YU ISSN 0042-8450

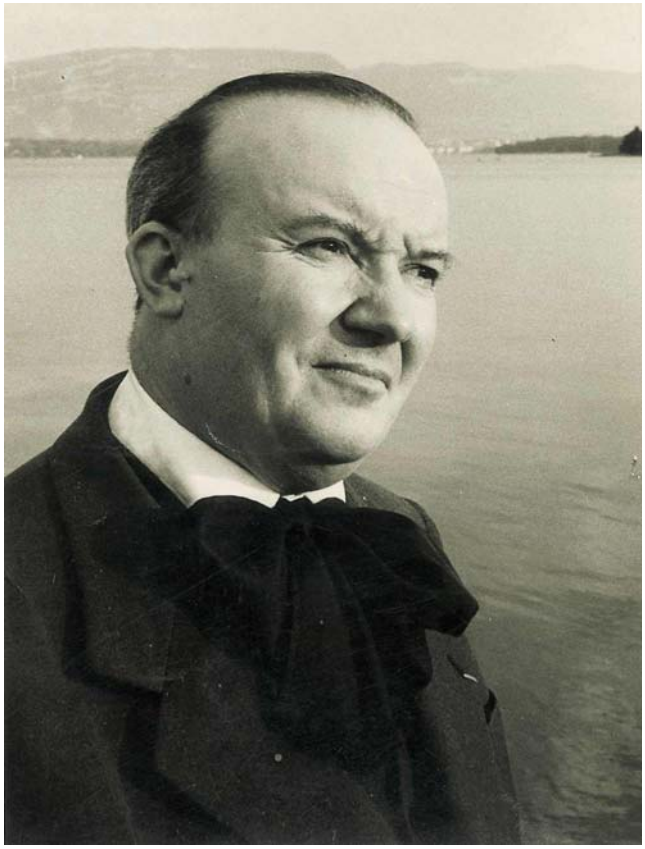
ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2017; January Vol. 74 (No. 1): p. 1–116.



Vojnosanitetski Pregled 2017 January Vol. 74 (No. 1): p. 1–116.

YU ISSN 0042-8450 vol. 74, br. 1, 2017.

VOJNOSANITETSKI PREGLED

Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine

Časopis nastavlja tradiciju *Vojno-sanitetskog glasnika*, koji je izlazio od 1930. do 1941. godine

IZDAVAČ
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Radove objavljene u „Vojnosanitetskom pregledu“ indeksiraju: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Sadržaje objavljuju Giornale di Medicine Militare i Revista de Medicina Militara. Prikaze originalnih radova i izvoda iz sadržaja objavljuje International Review of the Armed Forces Medical Services.

Časopis izlazi dvanaest puta godišnje. Pretplate: Žiro račun br. 840-314849-70 MO – Sredstva objedinjene naplate – VMA (za Vojnosanitetski pregled), poziv na broj 1227423129552141 5. Za pretplatu iz inostranstva obratiti se službi pretplate na tel. 3608 997. Godišnja pretplata: 5 000 dinara za građane Srbije, 10 000 dinara za ustanove iz Srbije i 150 € (u dinarskoj protivvrednosti na dan uplate) za pretplatnike iz inostranstva. Kopiju uplatnice dostaviti na gornju adresu.

Štampa Vojna štamparija, Beograd, Resavska 40 b.

YU ISSN 0042-8450 vol. 74, No. 1, 2017

VOJNOSANITETSKI PREGLED

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

PUBLISHER
Military Health Department, Ministry of Defence, Belgrade, Serbia

Editorial Office: Military Medical Academy, Institute for Scientific Information, Crnotravska 17, PO Box 33–55, 11 040 Belgrade, Serbia. E-mail: **vsp@vma.mod.gov.rs**

Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.

The Journal is published monthly. Subscription: Giro Account No. 840-314849-70 Ministry of Defence – Total means of payment – VMA (for the Vojnosanitetski pregled), refer to number 12274231295521415. To subscribe from abroad phone to +381 11 3608 997. Subscription prices per year: individuals 5,000.00 RSD, institutions 10,000.00 RSD, and foreign subscribers 150 €.

Printed by: Vojna štamparija, Beograd, Resavska 40 b.

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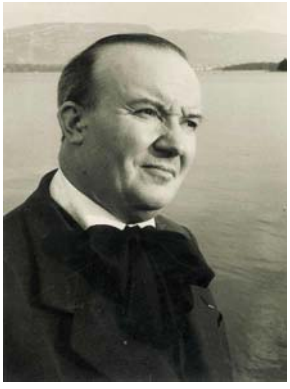

Raoul Follereau (August 17, 1903 – December 6, 1977), a French humanitarian to whom goes the credit of establishing the World Leprosy Day, observed even today in most countries in the world on the last Sunday of January each year. The day aims to raise awareness of a disease that many people believe to be eradicated, when in fact around 210,000 new cases are diagnosed each year.

Raul Folero (17. avgust 1903 – 6. decembar 1977), francuski humanitarac koji je najzaslužniji za ustanovljenje Svetskog dana borbe protiv lepre. Ovaj dan obeležava se, čak i danas, u većini zemalja širom sveta svake godine u poslednjoj suboti januara sa ciljem da se upozori na ovu bolest, za koju mnogi misle da je iskorenjena, iako se, u stvari, svake godine dijagnostikuje oko 210 000 novih slučajeva lepre.

E D I T O R I A L

UDC: 655.411
DOI: 10.2298/VSP1701005D

Towards 2017

U susret 2017.

