojima bi se mogao naslutiti. Međutim, u toku evolucije, komplikacije vezane za miksom mogu biti praćene biološkom aktivnošću i odgovarajućim poremećajima.

Miksomi srca imaju i svoje sistemske kliničke manifestacije koje se označavaju kao miksomski sindrom. Teško ih je uvek povezati sa miksomom, ali njihova učestalost i pojava samo kod osoba koje imaju miksom, dovodi ih u neku vezu. Takve promene su kožni lentigo, adrenalna kortikalna hiperplazija i miksoidna fibroadenomatoza, švanomi i kožni miksomi. Naše analizirane bolesnice nisu imale znake biološke aktivnosti miksoma.

Dijagnoza miksoma može biti laka, ako se on klinički ispoljava.

Anemija, malaksalost, gubitak telesne težine, hipergamaglobulinemija ili bakterijski endokarditis podjednako su učestali kod miksoma bilo koje lokalizacije u šupljinama srca.

Fizikalnim pregledom mogu se naći auskultatorni fenomeni na srčanim ušćima koji zavise od lokalizacije miksoma. Kod više od polovine bolesnika sa miksomom inicijalni auskultatorni nalaz je normalan [21]. Kada se počne auskultatorno „prikazivati“, čuje se ejekcioni sistolni šum, holosistolni šum kao odraz mitralne insuficijencije, dijastolni šum kod ispoljene mitralne stenoze, glasan S1, S2 i S4, klik otvaranja i drugi fenomeni koji su raznoliki. Naši bolesnice nisu imale ove nalaza.

Elektrokardiografski, miksom nema karakterističnih promena. Miksom leve pretkomore može dati gotovo sve promene kao i mitralna stenoza (P-mitrale, devijaciju električne ose udesno, ili čak iznake hipertrofije desne komore). Miksom u desnoj pretkomori može biti bez ikakvih promena na EKG, ali može dati samo promene u P-talasu.

Ehokardiografski nalaz zavisi od veličine i lokalizacije tumora. Veći tumori, narasli u levoj pretkomori, su najuočljiviji. Novije ehokardiografske tehnike su sve suverenije dijagnostičke metode za miksome bilo koje lokalizacije u srcu.

Veći miksomi mogu se dobro diferentovati i na klasičnoj radiografiji.

Kateterizacija srca jedna je od najpouzdanijih dijagnostičkih metoda za miksome u srcu. Ovom tehnikom je dijagnostikovan i prvi miksom za života bolesnika. Ipak, ovo je invazivna metoda, a nekada trošne osobine miksoma zahtevaju opreznost zbog moguće fragmentacije miksoma ili otkidanja tromba na njemu. Naročitu opreznost zahteva miksom desne komore. Usavršavanjem tehnika kateterizacije postignuta je dobra kontrola intervencije koja je nezamenjiva pri uzimanju materijala tumora za histomorfološku dijagnostiku, posebno kad se ona kombinuje sa angiografijom i ventrikulogafijom.

Angiografija i ventrikulografija daju veoma precizne podatke koji mogu voditi kardiohirurga tokom odstranjenja tumora: mogu se dobro uočiti položaj, veličina i oblik miksoma, ne i jasno odvojiti miksomi od tromba. Tu je od koristi kardiološka anamneza jer se nalaz tromba može očekivati pre kod pozitivne kardiološke anamneze za ranije obolelo srce.

Kompjuterizovana tomografija (KT) i magnetna rezonanca (MRI) mogu da utvrde preciznu lokalizaciju miksoma, pomognu u razlikovanju miksomskog tkiva od okolne strukture, posebno da procene malignost tumora koji izrasta iz endokardne podloge.

Dijagnostički postupci mogu se kombinovati do dobijanja dovoljno podataka za dijagnozu, ali je najvažnije imati morfološki uzorak koji određuje vid i obim lečenja.

U diferencijalnoj dijagnozi, miksome najpre treba razlikovati od primarnih malignih tumora koji rastu u istim lokalizacijama ili metastatskih koji se „naseljavaju“ u te prostore, papilarnih fibroelastoma, muralnih tromba i miksomskih embolusa, kao i nekih nemalignih procesa (mitralna stenoza, subakutni bakterijski endokarditis i dr) [2, 14]. Kada je miksom karakteristično ispoljen na predilekcionom mestu, diferencijalna dijagnoza obično nije teška.

Neki maligni tumori, kao što su sarkomi, mogu biti veoma slični miksomima. Sarkomi srca, takođe, češće se javljaju u levoj pretkomori, ekstenzivniji su u rastu i mogu imitirati miksome. Međutim, u sarkomima nema makrofagnih ćelija sa hemosiderinom kojih ima u miksomima. Miksoidnu formu mogu najčešće imati miksoidni fibrosarkom, hondrosarkom i miksoidni maligni fibrozni histiocitom. Uz druge karakteristične razlikosti najvažnija je citomorfološka osobina vidljivih čestih mitotskih figura u malignih tumora, kojih nema u miksomima.

Muralni trombovi vide se kao muralna fibrozna masa u srcu. Makroskopski, teško se razlikuju organizovani trombovi i miksomi. Na sreću, fibrozni miksomi su retki, jer bi oni tek uneli dijagnostičku dilemu. Miksoidne trombove treba razlikovati od miksoma.

Najzad, i neki nemaligni procesi mogu dovesti u dilemu da bi se radi o miksomu srca ili ne. Ipak postoje neke osobenosti koje ih razdvajaju. Nemiksomska mitralna stenoza ide češće sa uvećanjem pretkomora i sa poremećajem ritma (atrijalnom fibrilacijom ili flaterom). U subakutnom bakterijskom endokarditisu treba očekivati uvećanu slezinu, međutim, miksom je često praćen infekcijama endokarda druge etiologije, što otežava razdvajanje ova dva entiteta.

Imunohistohemija je od male koristi u dijagnostici miksoma, ali može biti od koristi kod diferencijalnog dijagnostikovanja, ukoliko postoje nejasnoće u odvajanju miksoma od drugih, posebno malignih tumora srca [22–25].

Lečenje je hirurško i najčešće veoma lako, bez komplikacija i posledica. Hirurški mortalitet je ispod 1%. Komplikacije nastaju uglavnom zbog nestručne revizije interatrijalnog septuma na koji je najčešće „nasađen“ miksom. Kod oko 5% bolesnika sa miksomom treba revidirati i atrioventrikularne valvule koje mogu biti ledirane miksomom. Uvek postoji mogućnost recidiva miksoma, ali je i taj procenat sve zanemarljiviji. Računa se da oko 2% miksoma recidivira i pored svih mera sprečavanja u inicijalnoj terapiji. Većina miksoma srca je izlečiva, ako se dijagnostika obavi na vreme. Međutim, ako se na ovaj tumor ne misli, ako se propusti da se dijagnostikuje, on raste i ugrožava život čoveka, dovodeći i do letalnog ishoda.

Zaključak

Prikazane su dve bolesnice sa miksomom leve, odnosno desne pretkomore koje predstavljaju reprezentativne uzorke za najčešće lokalizacije miksoma u srcu. Veličina izvađenih tumora iz pretkomora i njihova lokalizacija objašnjavaju deo smetnji koje su bolesnice imale, ali i izazivaju čuđenje da smetnje nisu bile veće. Ni kod jedne bolesnice rast miksoma nije doveo do komplikacija kao posledice opstrukcije protoka, okluzije ušća ili embolizacije, što bi verovatno bolesnice ranije navelo da se obrate lekaru. Operacija, kao jedini vid lečenja, bila je uspešna kod obe bolesnice, sa trajnim efektom. Pri višegodišnjim kontrolama nije zapažen recidiv tumora, a smetnje koje su se mogle vezati za miksom povukle su se.

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CASE REPORT

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Intracranial yolk sac tumor in an adult patient: MRI, diffusion-weighted imaging and ^{1}H MR spectroscopy features

Intrakranijalni *yolk sac* tumor kod odraslog bolesnika: karakteristike snimanja magnetnom rezonancom (MR), difuzionom MR i protonskom MR spektroskopijom

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Abstract

Introduction. Yolk sac tumors represent only 5%–7% of intracranial germ cell tumors, which comprise about 1% of all primary brain tumors in adults. Literature data about nonspecific imaging characteristics of these tumors are scant. We presented magnetic resonance imaging findings with diffusion-weighted imaging and proton magnetic resonance spectroscopy of this rare type of tumor in an adult patient. **Case report.** A 55-year-old man with progressive left side weakness, headache, dizziness and ataxia, underwent preoperative magnetic resonance imaging, diffusion-weighted imaging and proton magnetic resonance spectroscopy. After surgical resection and histological analysis, the final diagnosis of yolk sac tumor was established. Retrospective imaging analysis were performed in order to determine imaging and biochemical parameters that could be useful in the diagnostic evaluation of this tumor type. **Conclusion.** Though the imaging features of yolk sac tumor are not specific, morphoanatomical and metabolic imaging could offer the information that provides new insights into this tumor that may facilitate further therapeutic decision process and potentially provides better information regarding the disease prognosis.

Key words:
brain neoplasms; endodermal sinus tumor; diagnosis; diagnostic techniques and procedures; magnetic resonance imaging; magnetic resonance spectroscopy; alpha-fetoproteins.