Silva Dobrić

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

As usual, the Editorial of the first issue of each volume of the *Vojnosanititeski pregled* (VSP) is dedicated to the analysis of the work of the Editorial Staff of the Journal in the past year and plans for the future. Accordingly, the manuscripts received from the beginning of the year to, finally, December 20, 2016, as well as articles that were published in 2016, were analyzed.

In 2016 (from January 1 to December 20) we received 396 manuscripts, which is almost identical to the number of manuscripts we had received in the previous year, 2015. Of that number, 123 (31.1%) were rejected, 131 (33.1%) were accepted for publication, while the remaining 142 (35.8%) are still under review. The reasons for manuscript rejecting were usually negative opinion of the reviewers, and, then, the mismatch manuscripts to the technical requirements of the Journal, as well as their contents that are beyond the thematic framework of the VSP.

The largest number of submitted manuscripts, as in previous years was in the category Original articles (68.4) and Case reports (23.5%), followed by those from the category General reviews (3.3%), Current topics (1, 5%), Practical advices for physicians (1%), History of medicine (1%), Letters to the Editor (0.8%) and Meta-analyses (0.3%).

Analysis of submitted manuscripts in relation to the institutions of their authors, shows similar situation to that of previous years. Most of them (more than 80%) came from authors of the so-called civil academic and scientific institutions, of which about 11% from abroad, and the rest of about 17% of the authors from military medical institutions, primarily the Military Medical Academy (MMA) in Belgrade.

As it is known, any manuscript submitted for publication in the VSP, before it enters the review process, is subjected to checking to (self)plagiarism using the system CrossCheck Service (iThenticate software), which allows us to promptly recognize download larger parts of already published their own or someone else's papers without explicitly quoted sources from which the text is taken. Thanks to this, one of the submitted manuscripts was omitted from further procedures for publishing because it was determined that it is almost identical to the paper which the authors already had published in an international journal. Due to the attempt of such dishonest behavior, a decision to ban these authors from publishing in the VSP in next 5 years was made.

The number and structure of published papers in 2016 also were not significantly different compared to the past few years. A total of 186 articles in various categories were published including one Meeting report and one Book review (Table 1).

Table 1

Categories and the number of articles published in the Vojnosanitetski Pregled in 2016

Category	Articles	
	n	%
Editorial	7	3.9
Original Article	99	53.3
General Review	3	1.6
Current Topic	3	1.6
Case Report	51	27.5
Short Communication	6	3.2
Practical advices for the physicians	6	3.3
Letter to the Editor	4	0.5
History of Medicine	2	1
In focus	2	1
Personal opinion	1	0.5
Meeting report	1	0.5
Book Review	1	0.5
Total	186	100.0

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As in earlier years, the majority of published papers were from the category Original articles (53.2%) and Case reports (27.4%), which is not surprising having in mind that many years ago, as stated above, manuscripts from these categories were the most often submitted to the Journal.

As in the case of manuscripts submitted for publication, in the case of published papers in 2016, the largest number was from civil institutions (around 54.3%), including papers by authors from abroad (7.5%), as well as joint papers by local authors from civil institutions and authors from abroad (5.4%). The rest of published papers (45.7%) referred to those of authors from military institutions. Of these, 22.6% were written by local authors only from military institutions, 21.5% were common papers by local authors from civil and military institutions, 0.6% common papers by local authors from military institutions and authors from abroad, and 1% common papers written by local authors from military and civil institutions, and authors from abroad.

The above data on published papers relate to those published in printed version of the Journal, many of which were previously e-published as Online first with DOI number (available on the website of the Journal, as well as in the Directory of Open Acces Journal (DOAJ) database, and then, according to the earlier established order, transferred to a printed issues of the Journal.

In 2016, the practice of electronic publication of accepted papers as Online first with DOI number in the so-called "raw" form was introduced, with notice that the manuscript still has to be subjected to copyediting, typesetting, language editing, professional editing and authors` review of galley proof before publishing that could affect the final version of the manuscript.

In this way we enabled immediate availability of accepted papers to readers of the Journal with the possibility of their citation, which is the maximum short time of paper publication acceptance to its publishing. On the other hand, publishing of the paper in this way, authors can use as the proof that their paper has already been published, because it is, sometimes, a necessary condition for progress in professional and/or academic career for many of them.

Of papers that were accepted for publishing in 2016, two were found had been mostly self-plagiarized (i.e. the great parts of their contents had already been published in another journals). That is why these papers were withdrawn from further publishing processing, and their authors, like in the case of self-plagiarism discovered when submitting manuscripts, were punished by ban to publish in the VSP for next 5 years.

One of activities of the Editorial Staff of the VSP in 2016 was the full defining of all segments of the editorial policy of the journal, according to the principles of good practice in scientific publishing, and its renewed text is available on the website of the Journal. Also, the creating of the new website of the Journal, by modern design, and enriched with many contents that will be useful to our readers is currently in progress. The new website should soon be put into operation.

As before, a priority in the work of the Editorial Board and the Editorial Staff of the Journal will be raising its quality at the highest possible level, including publishing only papers with thematically actual and comprehensible contents of high quality. This is the only way to ensure greater influence of the Journal. That this is the right path tells us the value of impact factor (IF), which rises from year to year (the last IF of the VSP for 2015, awarded in mid-June 2016 amounted to 0.355, which is 21.5% more than the previous IF for 2014).

In realization of this goal we count, as earlier, on great support of our reviewers, to whom, as always, we most sincerely thank for their efforts in improving the quality of papers published in the VSP.

The names of those who were engaged in peer-reviewing manuscripts submitted for publishing in the VSP in 2016 are listed in Table 2.

Table 2

Reviewers of the Vojnosanitetski pregled in 2016

Ač Nikolić Eržebet
Aćimović Slobodan
Ajdinović Boris
Aleksić Petar
Aleksić Predrag
Antić Branislav
Antonijević Nebojša
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Krstić Zoran
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Schulz Richard
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ORIGINAL ARTICLES

UDC: 616.133-004.6::617.7-007.681
DOI: 10.2298/VSP150320058J

The importance of developing atherosclerosis in pseudoexfoliation glaucoma

Značaj ateroskleroze u pseudoeksfolijativnom glaukomu

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***Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; †Clinic of Ophthalmology, Clinical Center of Kragujevac, Kragujevac, Serbia**

Abstract

Background/Aim. Pseudoexfoliation syndrome (XPS) is an age-related systemic disorder characterized by increased production and accumulation of elastic microfibrillar material in different tissues of the body: skin, connective tissue portions of visceral organs, periphery blood vessels and the eye, as well. The aim of our study was to determine the significance of atherosclerotic changes in the carotid arteries in the development of XFS and pseudoexfoliation glaucoma (XFG). **Methods.** The study included 120 patients – 40 patients *per* each of the three defined groups: XFS group, XFG group and age- and sex-matched control subjects (control group) without XFG. Blood samples were collected from the patients before cataract surgery. Serum levels of total cholesterol, low-density lipoprotein – LDL, high density lipoprotein – HDL and triglycerides were analyzed by standard laboratory techniques. Standard ultrasonography of the carotid blood vessels was performed in all the participants. **Results.** Lipid's profile was disturbed in the patients with XFS and XFG with statistical significance p control group ($p < 0.01$). Systolic and diastolic pressure was elevated in the patients with XFS and XFG ($p < 0.01$). Resistance index was increased in the patients with XFG ($p < 0.01$). Intima-media thickness was prolonged in patients with XFG ($p < 0.01$). **Conclusion.** A disturbed lipid profile with elevated resistancy index and intima-media thickness and increased systolic and diastolic pressure were compulsory findings in patients with developed XFG. So, these factors could be considered as risk. It seems to be difficult to inhibit the process of pseudoexfolation production in the whole body, but it appears that with proper therapy (antihypertnesive, cardiotoncs, etc.) and adequate nourishing, the process of XFG development could be interrupted.

Key words:
exfoliation syndrome; atherosclerosis; carotid arteries.

Apstrakt

Uvod/Cilj. Pseudoeksfolijativni sindrom je sistemski poremećaj starijeg životnog doba, koji se karakteriše povećanom proizvodnjom i akumulacijom elastičnog mikrofibrilarnog materijala u različitim tkivima tela: koži, vezivnom tkivu unutrašnjih organa, perifernim krvnim sudovima i oku. Cilj istraživanja bio je da se utvrdi značaj aterosklerotičnih promena u karotidnim arterijama u razvoju pseudoeksfolijativnog sindroma i pseudoeksfolijativnog glaukoma. **Metode.** Studijom je bilo obuhvaćeno 120 bolesnika, po 40 bolesnika u svakoj od tri definisane grupe: sa pseudoeksfolijativnim sindromom (XFS), sa pseudoeksfolijativnim glaukomom (XFG) i kontrolna grupa bez XFG (uparena po starosti i polu). Uzorci krvi su sakupljeni kod bolesnika pre operacije katarakte. Nivo (ukupnog holesterola, *low-density lipoprotein* – LDL, *high density lipoprotein* – HDL i triglicerida u serumu analizirani su standardnim laboratorijskim tehnikama. Standardna ultrasonografija karotidnih arterija urađena je kod svih ispitanika. **Rezultati.** Lipidni profil bio je poremećen kod bolesnika sa XFS i XFG, sa statističkom značajnošću u odnosu na kontrolnu grupu ($p < 0,01$). Sistolni i dijastolni pritisak bio je statistički značajno povišen kod bolesnika sa XFS i XFG ($p < 0.01$). Indeks rezistencije bio je povećan kod bolesnika sa XFG ($p < 0,01$), dok je intimamedija komples bio statistički značajno produžen kod bolesnika sa XFG ($p < 0.01$). **Zaključak.** Poremećen profil lipida sa povišenim indeksom rezistencije i debljinom intimomedija kompleksa kao i povišenim sistolnim i dijestolnim pritiskom su ključni nalazi kod bolesnika sa razvijenim XFG. Zbog toga ih treba uzeti u obzir kao faktore rizika. Čini se da je teško da se inhibira proces proizvodnje pseudoeksfolijacija u celom telu, ali i da se uz pravilnu terapiju (antihipertnenzivni lekovi, kardiotonici, itd) i uz adekvatan režim ishrane, proces razvoja pseudoeksfolijativnog glaukoma može da prekine.

Ključne reči:
eksfolijativni sindrom; ateroskleroza; aa.carotis.

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Introduction

Pseudoexfoliation syndrome (XPS) is an age-related systemic disorder characterized by increased production and accumulation of elastic microfibrillar material in different tissues of the body: skin, connective tissue portions of visceral organs, periphery blood vessels and the eye, as well [1].

In the eye, pseudoexfoliation (PEX) is associated with high risk for the development of glaucoma, called pseudoexfoliative glaucoma (XFG) [2].

As PEX can be found in the whole body, especially in the blood vessel wall, it can be associated with different vascular diseases [3]. Exfoliation material was physiologically detected in vessel wall, myocardium, smooth and striated muscle cells, skin and visceral organs [3, 4].