Apstrakt

Uvod. Tumori porekla žumančane kese (*yolk sac* tumori) predstavljaju samo 5–7% intrakranijalnih tumora porekla iz germinativnih ćelija, koji čine oko 1% svih primarnih tumora mozga kod odraslih. Podaci iz literature o nespecifičnim karakteristikama ovih tumora na snimku su oskudni. Prikazali smo nalaz magnetne rezonancije sa difuzionim snimanjem i protonskom magnetno-rezonantnom spektroskopijom ovog retkog oblika tumora kod odraslog bolesnika. **Prikaz bolesnika.** Bolesnik, star 55 godina, sa progresivnom levostranom slabošću, glavoboljom, vrtoglavicom i ataksijom, preoperativno je podvrgnut magnetnoj rezonanciji, difuzionom snimanju i protonskoj magnetno rezonantnoj spektroskopiji. Nakon hirurške intervencije i histološke analize, postavljena je konačna dijagnoza *yolk sac* tumora. Retrospektivna analiza snimanja sprovedena je sa ciljem određivanja parametara snimanja kao i biohemijskih parametara koji mogu biti korisni u dijagnostičkoj proceni ovog tipa tumora. **Zaključak.** Iako su karakteristike snimka *yolk sac* tumora nespecifične, morfoanatomsko i metaboličko snimanje može pružiti informacije koje daju novi uvid u ovu vrstu tumora, i time olakšati budući proces donošenja terapijske odluke. Osim toga, ono potencijalno obezbeđuje preciznije informacije, što je značajno za prognozu bolesti.

Ključne reči:
mozak, neoplazme; endodermalni sinus tumor; dijagnoza; dijagnostičke tehnike i procedure; magnetna rezonanca, snimanje; magnetna rezonanca, spektroskopija; alfa fetoproteini.

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Introduction

Yolk sac tumors (YST) represent only 5%–7% of intracranial germ cell tumors (GCT), which comprise about 1% of all primary brain tumors in adults and 3%–8% of all primary brain tumors in children. The peak incidence of intracranial GCT is between 10 and 14 years, 95% of them occurring before the age of 35 [1–5]. Based on literature data, there are only two previously reported cases of patients with intracranial GCT elder than 45 years.

Since radiological appearance can be nonspecific and literature data of these tumors are scant, differentiation of YST from other neoplasms may be difficult. Conventional magnetic resonance imaging (MRI) with advanced MRI techniques, such as magnetic resonance diffusion [diffusion-weighted imaging (DWI) and proton magnetic resonance spectroscopy (^{1}H MRS)], can provide additional information to improve tumor characterization.

We reported the second case of YST and the third case of all intracranial GCT diagnosis in a 55-year-old patient using conventional MRI with DWI and ^{1}H MRS.

Case report

A 55-year-old man, was originally presented in March 2009, with a few-weeks history of progressive left side weakness, headache, dizziness and ataxia. Brain computed tomography (CT) scan showed expansive lesion with the localization on the right side of mesencephalon and cerebral peduncle. MRI revealed an expansive ovoid mass, 35 × 23 × 27 mm in size, localized in the region of the dorsal thalamus, cerebral peduncle, tegmentum mesencephali and ventral and proximal aspect of pons, dominantly on the right side. The tumor showed compression on the ventricle III and mediosagital structures with mild perifocal edema (Figure 1). The mass showed as heterogeneous, hypo- to isointense with hiperintense rim on T2-weighted (Figure 1a) and fluid-attenuated inversion-recovery (FLAIR), and hypointense with hiperintense focus on T1-weighted images (Figure 1b). The lesion displayed discretely enhancement (Figures 1c, d). DWI with calculated apparent diffusion coefficient (ADC) map revealed facilitated diffusion (1.44×10^{-3} mm^2 sec^{-1}) in the enhanced component of the lesion (Figure 2a). Multivoxel ^{1}H MRS with short echo time (TE = 30 ms) and selected voxel (Figures 2b, d) positioned in the rim of the lesion showed increased choline/creatine (Cho/Cr), decreased N-acetylaspartate/Cr (NAA/Cr) ratio and the presence of prominent lipid peak (Figures 2c, d). The radiological differential diagnosis included central nervous system (CNS) lymphoma and germinoma. Since the diagnosis of GCT was suspected, α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) levels were checked preoperatively in the serum and cerebrospinal fluid (CSF). Laboratory tests showed normal values of AFP β-HCG in the serum (AFP: 7,46 ng/mL; β-HCG: 0,01 mIU/mL), and in the CSF (AFP: 0,56 ng/mL; β-HCG: 2,15 mIU/mL). Based on the extent of the lesion, no surgery was applied. Since biochemical analysis was negative, the patient underwent biopsy of the tumor in

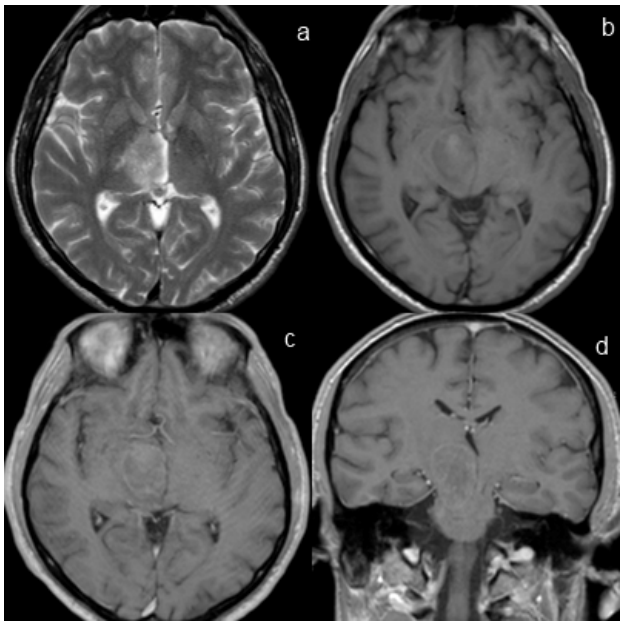

Fig. 1 – Tumor occupies dorsal thalamus, cerebral peduncle, mesencephalic tegmentum and pons with compromitation of third ventricle and adjacent structures Axial T2-weighted image (b) Axial T1-weighted image (c) Axial T1-weighted postcontrast image (d) Coronal T1-weighted postcontrast image

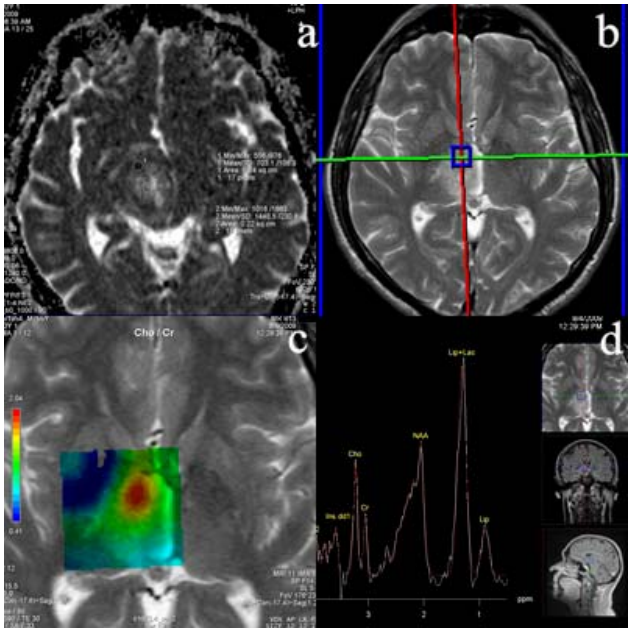

Fig. 2 – (a) Apparent diffusion coefficient (ADC) map with measured high ADC value; (b) One voxel from chemical shift imaging (CSI) position in the rim of the lesion, corresponding to an area of maximal choline/creatine (Cho/Cr) ratio; (c) Color map of CSI spectrum showing area of maximal Cho/Cr ratio with red color; (d) Spectrum from voxel corresponding to an area of maximal Cho/Cr ratio showing a marked decrease in N-acetylaspartate, increase in Cho and prominent lipids at 1.3 ppm

April 2009. Histological examination with immunohistochemistry showed polymorphic tumor proliferation, consisted of primitive epithelial cells, with isolated giant cells and hyaline globules within loose myxoid matrix (Figure 3a). The epithelial component of the tumor showed characteristic cytoplasmatic immunolabeling for AFP (Figure 3b). Since patient health status deteriorated, control brain CT and MRI were performed. Imaging findings showed progression of the lesion and the presence of hydrocephalus. A CSF shunt system was implanted, and antiedematose and hemiotherapy were introduced (CDDP Cisplatin, 35 mg). Five days after hemiotherapy, health state of the patient deteriorated for the second time and cardiac arrest emerged.