Today, it is not yet clear what is the key factor in the pathogenesis of different vascular diseases. Iris and conjunctival vasculopathy is documented by indocyanin green angiography [5, 6]; exfoliation material is physiologically presented in the vessel's wall and pericytes in the whole body [3, 4, 7] as well as elevated homocystein level in the serum of the patients with PEX [8]. PEX is indicated for high risk for vascular disease: like stroke, myocardial infarction, and venous occlusions. It is also known that PEX can be found in patients with aortic aneurism which can be explained by abnormal fiber accumulation in the vessel wall [9].

Atherosclerosis is the process closely related with a vascular disease [10].

Abnormal lipid's profile, deregulated glycemia and high blood pressure can be the potential risk factor for vascular disease in the whole body [11]. The systemic manifestations of XFS and XFG, with emphasis on changes in the blood vessels (carotids) as well as changes in the metabolism of lipid material, can be defined as an atherosclerosis risk factor. The aim of our study was to determine the significance of atherosclerotic changes in carotid arteries in the development of XFS and XFG.

Methods

The study included 120 patients – 40 patients *per* each of the three defined groups: the XFS group, the XFG group and age/sex-matched control subjects without PEX. Complete ophthalmological examination was performed for each participant: measurement of best-corrected visual acuity (Snellen charts), intraocular pressure (IOP) measured by Goldmann applanation tonometry, detailed slit-lamp examination, gonioscopy, perimetry (Octopus 900; Haag Strait, Koeniz, Switzerland), and indirect ophthalmoscopy. Slit lamp examination, as well as gonioscopy, was the basis for the diagnosis of PEX in the eye – exfoliation material on the anterior lens capsule or pupillary margin in at least one eye; and high pigmented iridocorneal angle.

PEX deposition with elevated IOP, optic disc glaucomatous changes [(neuroretinal rim and inferior-superior-nasal-temporal (ISNT rule)] and functional failure of the visual field (generalized depression, paracentral scotoma, arcuate or Bjerrum scotoma, nasal step, altitudinal defect temporal wedge, central island) were the entries for XFG group. The patients with the history of inflammatory eye disease, ocular trauma, ocular infection, severe retinal disease, myopia, intraocular surgery within the last 12 months, or laser surgery within the last 3 months were excluded from the study.

Blood samples were collected from the patients before cataract surgery. Biochemical analyses were done for responders fasting for at least 12 hours. Standard laboratory techniques were used for analyzing serum levels of lipid profiles including total cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL) and triglycerides.

Prior to blood pressure measurement the participants were asked to rest for 5 minutes. Blood pressure was measured, using an Omron M1 plus (OMRON Matsusaka Co. Ltd., Japan) digital blood pressure monitor with an appropriate-sized cuff. Arterial hypertension was diagnosed if the systolic blood pressure was 140 and/or diastolic blood pressure 90 mmHg or higher and antihypertensive drugs were used during the past 2 weeks [12]. Three consecutive measurements with a two-minute interval between measurements were performed and the mean value was used for analyses.

Measurements of the resistance index and intimaemedia thickness during the arterial pressure pulse were performed using ultrasonography (conventional ultrasound scanner – Portable Digital Ultrasound machine Scanner system 3.5 Mhz, Convex probe with 3D, Hongkong, China).

The study was conducted in accordance with the Declaration of Helsinki and it was approved by the local ethics committee. All the subjects were informed about the study procedure and they consented to participate. Informed consent was obtained from each participant.

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

The distribution of the variables was checked with Kolmogorov–Smirnov's test. As all variables were distributed normally, they were expressed as the mean ± SD (Kruskal-Wallis test was used to compare the groups).

Results

The biochemical parameters of the elected groups are given in Figure 1. The mean serum total cholesterol (XFS/XFG: 205.32 ± 33.25/ 205.7 ± 29.38 mg/mL), LDL (XFS/XFG 125.22 ± 15.71/133.4 ± 18.42 mg/mL), and triglycerides: (XFS/ XFG: 133.5 ± 11.23/ 133.15 ± 13.84 mg/mL) levels were significantly higher and mean serum HDL (XFS/XFG: 44.25 ± 7.81/ 39.02 ± 7.38 mg/mL) level was significantly lower in the PEX groups (XFG and XFS) than in the control group (cholesterol: 141.42 ± 28.23 mg/mL, LDL: 105.42 ± 16.21 mg/mL, triglycerides: 107.93 ± 10.65 mg/mL, HDL: 46.322 ± 6.38 mg/mL ($p < 0.01$). The mean serum total cholesterol, LDL, and triglycerides levels were significantly higher and the mean serum HDL level was significantly lower in the PEX group (XFG and XFS) than in the control group ($p < 0.01$).

Systolic and diastolic pressure values were significantly higher in the PEX groups (systolic XFS/XFG 129.92 ± 13.83 mmHg/135 ± 9.84 mmHg; diastolic XFS/XFG 77.12 ± 9.81

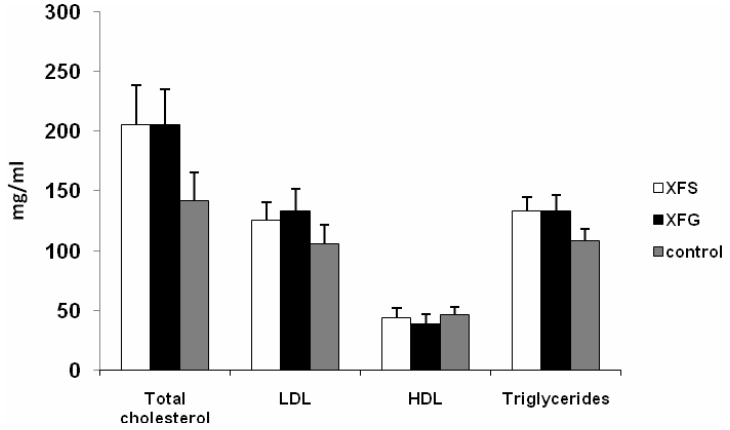

Fig. 1 – Disturbed lipid profile in the patients with pseudoexfoliation syndrome (XFS) and pseudoexfoliation glaucoma (XFG).
LDL – low density lipoproteins;
HDL – high density lipoproteins.

mmHg/80.44 ± 6.89 mmHg) than in the control group (systolic/diastolic: 118.22 ± 9.87 mmHg/135 ± 9.94 mmHg). The systolic and diastolic values are graphically shown in Figure 2. Systolic and diastolic pressure values were significantly higher in the PEX groups than in the control group ($p < 0.01$).

Resistance index was significantly higher ($p < 0.01$) in the XFG group (0.77 ± 0.04) in comparison with the XFS (0.67 ± 0.05) and the control group (0.63 ± 0.05). The patients with XFG (0.91 ± 0.13) had significantly higher values $p < 0.01$ in comparison with XFS patients (0.76 ± 0.09) and the patients from the control group (0.66 ± 0.11) and the results were presented in Figure 3. The patients with XFG had significantly higher values ($p < 0.01$) in comparison with the XFS patients and the patients from the control group.

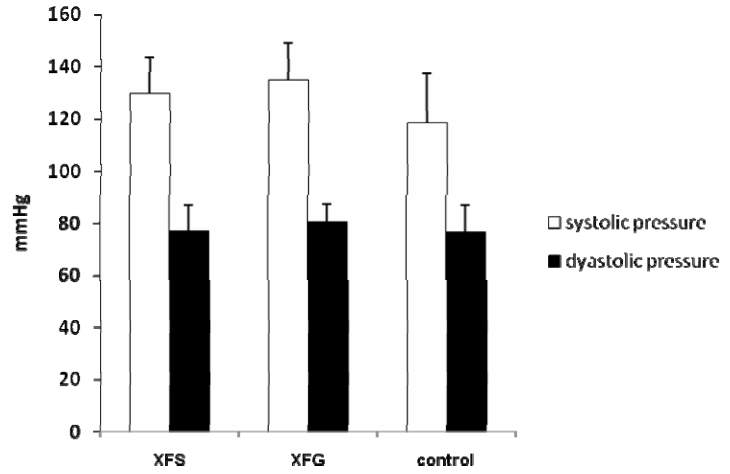

Fig. 2 –Elevated systolic and diastolic pressure in the patients with pseudoexfoliation syndrome (XFS) and pseudoexfoliation glaucoma (XFG).

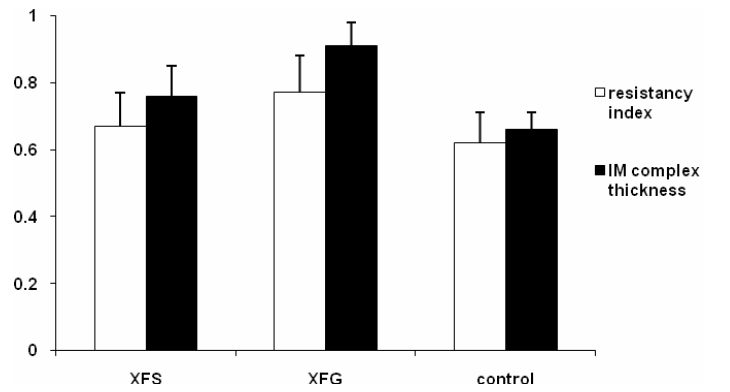

Fig. 3 – Increased resistance index in the patients with pseudoexfoliation glaucoma (XFG). Prolonged intima-media (IM) complex thickness in the patients with XFG.

Disscusion

Pseudoexfoliation syndrome is an age-related disorder in which white flakes accumulate in different tissues in the anterior eye as well as in the whole body, caused by a generalized fibrillopathy [7]. Its pathogenesis is not completely known, but it results in electron-dense microfibrils tissue deposition [13]. The gray-white material can be presented on anterior lens surface and pupillary margin, and can be scraped by papillary movement [14, 15]. Concomitant pigment dispersion with its deposition on anterior chamber structures can be obtained by detailed slit-lamp examination and gonioscopy [15]. Exfoliation material can be found in many different organs: skin, heart, liver, brain, kidney, and eye, too [1]. Earlier studies indicated that iris vasculopathy was described in XFS/XFG [5, 6]; PEX material can be histologically detected in the vessel wall, and pericytes in the whole body [3, 4] and homocystein concentration was elevated [1]. All those findings indicate that vascular diseases could be in a tight junction with XFS/XFG including transient ischemic attacks, hypertension, angina, myocardial infarction, cerebrovascular and cardiovascular disease, aortic aneurysm, Alzheimer-disease and hearing loss [8]. Deregulated parasympathetic vascular control and baroreflex sensitivity, increased vascular resistance and decreased blood flow velocity, arterial endothelial dysfunction, high levels of plasma homocystein and arterial hypertension have been described in PEX patients [16].