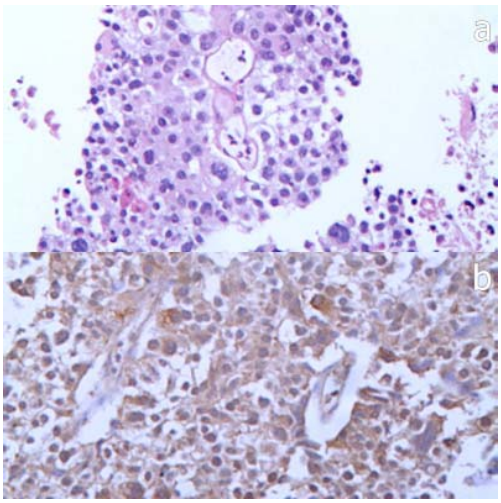

Fig. 3 – (a) Polymorphism, primitive appearing epithelial cells and hyaline globules in yolk sac tumor (YST) (H&E × 20); (b) the alpha fetoprotein (AFP) cytoplasmatic immunolabeling of YST epithelial component (AFP × 20)

Discussion

The World Health Organization classificated intracranial GCT as: germinomas, embryonal carcinomas, YST (s. endodermal sinus tumors), choriocarcinomas, teratomas (mature and immature), teratomas with malignant transformation and mixed germ cell tumors [2]. Intracranial GCT comprises about 1% of all primary brain tumors in adults [2–7] and 3%–8% of all primary brain tumors in children [8–12]. Among all primary intracranial GCT, the most common histological types are germinomas (60%), while YST represent only 5%–7% of these tumors [2, 5]. The peak incidence of intracranial GCT is between 10 and 14 years, and almost 95% of these tumors occur before the age of 35 [1–5]. Although the vast majority of cases are diagnosed in young children, there have been isolated case reports in adults. Kirikae et al. [13] reported the eldest patient with intracranial GCT who was a 65-year-old man with YST. Park and al. [14] reported a 47-year-old woman with intracranial mature teratoma. Based on literature data, our case is the second one with YST and the third one of all intracranial GCT in a patient elder than 45 years.

The biochemical assessment of intracranial GCT serves as an accepted method for initial classification without tissue sampling, while CSF cytology is an evidence of tumor dissemination into the neuroaxis [14–17]. Laboratory diagnosis of GCT is based on tumor markers analysis in the serum and CSF, and CSF cytology [2, 3]. The normal range of AFP in the serum and CSF for adults is 0–15 ng/mL, and normal serum and CSF β-HCG levels are less than 2,5 mIU/mL in men, and less than 5,0 mIU/mL in non-pregnant women [14–17]. Associated predominantly with YST, AFP can also be expressed by embryonic carcinomas and immature teratomas, while β-HCG is markedly elevated in association with choriocarcinomas and germinomas with the presence of syncytiotrophoblastic giant cells [14–17]. Although YST is known to be an AFP-producing tumor, our patient showed normal values of AFP. As in other cases, production of β-HCG was not present in our case, too.

As typical for GCT, YST arises as midline tumors, commonly localized in the pineal or suprasellar region [5–11]. Since radiological manifestation can be nonspecific, especially in adults, differentiation of YST from other neoplasms is difficult [18, 19]. Literature data of YST, especially about their radiological appearance, are scant [1, 2, 17, 18, 20–22]. On MRI, YST is usually shown as heterogeneous mass with foci of calcification and cysts, and contrast enhancement [1, 2]. As in our case, there are cases described with T1-weighted iso-/hypointense and T2-weighted iso/hyperintense appearance of these tumors [20–23]. MRI presentation of our case only confirms unspecific manifestation of YST. Based on conventional MRI findings, differential diagnosis included primary CNS lymphoma and germinoma. Advanced MR techniques offered additional information which could improve tumor characterization. Based on ^{1}H MRS lymphoma and germinoma were highly suspected. Like in lymphomas and germinomas [21], ^{1}H MRS of YST showed increased Cho/Cr, decreased NAA/Cr ratio and the presence of prominent lipid peak. Since ^{1}H MRS of these tumors is very similar, usefulness of these findings was limited. Lipid resonances may originate from mobile lipid molecules, based on tissue degradation and necrosis, or from B-lymphocytes, transformed T-lymphocytes, cultured human leukemic lymphocytes and macrophages [24]. A strongly increased Cho/NAA ratio and lipid resonances in the absence of necrotic area on MRI, is suggestive for lymphocytes infiltration. However, based on DWI, differential diagnosis can be made. DWI evaluates size of extracellular space, cellularity and cytoplasm/extracellular space ratio [25]. Intracranial primary lymphomas show restrictive diffusion due to their hipercelullarity [2, 5, 21]. Similar to lymphomas, germinomas demonstrate restrictive diffusion with low ADC values [2, 5]. Unlike lymphomas and germinomas, YST shows facilitated diffusion. This information is important for MR diagnosis of YST, and consequently for patient's therapeutic treatment and prognosis.

While germinomas are exquisitely radiosensitive, with a 5-year survival rates of roughly 90% with radiotherapy alone, for other intracranial GCT neoadjuvant chemotherapy is used in combination with radiotherapy and maximal surgical resection. YST, like most of other GCT, are associated

with the poorest prognosis, with a 5-year survival rates in the range of 9% to 49%, even with aggressive therapy [2, 7, 15, 26, 27].

Conclusion

There are no specific imaging features of YST, but DWI and ^{1}H MRS offer information that provides new insights into these tumors, and may play the role in differentiation from other neoplasms. Still, histological verification remains necessary.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Elektivna visceralna hibridna rekonstrukcija aneurizme torakoabdominalne aorte tipa III

Elective visceral hybrid repair of type III thoracoabdominal aortic aneurysm

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Apstrakt

Uvod/Cilj. Aneurizme torakoabdominalne aorte (TAAA) tipa III predstavlja proširenje aorte od nivoa 6. rebra, pa sve do dela aorte ispod odvajanja renalnih arterija, zahvatajući sve visceralne grane aorte.Visceralna hibridna rekonstrukcija TAAA tipa III predstavlja proceduru razvijenu u svetu zadnjih godina, a koja podrazumeva kombinaciju klasične i endovaskularne hirurgije u rekonstrukciji aorte, od nivoa odvajanja leve podključne arterije, pa sve do račve bedrenih arterija. **Prikaz bolesnika.** U radu je prikazan bolesnik muškog pola, star 75 godina, kod koga je učinjena elektivna visceralna hibridna rekonstrukcija TAAA tipa III. Bolesniku je kompijuterizovanom skenerskom aortografijom početkom 2010. godine dijagnostikovana TAAA tipa III sa najvećim poprečnim prečnikom od 92 mm. Početak aneurizme bio je u nivou šestog rebra, a kraj na 1 cm distalno od odvajanja renalnih arterija. Aneurizma je vršila kompresiju na jednjak, zbog čega je bolesnik imao otežan akt gutanja naročito čvrste hrane, česte bolove u leđima i lumbalnom delu kičme. Od drugih komorbidnih stanja, bolesnik se duže vreme lečio od hronične opstruktivne bolesti pluća i hipertenzije. U opštoj endotrahealnoj anesteziji, uz epiduralnu analgeziju, kod bolesnika je učinjena visceralna hibridna rekonstrukcija TAAA koja predstavlja kombinaciju klasične, otvorene vaskularne hirurgije i endovaskularne procedure. Klasična vaskularna hirurgija podrazumevala je visceralnu rekonstrukciju *by pass* procedurom sa distalne, normalne aorte, svih visceralnih grana: celijačnog trunkusa, gornje mezenterične arterije i obe renalne arterije, uz ligiranje istih na samom odstupu od aorte. U sledećem aktu, sinhrono endovaskularnom tehnikom izvršena je ekskluzija kompletne aneurizmatski izmenjene torako-abdominalne aorte torakalnim stent-graftom. Postoperativni tok protekao je uredno, a bolesnik je otpušten kući 21. postoperativnog dana. Na kontrolnoj skenerskoj aortografiji, tri meseca nakon izvedene operacije vaskularni status bolesnika bio je uredan sa funkcionalnim visceralnim *by pass*-evima, urednom pozicijom stent-grafta i bez značajnog endolika. **Zaključak**. Visceralna hibridna rekonstrukcija TAAA tipa III predstavlja komplementarnu hirurško tehniku torakofrenolaparotomijskom pristupu, kompletne otvorene rekonstrukcije TAAA, a da se pri tome ne ugoržava bezbednost bolesnika. Ovaj pristup predstavlja daleko manju traumu za bolesnika, a naročito je značajan kod bolesnika sa brojnim komorbidnim stanjima, jer nema torakotomije, dok je ishemijskoreperfuziona povreda organizma svedena na minimum, zbog kratkotrajnog prekida cirkulacije kroz aortu u infrarenalnom delu.

Ključne reči:
aneurizma, torakalna; hirurgija, vaskularna, procedure; dijagnoza; prognoza; postoperativne komplikacije; lečenje, ishod.

Abstract

Introduction. According to the classification given by Crawford et al. type III thoracoabdominal aortic aneurysm (TAAA) is dilatation of the aorta from the level of the rib 6 to the separation of the aorta below the renal arteries, capturing all the visceral branch of aorta. Visceral hybrid reconstruction of TAAA is a procedure developed in recent years in the world, which involves a combination of conventional, open and endovascular aortic reconstruction surgery at the level of separation of the left subclavian artery to the level of visceral branches of aorta. **Case report.** We presented a 75-years-old man, with elective visceral hybrid reconstruction of type III TAAA. Computerized scanning (CT) angiography of the patient showed type III TAAA with the maximum transverse diameter of aneurysm of 92 mm. Aneurysm started at the level of the sixth rib, and the end of the aneurysm was 1 cm distal to the level of renal arteries. Aneurysm compressed the esophagus, causing the patient difficulty in swallowing act, especially solid food, and fre-

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quent back pain. From the other comorbidity, the patient had been treated for a long time, due to chronic obstructive pulmonary disease and hypertension. In general endotracheal anesthesia with epidural analgesia, the patient underwent visceral hybrid reconstruction of TAAA, which combines classic, open vascular surgery and endovascular procedures. Classic vascular surgery is visceral reconstruction using by-pass procedure from the distal, normal aorta to all visceral branches: celiac trunk, superior mesenteric artery and both renal arteries, with ligature of all arteries very close to the aorta. After that, by synchronous endovascular technique a complete aneurysmal exclusion of thoracoabdominal aneurysm with thoracic stent-graft was performed. The postoperative course was conducted properly and the patient left the Clinic for Vascular Surgery on postoperative day 21. Control CT, performed 3 months after the surgery showed that the patient's vascular status was uneventful with functional visceral by-pass and with good position of a stent-graft without a significant endoleak. **Conclusion.** Visceral hybrid reconstruction represents a complementary surgical technique to that with open reconstruction of TAAA. This approach is far less traumatic to a patient, and is especially important in patients with lot of comorbidities, because there is no need for thoracotomy, and ischemic-reperfusion injury of the body is reduced to a minimum.