The association between different systemic vascular diseases and XFS/XFG remains controversial, despite earlier exposed data [1, 3, 4]. Thus, studies in this ophthalmological field are inconsistent. Our study indicates an association between elevated serum total cholesterol, LDL and triglycerides levels, and the mean systolic and diastolic blood pressures, which were significantly higher where the mean serum HDL level was significantly lower in PEX patients than in control subjects. We can find earlier data about elevated homocystein concentration [8], as well as human cartilage glycoprotein-39 (YKL-40) levels, a new biomarker of inflammation and vascular dysfunction [17, 18], so it can be interlocked with a high incidence of vascular disease in XFS/XFG subjects. Some studies indicated disturbed lipid's profile in PEX patients [18, 19], so previously stated facts can be implicated in the pathogenesis of PEX cardiovascular diseases. Our results concurred with some of numerous studies, in which serum total cholesterol, LDL, and triglycerides levels were significantly higher and the serum HDL level was significantly lower in the PEX groups (XFG and XFS) than in the control group ($p < 0.01$). On the other hand, some data show no significant differences between cholesterol and triglyceride levels in patients with and without PEX [16]. Also, higher arterial pressure, which we observed in our study, represents the risk factor for the development of serious vascular disease [16, 18]. Atherosclerosis is a compound process in the vessel wall, and final effect is the increased resistance and decreased blood flow, so tissue nourishment can be unsettled [19, 20]. Some atherosclerosis markers are the elements of lipid's profile and are useful to evaluate blood flow in the tissue. Also, ultrasonography research is a very important method for rating blood flow in the blood vessel and in the tissue, too. A high resistance index and elevated intima-media thickness are in tight junction with atherosclerotic process and can signify for decreased blood flow, which corresponds to our results. They are also directly associated with disturbed lipid's status. Glaucoma is an ocular disease characterized by disturbed oxidative/antioxidative status activated by increased intraocular pressure and decreased blood flow in the retinal blood vessel, and with the loss of retinal ganglion cells by the apoptotic process [21, 22]. Decreased blood flow of the optic head is the main step of its glaucomatous changes with appropriate functional visual field changes [21, 22]. Increased IOP in XFG is due to accumulated PEX material in the outflow of the humor aqueous; and decreased blood flow in the optic head [2]. Decreased blood flow of the head of optical nerve is due to increased vascular resistance in the carotid and other smaller cranial arteries due to disturbed lipid's profile, elevated homocystein and YKL-40 level [8, 16, 18].

Systemic and ocular blood flow changes, vascular resistance and arterial endothelial dysfunction, high levels of plasma homocystein and arterial hypertension have all been demonstrated in PEX subjects [23–25].

Conclusion

Based the obtained results, as well as on some earlier results, we can suggest new strategies for restraining of pseudoexfoliation glaucoma development. **A** disturbed lipid profile with elevated resistancy index and intima-media thickness and increased systolic and diastolic pressure were compulsory findings in patients with developed XFG. So, these factors could be considered as risk.

In this moment, it seems to be difficult to inhibit the process of pseudoexfoliation production in the whole body, but it appears that with proper therapy (antihypertnesive drugs, cardiotonics, etc.) and adequate nourishing, the process of pseudoexfoliation glaucoma development can be arrested.

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Received on March 20, 2015.
Revised on July 8, 2015.
Accepted on August 25, 2015.
Online First April, 2016.

ORIGINAL ARTICLE

UDC: 616.329-005.1-037
DOI: 10.2298/VSP150717147R

Creatinine-modified Child-Turcotte-Pugh score is a good predictor of a short-term survival in patients with bleeding from esophageal varices

Child-Turcotte-Pugh skor modifikovan u odnosu na nivo kreatinina dobar je prediktor preživljavanja bolesnika sa krvarenjem iz varikoziteta jednjaka

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Abstract

Background/Aim. Bleeding from esophageal varices is a significant factor in mortality of patients with terminal liver cirrhosis. This complication is a major health problem for recipients on the list for liver transplant. In that regard, studying predictors of variceal bleeding episode is very importatnt. Also, it is important to find the best survival predictor among prognostic scores. The aim of the study was to compare validity of prognostic scores in assessment of survival in hospital-treated patients after bleeding from esophageal varices, and to compare validity of baseline Child-Turcotte-Pugh (CTP) and Modul for End-stage Liver Disease (MELD) scores with CTP creatinine modified (CTP-crea) I and II scores in assessment of survival in patients within a long-term follow-up period after the episode of bleeding from esophageal varices. **Methods.** The study included a total of 126 patients suffering from terminal liver cirrhosis submited to testing CTP score score I and II, MELD score, MELD Na score, integrated MELD score, MELD sodium (MESO) index, United Kingdom Model for End-Stage Liver Disease (UKELD) score and updated MELD score. **Results.** Patients with bleeding from esophageal varices most often had CTP score rank C (46,9%). CTP score rank B had 37.5% patients, while the smallest percentage of patients had CTP rank A, 15.6% of them. Patients who have values of CTP score higher than 10.50 and bleeding from esophagus, have 3.2 times higher chance for death outcome compared to other patients. Patients who have values of CTP-crea I score higher than 10.50 and bleeding from esophagus, have 3.1 times higher chance for death outcome than other patients. Patients who have values of CTP-crea II score higher than 11.50 and bleeding from esophagus, have 3,7 times higher chance for death outcome compared to other patients. **Conclusion.** Survival of patients with bleeding from esophageal varices in the short-term follow up can be predicted by following CTP score and creatinine modified CTP scores. Patients with bleeding from esophageal varices who have CTP score and CTP-crea I score higher than 10.5 and CTP-crea II score higher than 11.5, have statistically significantly higher risk from mortality within one-month follow-up compared to patients with bleeding from esophageal varices who have lower numerical values of scores of the CTP group

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

Apstrakt

Uvod/Cilj. Krvarenje iz varikozoteta jednjaka je značajan faktor smrtnosti bolesnika sa terminalnom cirozom jetre. Ova komplikacija je i veliki zdravstveni problem za bolesnike na listi za transplantaciju jetre. U tom smislu proučavanje prediktora varicealnog krvarenja je veoma važno. Takođe, važno je pronaći najbolje prediktore preživljavanja među prognostičkim skorovima. **Metode.** Analizom je obuhvaćeno 126 bolesnika koji boluju od terminalne ciroze jetre. Testirani su Child-Turcotte-Pugh (CTP) skor, CTP kreatinin (CTP-crea) skor I i II, Model for End-Stage Liver Disease (MELD) skor, MELD natrijum (Na) skor, integrisani MELD skor, Meld-Sodium (MESO) indeks United Kingdom Model for End-Stage Liver Disease (UKELD) skor i ažurirani MELD skor. **Rezultati.** Bolesnici sa varicealnim krvarenjem najčešće su imali CTP skor ranga C (46,9%). CTP skor ranga B imalo je 37,5% bolesnika, dok je najmanji procenat bolesnika imao CTP ranga A, njih 15,6%. Bolesnici koji su imali vrednost CTP skora veću od 10,50 i krvarenje iz varikoziteta jednjaka imali su 3,2 puta veći rizik od smrtnog ishoda u odnosu

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na ostale bolesnike. Ispitanici koji su imali vrednost CTP-crea I skora veću od 10,50 i krvarenje iz varikoziteta jednjaka imali su 3,1 puta veći rizik oh smrtsnog ishoda u odnosu na ostale ispitanike. Ispitanici koji su imali vrednost CTP crea II skora veću od 11,50 i krvarenje iz varikozitetea jednjaka imali su 3,7 puta viši rizik od smrtnog ishoda u odnosu na ostale bolesnike. **Zaključak.** Preživljavanje bolesnika sa krvarenjem iz ezofagusnih varikoziteta u periodu kratkoročnog praćenja mogu se predvideti CTP skorom i CTP modifikovanim skorovima. Bolesnici sa krvarenjem iz ezofagusnih variksa koji imaju CTP skor i CTP-crea I skor veći od 10,50 i CTP-crea II skor veći od 11,50 imaju statistički značajno veći mortalitet tokom jednomesečnog praćenja u odnosu na bolesnike sa krvarenjem iz varikoziteta jednjaka i niže numeričke vrednosti skorova CTP grupe.

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

Introduction

Bleeding from esophageal varices is a significant factor in mortality of patients with terminal liver cirrhosis. This complication is also a major health problem for potential recipients on the list for liver transplant.

Advanced liver disease, in addition to portal hypertension and bleeding from esophageal varices, also brings disorders of platelet number and function, coagulation cascade disorders, so that bleeding is difficult to control and is associated with the increased risk of death as outcome.

Episode of dramatic digestive bleeding is the reason for the occurrence of hemorrhagic shock which becomes the trigger for deterioration of hepatic encephalopathy, deepening on consciousness disorders leading to hepatic coma, as well as for the occurrence of hepatorenal syndrome. A large number of studies clearly show that exactly bleeding from esophageal varices, joined with hepatic encephalopathy, deteriorates survival in patients with terminal liver cirrhosis [1–3].

Exactly due to the abovementioned reasons, dealing with variceal bleeding is very important both from the standpoint of clinical medicine, and from the perspective of scientific research. Probably, the most important segment of dealing with this problem is related to the struggle for reduction of mortality rate on the list for liver transplant.

In that regard, studying predictors of variceal bleeding episode is very importatnt. The study of Alempijević et al. [4] contributed to assessing the presence and size of esophageal varices in cirrhotic patients by using a non-invasive method.

Many recent studies have tried to give an answer to the question which prognostic score has the best features in prediction of episodes of bleeding from esophageal varices. However, there is no clear confirmation that Child Turcotte-Pugh (CTP) or Model for End-Stage Liver Disease (MELD) score have advantages over each other. Also, when it comes to predicting survival of a bleeding episode, opinions are divided. Some studies give more positive opinion on CTP score, while other – on MELD score [5, 6].

The aim of the study was to compare validity of prognostic scores in assessment of survival in hospital-treated patients after bleeding from esophageal varices; and to compare validity of baseline CTP and MELD scores with CTP creatinine modified (CTP-crea) I and II scores in assessment of survival in patients within a long-term follow-up period after the episode of bleeding from esophageal varices.

Methods

The study included a total of 126 patients suffering from terminal liver cirrhosis, who underwent hospital treatment at the Clinic for Gastroenterology and Hepatology, Clinical Centre Niš.

The condition of the patients was expressed by numerical values of prognostic scores calculated according to the applicable formulas for calculating. We tested CTP score, CTP creatinine modified (CTP- crea) score I and II, MELD score, MELD New Model (MELD Na) score, integrated MELD (iMELD) score, Meld-Sodium (MESO) index, United Kingdom Model for End-Stage Liver Disease (UKELD) score and updated MELD score. The scores were calculated according o the following formulas:

CTP scores

CTP-A score includes numerical value from 5–6 points. CTP-B score includes numerical value from 7–9 points. CTP-C score includes numerical value from 0–15 points (Table 1).