Key words:
aortic aneurysm, thoracic; vascular surgical procedures; diagnosis; prognosis; postoperative complications; treatment outcome.

Uvod

Torako-abdominalna aneurizma aorte (TAAA) je patološko proširenje aorte za više od 50% njenog normalnog prečnika u delu od odvajanja leve potključne arterije, pa sve do račve ilijačnih arterija, pri čemu su zahvaćene i visceralne grane aorte. Tip III TAAA, po podeli koju su dali Crawford i sar. [1, 2] predstavlja proširenje aorte od nivoa 6. rebra, pa sve do dela aorte ispod odvajanja renalnih arterija, zahvatajući sve visceralne grane aorte.

Otvorena, klasična rekonstrukcija TAAA podrazumeva torakofrenolaparotomijski pristup aorti, rekonstrukciju iste uz implantaciju svih visceralnih grana aorte u graft. Ovakva hirurška procedura praćena je, zbog značajne ishemijskoreperfuzione povrede organizma, kao i mutilantnosti, i značajne traume ove hirurške procedure, velikim brojem perioperativnih i postoperativnih komplikacija i značajnom stopom smrtnosti koja se po podacima nacionalne baze podataka Sjedinjenih Američkih Država kreće oko 20%, a po hirurškom Registru kardiovaskularnih bolesti Velike Britanije oko 34% [3–5].

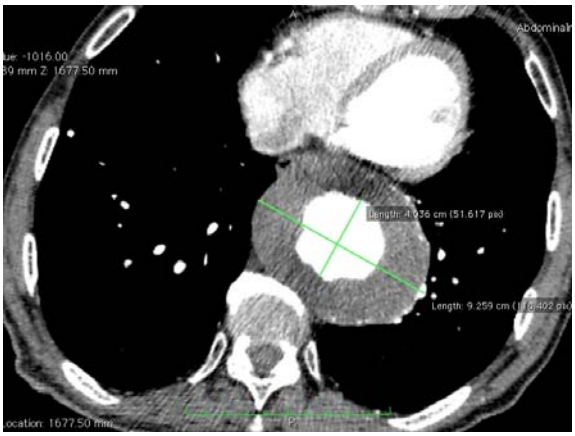
Razvoj endovaskularne hirurgije krajem XX veka omogućio je primenu ove hirurške tehnike za lečenje, osim izolovanih aneurizmi abdominalne i torakalne aorte, i kompleksnih aneurizmi torakoabdominalne aorte. U tom smislu, endovaskularna hirurgija razvijala se u dva pravca. Jedan pravac bio je stvaranje bifurkacionih i tubularnih stent graftova sa fabrički implantiranim visceralnim granama, radi izvođenja kompletne rekonstrukcije TAAA endovaskularnom tehnikom. Ova procedura je tehnološki i tehnički jako zahtevna, ali početni rezultati ohrabruju [6].

Drugi način rekonstrukcije komplesnih TAAA bio je usmeren ka hibridnim rekonstrukcijama, tj. ka kombinaciji klasične i endovaskularne rekonstrukcije TAAA. Prvi objavljeni rezultati malih serija bolesnika pojavili su se u svetskoj literaturi 2002. i 2003. godine sa opisom hibridne visceralne retrogradne rekonstrukcije grana aorte uz endovaskularno isključenje aneurizme iz cirkulacije stent-graftom, i ti rezultati bili su jako ohrabrujući. Autori su kao osnovne prednosti ove metode u odnosu na klasičnu, otvorenu rekonstrukciju TAAA, navodili da nema torakotomije i klemovanja aorte iznad odstupa celijačnog trunkusa, kao i da nema potrebe za uspostavljanjem šanta između levog srca i distalnih organa [7–10].

Prikaz bolesnika

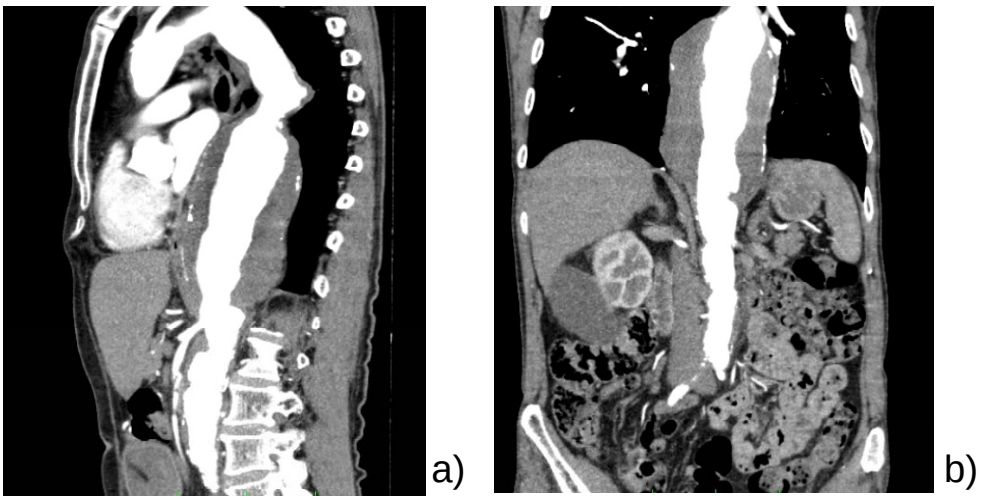
U radu je prikazan bolesnik muškog pola, star 75 godina, kod koga je urađena elektivna visceralna hibridna rekonstrukciju TAAA tipa III.

Kod bolesnika početkom 2010. godine, skenerskom aortografijom dijagnostikovana je TAAA tipa III sa najvećim poprečnim prečnikom aneurizme od 92 mm u nivou aorte neposredno iznad dijafragme, sa masivnim parijetalnim trombom (slika 1). Aneurizma je zahvatala sve visceralne arterije aorte i prostirala se do nivoa 1 cm distalno od odvajanja renalnih aretrija (slika 2).



Sl. 1 – Poprečni presek aneurizmatski izmenjene aorte u nivou iznad dijafragme

Prečnik normalnog dela descedentne torakalne aorte proksimalno od aneurizme bio je 29 mm, a prečnik distalnog dela abdominalne aorte iznad račvi ilijačnih arterija bio je 26 mm. Ukupna dužina aneurizmatski izmenjene torakoabdominalne aorte bila je 30 cm. Ovi parametri bili su neophodni zbog određivanja proksimalne i distalne zone fiksiranja torakalnog stent-grafta.



Sl. 2 – a) aksijalni presek i b) sagitalni presek torakoabdominalne aneurizme aorte (TAAA)

Zbog kompresije jednjaka i traheje od strane aneurizme, bolesnik se žalio na otežan akt gutanja, naročito čvrste hrane, i suv nadražajni kašalj. Takođe, zbog kompresije na okolne nervne strukture, bolesnik je imao povremeno bolove kako u predelu grudne, tako i u predelu lumbalne kičme.

Od drugih komorbidnih stanja, važno je napomenuti da se bolesnik duže vreme lečio od hronične opstruktivne bolesti pluća i hipertenzije.

Uzimajući u obzir sve navedene parametre, doneta je odluka da se kod bolesnika učini visceralna hibridna rekonstrukcija TAAA, a da se za ekskluziju aneurizme endovaskularno plasiraju dva torakalna stent-grafta: TAG 3420 i TAG 3115 (proizvođač GORE).

U opštoj endotrahealnoj anesteziji uz epiduralnu analgeziju, učinjena je medijalna laparotomija. Bolesnik je imao dve centralne venske linije i arterijski monitoring postavljen preoperativno. Prvi deo hibridne rekonstrukcije TAAA sastojao se od klasične, otvorene revaskularizacije visceralnih i bubrežnih grana aorte.

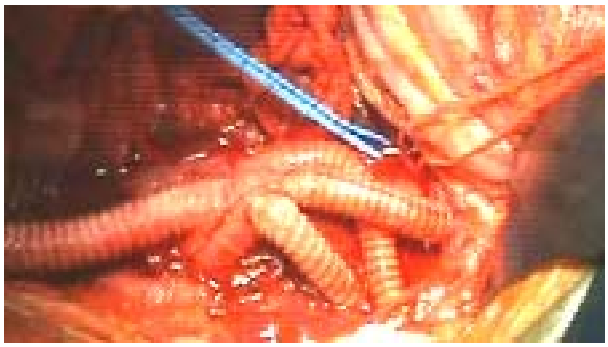
Pozicija bolesnika bila je na leđima, u ravnom položaju.

Gornjom i donjom medijalnom laparotomijom, po otvaranju trbušne duplje, nakon pomeranja tankih creva desno lateralno i poprečnog kolona kranijalno, presecanjem retroperitoneuma pristupilo se abdominalnoj aorti i ilijačnim arterijama. Nakon toga, ispreparisane su u nivou odvajanja od aorte i zaomčene redom: leva i desna bubrežna arterija, gornja mezenterična arterija i celijačni trunkus.

Zatim se pristupilo kreiranju grafta za visceralnu hibridnu rekonstrukciju. U tu svrhu iskorišćen je standardni bifurkacioni Y dakronski graft prečnika 16 × 8 mm, gde je bočno na samoj račvi sa obe strane anastomoziran po jedan dakronski graft prečnika 8 mm. Takođe, na telo osnovnog grafta sa gornje strane anastomoziran je još jedan dakronski graft prečnika 10 mm na oko 1 cm od račve koji je služio kao uvodnik za torakalne stent-graftove.

Nakon heparinizacije bolesnika (1 mg/kg heparina) pristupilo se kreiranju vaskularnih anastomoza. Najpre je kreirana anastomoza distalne abdominalne aorte iznad same račve ilijačnih arterija sa telom grafta, po tipu laterotерminalne anastomoze. Nakon toga se graft retrogradno usmerio i kreirane su redom anastomoze četiri kraka grafta sa visceralnim i bubrežnim granama aorte: obe bubrežne arterije, gornja mezenterična arterija i celijačni trunkus. Sve visceralne anastomoze između grafta i arterija urađene su kao terminolateralne anastomoze, uz proksimalno ligiranje arterija na odstupu od aorte nakon sonografske dopler potvrde prohodnosti kreiranih anastomoza. Ligiranje visceralnih grana aorte neposredno po odstupu je neophodno da bi se po endovaskularnoj ekskluziji aneurizme stent-graftom sprečio endolik tipa II. Takođe, važno je napomenuti neophodnost kreiranja takozvane „S" krivine grafta koji se anastomozira sa gornjom mezenteričnom arterijom, da ne bi, nakon spuštanja mezoa crva na anatomsku poziciju, došlo do presavijanja i opstrukcije istog.

Zatim se pristupilo endovaskularnoj rekonstrukciji torakoabdominalne aorte. Kroz levu brahijalnu arteriju, najpre je plasiran pigtejl kateter i vrh doveden u početni deo descedentne aorte. Učinjena je kontrastna aortografija, i određen nivo proksimalnog i distalnog vrata aneurizme, kao i mesto anastomoze hibridnog grafta sa aortom i ustanovljena prohodnost svih visceralnih anastomoza. Kroz postavljeni dakronski graft (10 mm) kao uvodnik (slika 3), plasiran je preko žičane sajle najpre dilatator sa štitom 22 Fr, kroz koji su endovaskularno sprovedene u poziciju dva torakalna PTEF stent-grafta: TAG 3420 i TAG 3115, uz preklapanje dva grafta u dužini od 5 cm.

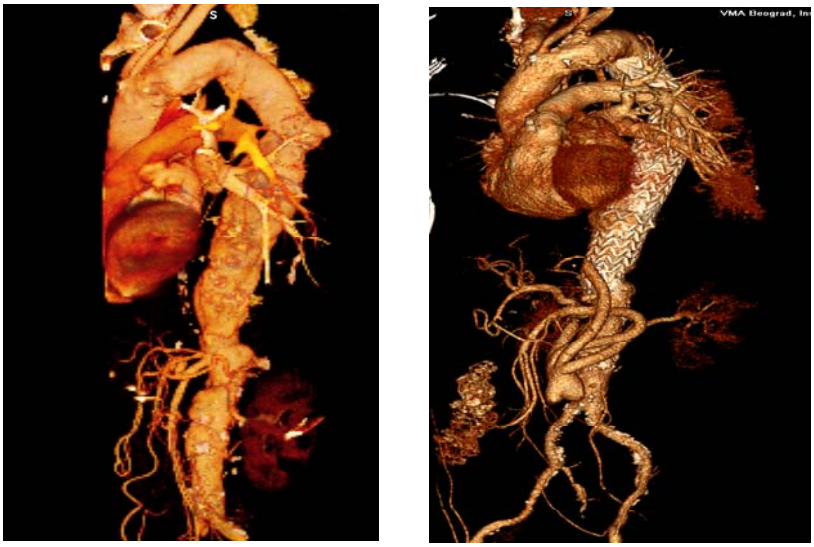


Sl. 3 – Završni izgled anastomoza visceralne hibridne rekonstrukcije torakoabdominalnia aneurizma aorte (TAAA)

Trajanje klemovanja abdominalne aorte bilo je 16 minuta. Topla ishemija desnog bubrega iznosila je 16 minuta, levog bubrega 23 minuta, organa koje ishranjuje gornja mezenterična arterija 20 minuta, i organa koje perfunduje celijačni trunkus 22 minuta.

Nakon završene operacije bolesnik je premešten u hirušku intenzivnu negu, gde je zadržan naredna 72 sata sa mehaničkom ventilacijom u trajanju od 48 sati, a onda preveden na samostalno disanje.

Bolesnik je otpušten sa klinike 21. dan nakon operacije. Na kontrolnoj skenerskoj aortografiji, tri meseca nakon izvedene operacije, vaskularni status bolesnik bio je uredan sa urednom pozicijom stent-grafta, bez značajnog endolika i sa prohodnim svim visceralnim anastomozama. Na slici 4 prikazana je skenerska aortografija kompletne aorte pre operacije i kontrolni snimak tri meseca nakon visceralne hibridne rekonstrukcije.



Sl. 4 – Skenerska aortografija torakoabdominalnia aneurizma aorte (TAAA) tipa III pre (levo) i posle (desno) hibridne rekonstrukcije

Diskusija

Rekonstrukcija TAAA predstavlja najveći izazov u vaskularnoj hirurgiji kako sa tehničke strane, tako i u pogledu preoperativne strategije i postoperativne terapije.

Osnovne komplikacije koje mogu ozbiljno ugroziti zdravlje bolesnika, su visceralna i bubrežna ishemija, kao i ishemijska povreda kičmene moždine (posledična paraplegija), komplikacije koje mogu nastati kako tokom same hirurške rekonstrukcije TAAA, tako i u postoperativnom toku [11].

Hibridna visceralna retrogradna rekonstrukcija predstavlja komplementarnu proceduru otvorenoj, klasičnoj rekonstrukciji aneurizme torakoabdominalne aorte. Hibridna visceralna rekonstrukcija TAAA podrazumeva rekonstrukciju u dva koraka. Najpre se vrši revaskularizacija *by-pass* procedurom visceralnih i bubrežnih grana aorte uz njihovo proksimalno ligiranje, a nakon toga, sinhrono, u drugom aktu, vrši se endovaskularno isključenje (ekskluzija) aneurizme torakalnim stent-graftom. Komplikacije ove hirurške tehnike mogu biti opšte i specifične. Opšte komplikacije su: paraplegija, ishemija bubrega kao i organa trbušne duplje, plućna i srčana insuficijencija, infekcija i krvarenje. Specifične komplikacije koje su karakteristične za endovaskularnu proceduru su: endolik i disekcija zida aorte [12].

Endolik predstavlja perzistentni protok krvi u aneurizmatskoj vreći nakon endovaskularne ekskluzije aneurizme, koji može dovesti do uvećanja aneurizme i njene rupture sa smrtnim ishodom. Upravo ligiranje svih visceralnih grana koje se revaskularizuju, na samom odstupu od aorte, kao i pravilno preoperativno planiranje torakalnih stent-graftova i zona fiksiranja, predstavljaju najbolju prevenciju pojave endolika i svih komplikacija koje nosi.

Hibridna visceralna rekonstrukcija TAAA naročito je pogodna za bolesnika sa prethodnim rekonstruktivnim procedurama na ushodnoj aorti, luku aorte i abdominalnoj aorti, jer je kod takvih bolesnika zbog prethodnih operacija znatno otežan otvoreni klasičan pristup [13].

Prikazanom bolesniku uspešno je učinjena elektivna visceralna hibridna rekonstrukcija aneurizme torakoabdominalne aorte tipa III što nas je ohrabrilo da nastavimo sa operacijama u ovoj oblasti.

Zaključak

Hibridna visceralna retrogradana rekonstrukcija aneurizme TAAA tipa III predstavlja komplementarnu proceduru torakofrenolaparotomijskoj otvorenoj, klasičnoj rekonstrukciji, a da se pri tome ne ugoržava bezbednost bolesnika i sigurnost adekvatne rekonstrukcije aorte. Ova procedura predstavlja daleko manju traumu za bolesnika, a naročito je značajna kod bolesnika sa velikim komorbiditetom, jer nema torakotomije i klemovanja aorte proksimalno od celijačnog trunkusa i svih komplikacija koje iz toga proizilaze.

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CASE REPORT

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Unilateral optic nerve aplasia associated with microphthalmos

Jednostrana aplazija nervusa optikusa udružena sa mikroftalmusom

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Abstract

Intraduction. Optic nerve aplasia is a rare developmental anomaly characterised by the congenital absence of the optic nerve, central retinal vessels and retinal ganglion cells that is seen most often in a unilaterally malformed eye. **Case report.** We reported a girl with a very rare anomaly of the eye, unilateral aplasia of the optic nerve and microphthalmia. We carried out a complete ophthalmological examination, A- and B-scan ultrasonography, magnetic resonance imaging (MRI) of the orbit and brain, pediatrician, neurological examinations and karyotype determination. The examined child was a third child from the third regular pregnancy, born at term (39 GS, BM 3100 g). Family ocular history was negative. The right corneal diameter was 7.5 mm and left 10 mm. On dilated fundus examination, the right eye showed the absence of optic nerve and central retinal vessels. B-scan echography showed a small right globe (axial length 13.80 mm), normal size left globe (axial length 18.30 mm) and the absence of optic nerve on the right eye. Physical and neurological findings and karyotype was normal. MRI of the orbits and brain marked asymmetry of globe size and unilateral absence of the optic nerve. The patient is under the control of a competent ophthalmologist and prosthetic. **Conclusion.** Further aesthetic and functional development of a young person is the primary goal in tracking this rare congenital optic nerve anomalies in the malformed eye.

Key words:
optic nerve; congenital abnormalities; microphthalmos; diagnostic techniques and procedures; therapeutics.

Apstrakt

Uvod. Aplazija nervusa optikusa retka je razvojna anomalija oka. Odlikuje je kongenitalni nedostatak n. optikusa, centralnih retinalnih krvnih sudova i retinalnih ganglijskih ćelija. Često je jednostrano prisutna u malformisanom oku. **Prikaz bolesnika.** Prikazali smo devojčicu sa mikroftalmusom i aplazijom optikusa desno kod koje je sprovedeno kompletno oftalmološo ispitivanje, A- i B-ultrasonografija oka, magnetna rezonanca (MR) endokranijuma, pedijatrijski, neurološki pregled i određen kariotip. Devojčica je treće dete iz treće uredne trudnoće, rođena u terminu. Neonatalni period protekao je bez osobenosti. Porodična očna anamneza bila je negativna. Prečnik rožnjače desnog oka bio je 7,5 mm i 10 mm levo. Oftalmoskopski na desnom oku bili su odsutni glava optičkog živca i centralni retinalni krvni sudovi. B-sken ehografija potvrdila je manje desno oko (Lax 13,80 mm), odsustvo n. optikusa i normalnu veličinu levog oka (Lax 18,30 mm). Pedijatrijski, neurološki pregledi i kariotip bili su normalni. Magnetna rezonanca endokranijuma pokazala je asimetričnu veličinu oka i unilateralno odsustvo n. optikusa. U toku je dalje oftalmološko i protetičko praćenje. **Zaključak.** Dalji estetski i funkcionalni razvoj mlade osobe, primarni su cilj u praćenju ove retke kongenitalne anomalije n. optikusa u malformisanom oku.

Ključne reči:
n. opticus; anomalije; mikroftalmos; dijagnostičke tehnike i procedure; lečenje.

Introduction

Aplasia of the optic nerve is a rare developmental anomaly of the eye characterized by congenital absence of the optic nerve, central retinal vessels and retinal ganglion cells [1–15]. Ophthalmoscopies note the absence of the optic nerve head. Endocranial magnetic resonance (MR) does not visualize the optic nerve and chiasm part. Histological char-

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acteristics are the absent optic nerve, retinal ganglion cell layer of nerve fibers and blood vessels [10].

Aplasia of the optic nerve can be uni- or bilateral. Bilateral aplasia of the optic shall be communicated in an otherwise healthy person [1, 2], or accompanied by severe congenital anomalies such as septooptic dysplasia, a fatal outcome in the newborn [4], hydrocephalus, along with other multiple congenital anomalies [6] with congenital hypopituitarism and posterior pituitary ectopia [5]. Unilateral aplasia of the optic nerve is often present in the malformed eyes, with no change in the brain tissue [1–6]. Malformations of the eye, other than microphtalamos, are possible even cataracts, malformations of the chamber angle, retinal dysplasia, coloboma of iris and ciliary body, iris hypoplasia, persistent hyperplasic primary vitreus [6, 15].

According to Weiter et al. [15] aplasia of the optic nerve is typically unilateral in otherwise healthy individuals. It shows no gender, neither racial predilection, with no recorded share of hereditary factors and occurs as a result of abnormal ventral invagination [15].

According to many previous statements aplasia of the optic nerve is a part of hypoplasia of optic spectrum. According to the analysis performed by Alqahtani [11], of 42 statements in the literature, 29 are real aplasia of the optic nerve, others are hypoplastic optic nerve and among 4 bilateral aplasia communications only one is true aplasia of the optic nerve [11].

Microphthalmia of the affected eye is often followed by the finding of aplasia of the optic nerve. Microphthalmia *seu* microphtalamos is also a rare developmental anomaly of the eyeball, which is characterized by the reduced volume of the eye. Microphthalmia may occur isolated or in one third of cases of various syndromes. The average length of the eye at birth (newborn futures) is 17 mm, or about 70% of the size of the adult eye, compared to 23.8 mm which is the average axial length of the adult eye in persons with emmetropia. The diameter of the cornea in the case of microphtalmia is less than 10 mm and the axial axis of the eye is less than 20 mm. Adnexa and eyelids are usually present. In unilateral anomalies of the eye – orbital no asymmetry is more pronounced with growing up [16].

Case report

We presented a girl with a very rare anomaly of the eye – unilateral aplasia of the optic nerve and microphthalmia. The parents presented their daughter due to the smaller right eye. Ophthalmic examination included: measurement of corneal diameter, motility test, caver test, checking the intraocular pressure of the Goldman tonometer, slit lamp, indirectly ophthalmoscopies (Heine500, Germany) with a magnifying glass + 20 D, determination of objective refraction of the left eye (Sol. Atropin 0.10%) to computerized refractometer (Speedy Righton – K), and the control visits and verification of subjective visual acuity for optotypes with pictures, at the distance of 3 m. Ultrasonography of both eyes was carried out in the Depatment for Ehosonography, Clinic for Eye Diseases in Niš (Ultrasound A / B Scanner UD – 6000), Tomey, A-scan probe, inflexible, with a frequency of 10 MHz, the top dimension of 5.3 mm ø flat with local anesthesia (Sol. Tetracaine) and in the Clinic for Eye Diseases in Novi Sad (AB Sonomed EZ Scan 5500 +, the probe 10 MHz, 30 frames / sec). Additional tests were conducted: endocranial magnetic resonance (MR) by standard protocol (magnet Avanto 1.5 T, Siemens) in the Center for Radiology, Clinical Center Niš, then pediatric, neurological observation and karyotype implemented in the appropriate organizational units in the Clinical Center Niš.

The examined child was a third child from the third regular pregnancy, born at term (39th gestational week, body mass 3100 g). Neonatal period was eventless. Older children were healthy, family ocular history was negative. Ophthalmologic findings: right eye did not fix, more often eso in position. The whole right eye was smaller. The right corneal diameter was 7.5 mm and the left 10 mm. The anterior segment was without any abnormality on both sides. Refraction of the left eye was -1.75 / -1.0 (10°). Intraocular pressure was 18 mmHg bilaterally. Indirectly, ophthalmoscopy showed no optical drive to the right, much of the coverage of the retina which choriocapillaris vascularization in the foramen could correspond to the place of departure of the optic nerve. On the left eye it was the optic nerve head round, clear boundaries, the level of other retinal arteriovenous ratio was normal, the area moved an inch-preserved appearance and reflexes. Ultrasonography, B-scan showed no up right optic taper, the bulb as a whole was smaller (Figure 1), and the left eye – the last segment of echographic neat. A-scan showed axial diameter of the right eye, 13.80 mm and 18.30 mm of the left eye.

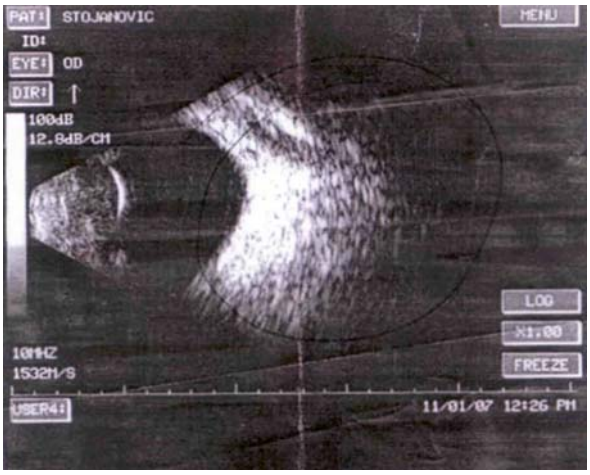

Fig. 1 – Right-sided microphthalmia and aplasia of the optic nerve. Ultrasonography and B-scan did not show upright optic taper, a smaller bulb in size (AB Sonomed EZ Scan 5500 +, the probe 10 MHz, 30 frames / sec)

After ophthalmological examination we performed additional examinations. Endocranial MR showed not only the eyeball smaller diameter, but also absence of the right optic nerve (Figure 2, a), and no anomalies in the central nervous system (Figure 2, b). Karyotype, pediatric (clinical examination and echosonographic examination of the abdomen) and neurological examination were normal.

We explained to the parents the nature of abnormalities of the right eye in their child. The girl was sent to the

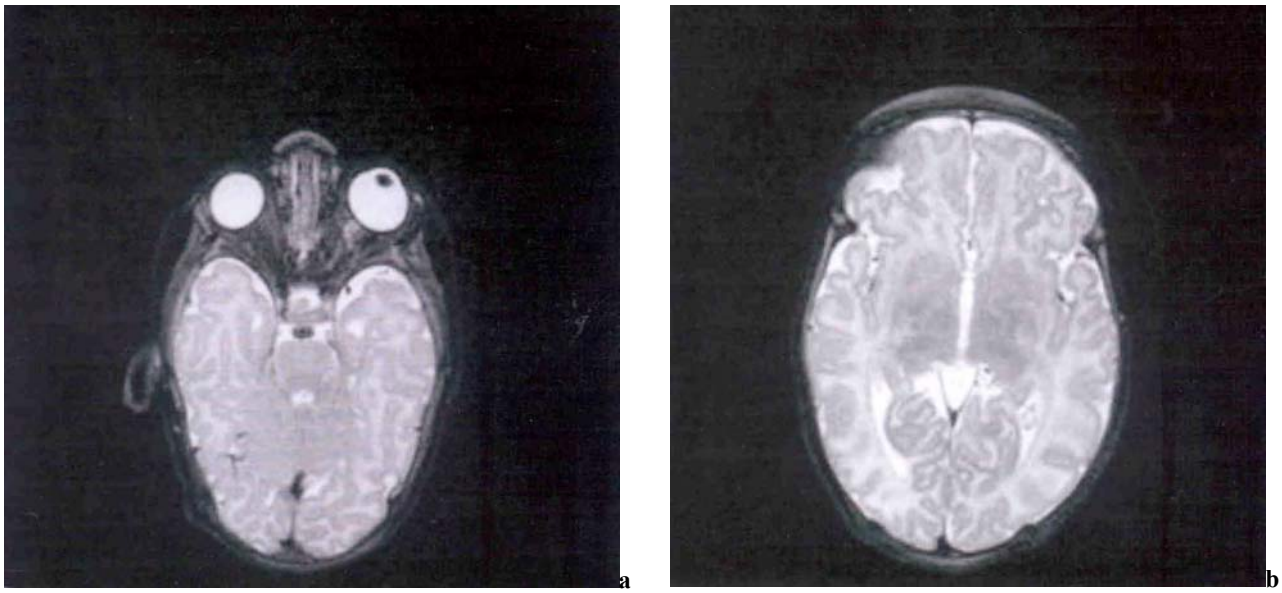

Fig. 2 – Right-sided microphthalmia and aplasia of the optic nerve. Magnetic resonance of endocranial port of the eyeball except smaller diameters, observed the absence of the right optic nerve (a), no anomalies in the central nervous system (2) (Avanto 1.5 T, Siemens)

appropriate prosthetic center for further treatment and monitoring.

On subsequent check-ups, in accordance with the objective refraction of the left eye, the girl was given an appropriate adjustment for the left eye -1.0 / -0.50 (10°) (right eye without correction, plan glass), with whom she recorded visual acuity near the maximum for the age (VOS = cc = 0.6–0.8, 3 m, frames).

In the appropriate time period, a temporary ocular prosthesis was changed for the new one. The patient is under control of the competent ophthalmologist and prosthetic (Figures 3, a and b).

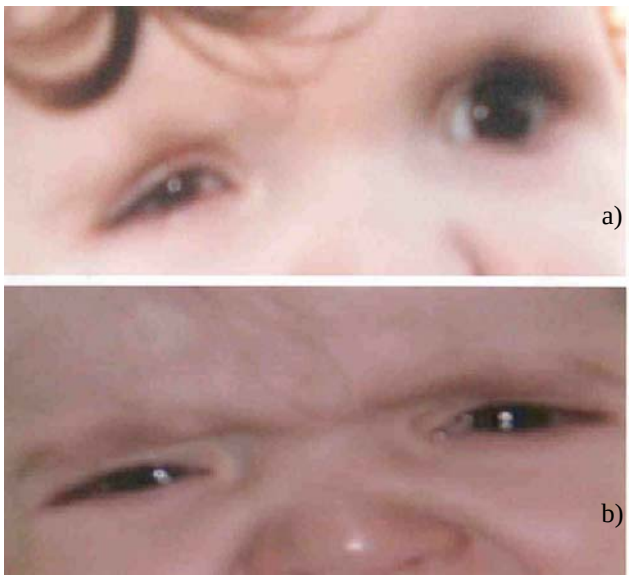

Fig. 3 – Right-sided microphthalmia and aplasia of the optic nerve.
The first ophthalmic examination in a 11-month-old child (a); one of the temporary prosthesis, check-up a few months later (b)

Discussion

The eye starts to develop early in about week 4 (day 22) before joining the neural folds in the neural tube. The distal part of optic vesicles (day 32) invaginites and transforms into the optical cup from which later the retina is formed and proximal remains narrow and makes the optical stalk which resultes in the ocular nerve [17, 18]. Embryological disturbance events and interactive process between the different embryonic structures and cell types are the base for the development of congenital anomal [19].

The pathogenesis of optic nerve aplasia remains unclear. Aplasia of the optic nerve was first described 140 years ago by von Graef's, but the cause of it is still unclear. The defective embryonic fissure forms, the failure of mesenchymal angle hyaloid system to infiltrate the embryonic fissure, or primary agenesis of retinal ganglion cells are referred as potential causes.

Animal models showed that aplasia of the optic nerve can occur spontaneously in several animal species, and experimentally can be induced by treating pregnant bunnies with hypoglycemic sulfonamides, creating a deficit of folic acid in pregnant muscle, exposing mice and fetal mice to X-rays, and treating bunnies at the time of fertilization with actinomycin D. Multiple ocular abnormalities are basically the result of the loss of cells: nerve, retinal pigment epithelial cells, corneal endothelium, retinal coloboma, iris hypoplasia, microphtalmia [13].

Aplasia of the optic nerve is characterized by afferent pupillary defect, reduced vision in the absence of light perception, a typical ophthalmologic picture, and fluorescein angiography demonstrates the absence of retinal blood vessels at the side of aplasia. Perimetry is not registered in cell aplasia, ERG and EOG are abnormal. Echography does not show optic taper, and bulb as a whole is smaller. Radiologi-

cal examination shows small optic foramen on the side of aplasia, the orbit is smaller, while documenting the absence of endocranial MRI optic nerve affected side [1–15]. There are predilections in regard to sex and race of patients with aplasia of the optic nerve. In our case family history was negative as well as genetic examination. Pregnancy has been described as neat, though the possible influence of external factors such as episodes of viral infections in the first trimester, smoking, exposure to acetone could not be excluded. Microphtahalmos, enoftalmus and ptosis are the most common associated anomalies with aplasia of the optic nerve, wherein the microphtalamos is found in 20 of 25 releases as a follow-up of anomalies [13].

Microphthalmia is located in 3.2%–11.2% of blind children. Predilection with respect to gender or race can be simple or complex [16], unilateral or bilateral in over 50% of cases associated with systemic abnormalities. Anophthalmia and microphthalmia are estimated to 3–14 to 100.000 [20]. Epidemiological data indicate the following risk factors: maternal age (over 40 years of age), multiple pregnancies, children with low birth weight, low gestational age [16], prenatal infection with rubella, cytomegalovirus, fetal alcohol [21] etc.

Ragge et al. [20] recommend anophthalmia/microphthalmia with a complete ophthalmic examination and electrodiagnostic procedures – flash VEP in anophthtalmia/microphthalmia, pattern VEP in detection of a dysfunction of the optic nerve and retinal ERG in case of dysfunction. There is a need to correlate ocular abnormalities with brain development and a good radiological perception of such patients. Due to better contrast resolution and the absence of multiplane radiation, MRI with sophisticated radiological imaging is preferable and becoming an imperative in modern ophthalmology. Morphophysiological differences in orbital structures, and the difference in tissue density in anatomical parts of the intra- and extraconal segment, the possibility of perceiving the sellers region, optic chiasm and endocranial structures in the exclusion of the central causes of clinical symptoms and signs, provide an almost perfect MRI visualization of different incipient and advanced pathological states in eye diseases [20].

In case of microphtalamos, a coordinated team of ophthalmologists, pediatricians, radiologists is needed in neonatal period. A complete pediatric examination and a system to search abnormalities associated with early ophthalmic examination (in case of severe abnormalities of the eye, but during the first 2 weeks of age) are required. Ophthalmologic diagnosis and assessment of vision are crucial for planning further treatment and monitoring of patients [21]. It is necessary for the parents to explain the nature of the anomaly, further observation and monitoring plan for the child, with mandatory genetics consultation.

In pediatrics, renal ultrasonography is required to exclude associated anomalies of the eye and kidney disease, as well as screening for intrauterine infections (rubella, varicella, toxoplasmosis gondii, herpes simplex virus, cytomegalovirus), and testing of other family members in relation to ocular pathology (anophthalmia or microphthalmia, anterior segment malformations, glaucoma, coloboma, retinal dystrophy and optic hypoplasia). Genetic tests are necessary for chromosomal analysis and testing of individual gene is required [20].

It is noted that the rapid increase in the first three years of life [16, 17] reach 78% of the size of the fourth year, and the size of adults of twenty [17]. In the third month of life, a person reaches 40% of adult size. The rapid growth of persons recorded in the second year to 70% and from 5.5 years 90% of the size of an adult person [16]. For these reasons, it is necessary to monitor and correct developmental anomalies of the eye and/or orbit in the appropriate prosthetic center. To correct the anomaly is to minimize deformity of the face and prevent any consequences of a sociomedically handicapped child, to increase opportunity of education, correct development, socialization and integration of a patient into active working population. Children with this rare anomaly of the optic nerve require to be treated by a team of ophthalmologists, prosthodontists, pediatricians, geneticists, radiologists at an early age.

Conclusion

Further aesthetic and functional development of young people is a primary goal in monitoring aplasia of the optic nerve, rare congenital anomalies in the malformed eye. It is realized through the coordinated team of ophthalmologists, prosthodontists, pediatricians, geneticists at the earliest stage. Pediatric review and search for associated systemic abnormalities, early ophthalmologic examination and assessment of vision are essential for further treatment planning. Parents should be aware of the circumstances, the need and plan for monitoring of their child.

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Matko Marušić – Life of an Editor

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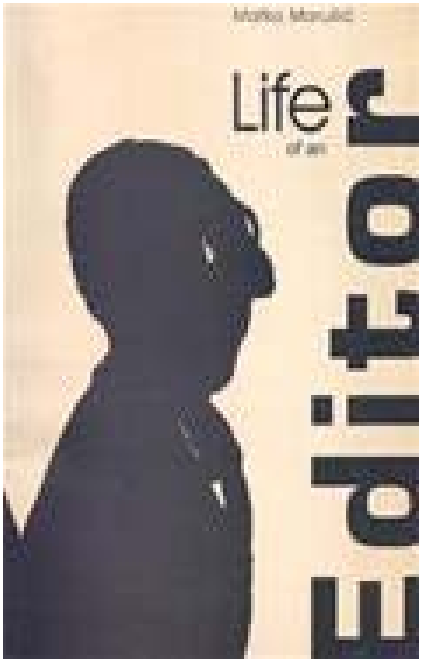

The author of this booklet, Matko Marušić, is the founder of the Croatian Medical Journal (CMJ). He was the Editor-in chief of this journal for 17 years (1991–2009) and Editor Emeritus (since 2009). In this booklet, he uses a light and humorous way to explain his efforts and difficulties he faced trying to make final this journal from scientific periphery a good and true international journal – the aim he finally achieved.

Acquisition of new contributions was the main duty of the editor-in-chief of this new journal, and this duty is described in the first chapter of this booklet. Further description deals with the editor's efforts to improve submitted manuscripts, and his introduction of pre-review was helpful. The role of coeditor in-chief, the entire editorial board and reviewers was also explained and gratefully acknowledged. However, for authors intending to submit their manuscripts to any journal, the most valuable part of this chapter is listing of common mistakes, errors and omissions in submitted manuscripts. Finally, the author's duties regarding proofs, and editors' duties regarding printing, are also explained.

The entire second chapter describes how important was to write "Instructions for authors" in such a way to make them clear, instructive, and understandable. Undoubtedly, strict adherence to the rules of scientific publishing listed in these instructions is of great help in making manuscripts suitable for submission.

In the third chapter of the book Matko Marušić pays tribute to hard, diligent, honest and dedicated job of editors, particularly to his coeditor-in-chief, Ana Marušić, to whom the CMJ owes the great achievement – to become a reputable international journal.

A chapter entitled "The end article" tells the story about how, and why, the author decided to take a leave from his 17-year-long position as editor-in-chief of the CJM. This decision originated from the notorious affair of Asim Kurjak, the author whose plagiarized articles, uncovered abroad, were retracted according to the good editorial practice. This resulted in the orchestrated attacks to editorial freedom and attacks ad hominem by the authorities of the Zagreb University School of Medicine. Although the editors of the CMJ had the entire international scientific community on their side, Matko Marušić finally resigned from the position of editor-in-chief and took the position of dean of the University of Split's School of Medicine. Interestingly, these sad events did not exasperate him; only a trace of disappointment relates to the fact that fairness came from legal authorities, but not from his colleagues.

In spite of the title of this booklet, the contents is interesting not only for the editors, but also, and very much so, to the authors. Since every step of writing for scientific journals is described in detail, and since further destiny of submitted manuscripts is also described, the authors can learn how to write articles and get it published in good and reputable international journals. A long list of relevant literature is provided to those readers who are willing to learn even more on each and every step of publishing for medical journals.

I think that the other quality of this lovely book should be emphasized: although the booklet deals with very serious and important topic, it is written in such an amusing and humorous style that it reads with great pleasure. That is why I recommend this booklet to the larger scientific audience.

Research Adviser,,
M.D., Ph. D Ljiljana Vučković-Dekić

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Od 1. januara 2012. godine Vojnosanitetski pregled prelazi na e-Ur: Elektronsko uređivanje časopisa.

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Priprema rada

Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** i **literatura.**

1. ***Naslovna strana***

a) Naslov treba da bude kratak, jasan i informativan i da odgovara sadržaju rada. Podnaslove treba izbegavati.

b) Ispisuju se puna imena i prezimena autora.

c) Navode se puni nazivi ustanove i organizacijske jedinice u kojima je rad obavljen i mesta u kojima se ustanove nalaze, sa jasnim obeležavanjem odakle je autor, koristeći standardne znake za fus-note.

2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **uvod i cilj** rada, osnovne procedure - **metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi - **rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt (**250** reči) ima podnaslove: *uvod/cilj, metode, rezultati* i *zaključak*. Za apstrakte na engleskom dozvoljeno je i do **450** reči. Strukturisani apstrakt je obavezan za metaanalize (istog obima kao i za originalne članke) i kazuistiku (do 150 reči, sa podnaslovima *uvod, prikaz slučaja i zaključak*). Ispod apstrakta, pod podnaslovom „Ključne reči" predložiti 3–10 ključnih reči ili kratkih izraza koji oslikavaju sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Zaključak** može da bude posebno poglavlje ili se iznosi u poslednjem pasusu diskusije. U **uvodu** ponovo napisati naslov rada, bez navođenja autora. Navesti hipotezu (ukoliko je ima) i ciljeve rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo strogo relevantne podatke iz literature i ne iznositi opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

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Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

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Literatura se u radu citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i dodaje et al. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi". Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci" (u zagradi). Podaci sa *Interneta* citiraju se uz navođenje datuma.

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

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

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Koristiti samo standardne skraćenice, izuzev u naslovu i apstraktu. Pun naziv sa skraćenicom u zagradi treba dati kod prvog pominjanja u tekstu.

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www.vma.mod.gov.rs/vsp/download/uputstvo_za_autore.pdf.

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General review papers type will be accepted by the Editorial Board only if the authors prove themselves as the experts in the fields they write on by citing not less than 5 self-citations.

Papers should be written on IBM-compatible PC, using 12 pt font, and double spacing, with at least 4 cm left margin. **Bold** and *italic* letters should be avoided. Observational and experimental articles, reviews and meta-analyses, should not exceed 16 pages (including tables and illustrations); case reports – 6; short communications – 5; letters to the Editor, reports on scientific meetings and book reviews – 2.

All measurements should be reported in the metric system in terms of the International System of Units (SI). Standard, internationally accepted terms should be used. Papers should be submitted on a diskette (CD) in triplicate (original and two copies).

MS Word for Windows (97, 2000, XP, 2003) is recommended for word processing; other programs are to be used only exceptionally. Illustrations should be made using standard **Windows** programs**.** Avoid the use of colors in graphs.

Papers are reviewed anonymously by at least two editors and/or invited reviewers. Remarks and suggestions are sent to the author for final composition. Galley proofs are sent to the first author for corrections that should be returned within 3 days. Manuscripts accepted for publication are not being returned.

Preparation of manuscript

Parts of the manuscript are: **Title page; Abstract with key words; Text; References**.

1. ***Title page***

a) The title should be concise but informative. Subheadings should be avoided;

b) full name of each author;

c) name and place of department(s) and institution(s) of affiliation, clearly marked by standard footnote signs.

2. ***Abstract and key words***

The second page should carry a structured abstract with the title for original articles, metanalyses and case reports. The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations. S t r u c t u r e d abstract should contain typical subtitles: *background/aim, methods, results* and *conclusion*. The abstract for metaanalyses and obrginal papers should have up to 450 words, and up to 150 words for case reports (with subtitles *background, case report, conclusion*). Below the abstract authors should provide, and identify as such, 3–10 key words or short phrases that will assist indexers in cross-indexing the article and will be published with the abstract.

3. ***Text***

The text of original articles is divided into sections with the headings: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

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Methods. Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approvement of the Ethnics Committe for the tests in humans and enimals.

Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is to emphasize the new and important aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

References

References should be superscripted and numbered consecutively in the order in which they are first mentioned in the text. **The references must be verified by the author(s) against the original document.** List all authors, but if the number exceeds 6, give 6 followed by et al. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be designated as ”in press“. Information from manuscripts not yet accepted should be cited in the text as ”unpublished observations“. References are cited according to the ***International Committee of Medical Journal Editors.*** *Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med 1997; 126: 36–47. Updated October 2001.*

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. 413-28.

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

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

Tables

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.

Illustrations

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Legends for illustrations are typed on a separate page, with arabic numerals corresponding to the illustrations. Identify and explain each one clearly in the legend symbols, arrows, numbers, or letters used to identify parts of the illustrations. Explain the internal scale and identify the method of staining in photomicrographs.

Abbreviations and symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstracts. The full term for which an abbreviation stands should precede its first use in the text.

Detailed Instructions are available at the web site:
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