Creatinine-modified CTP (CTP-crea) scores

a) CTP-crea I score (numerical values 5–19) was calculated by adding the points determined by serum creatinine level. With no added points were patients whose serum creatinine level was less than 1.3 mg/dL, and 4 points were added to numerical value of CTP score in patients whose serum creatinine level was higher than 1.3 mg/dL;

b) CTP-crea II score (numerical values 5–19) includes three categories as follows:

0 points are added to patients whose serum creatinine

Table 1

Child Turcotte Pugh (CTP) Score

Parameter	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
PT/INR	< 1.7	1.71–2.30	> 2.30
Ascites	No ascites	Medium quantity	Medium to large quantity
Hepatic encephalopathy	Stage 0	Stage I–II	Stage III–IV

PT/INR – prothrombin time/international normalised ratio.

level does not exceed 1.3 mg/dL (114.92 μmol/L); 2 points are added to patients whose serum creatinine level is between 1.3–1,8 mg/dL (114.92–159.12 μmol/L); 4 points are added to patients whose serum creatinine level exceeds 1.8 mg/dL (159.12 μmol/L);

MELD

MELD = {9.57 × ln [creatinine(mg/dL)] + 3.78 × ln [bilirubin(mg/dL)] + 11.2 × ln (INR) + 6.43};

MELD Na score = [MELD-Na (mmol/L) - (0.025 × MELD) × 140-Na (mmol/L) + 140]:

MELD Sodium (MESO) index = [MELD/Na(mmol/L) × 100];

Integrated MELD (iMELD) score = {MELD + age (in years) × 0,3) – [0,7 × Na (mmol/L)] + 100};

United Kingdom Model for End Stage Liver Disease (UKELD) score = {5 × [1.5 × ln (INR) + 0.3 × ln (creatinine (μmol/L)] + 0.6 × ln [bilirubin (μmol/L) – 13 × ln (Na (mmol/L) + 70]};

Updated MELD score = {[1.27 × ln (1 + creatinine (mg/dL)] + 0.94 × ln [1 + bilirubin (mg/dL)] + 1.66 × ln (1 + INR)]}.

The abovementioned scores were tested as predictors of the episode of bleeding as well as predictors of mortality in patients with bleeding from esophageal varices.

complications. In addition, the Kaplan-Meier survival curve was established in relation to the variables examined. Log rank test was used to compare the average survival in relation to the parameters examined. Cox's regression analysis was used to determine hazard ratio (HR) for each of the examined biochemical parameters.

Results

From the total number of patients (126), 26 had 32 episodes of bleeding from esophageal varices.

Bleeding from varices occurred in 19 (73.1%) male patents and in 7 (26.9%) female patients. It was found no statistically significant corelation between gender and the occurance of the complication ($p = 0.702$).

The patients with bleeding from esophageal varices were of similar age as other patients (57.27 ± 12.58 *vs* 55.79 ± 10.51, respectively; $p = 0.586$).

Bleedings occurred most often in alcoholic liver cirrhosis (61.5%). No relation between the occurrence of bleeding and etiology of liver cirrhosis ($p = 0.184$) was found as shown in Table 2.

The patients with bleeding from esophageal varices were hospitalised statistically significantly longer ($z = 2.407$; $p = 0.009$) and they spent statistically significantly more time in intensive care unit ($z = 3.242$; $p = 0.001$).

Table 2

Etiology of liver cirrhosis in relation to bleeding from varices

Etiology of cirrhosis	Bleeding from esophageal varices		*p*
	Yes, n (%)	No, n (%)	
Alcoholic	16 (61.5)	71(71.0)	
B virus	0	9 (9.0)	
C virus	3 (11.5)	7 (7.0)	
Cryptogenic	6 (23.1)	8 (8.0)	0.473
PBC	0	1 (1.0)	
Autoimmune	0	1 (1.0)	
Morbus Wilson	0	1 (1.0)	
Unknown	1 (3.8)	2 (2.0)	
Total	26 (100.0)	100 (100.0)	

PBC – primary billiary cirrhosis.

The obtained data were entered into the database, arranged in tables and presented graphically. Within the scope of descriptive statistics, data were presented in the form of arithmetic mean and standard deviation, median and interquartile range, or in the form of absolute or relative numbers. The normality of data was tested by Kolmogorov-Smirnov test. For comparing two sets of data, in case of normal data distribution we used the *t*-test and if data distribution was not normal, the Mann-Whitney's *U*-tests.

Survival analysis is used for the particular event (e.g. death) during the time, with recording the time when the particular event occurred, while in doing so, the initial time of follow-up was well-defined.

In survival analysis, life tables were applied in order to calculate one-year survival period both in relation to overall mortality as well as in relation to the occurance of various

It was found that patients with bleeding had statistically significantly higher concentration of urea ($z = 2.752$; $p = 0.006$).

In the patients with bleeding statistically significantly lower values of the following parameters were found: total proteins ($z = 2.928$; $p = 0.003$), the number of erythrocytes ($z = 2.957$; $p = 0.003$), hemoglobin ($z = 3.727$; $p < 0.001$), hematocrit ($z = 3.952$; $p < 0.001$).

The patients with bleeding from esophageal varices most often had CTP score rank C (46.9%). CTP score rank B had 37.5% patients, while the smallest percentage of patients had CTP rank A, 15.6% of them.

We compared the length of survival in patients with bleeding from esophageal varices independently from prognostic scores with that of the followed-up population of patients with terminal cirrhosis of the liver with no

complication. It was shown that the patients with variceal bleeding lived shorter than those who did not have complication. However, among the compared parameters there was no stastistically significant difference.

During the first month of follow-up, 6 patients died from bleeding from esophageal varices, in the first three months 7 of them died, and in the first six months 8 of them died.

The survival in the period between 3 and 18 months of the follow-up was on the average 68% (Figure 1).

Between 18-month- and 24-month-period the survival rate decreased, so it was found that two years after bleeding from esophageal varices only 23% of the patients survived (Figure 1).

Tables 3 and 4 show threshold values of prognostic scores of patients in relation to survival up to 30 and 90 days.

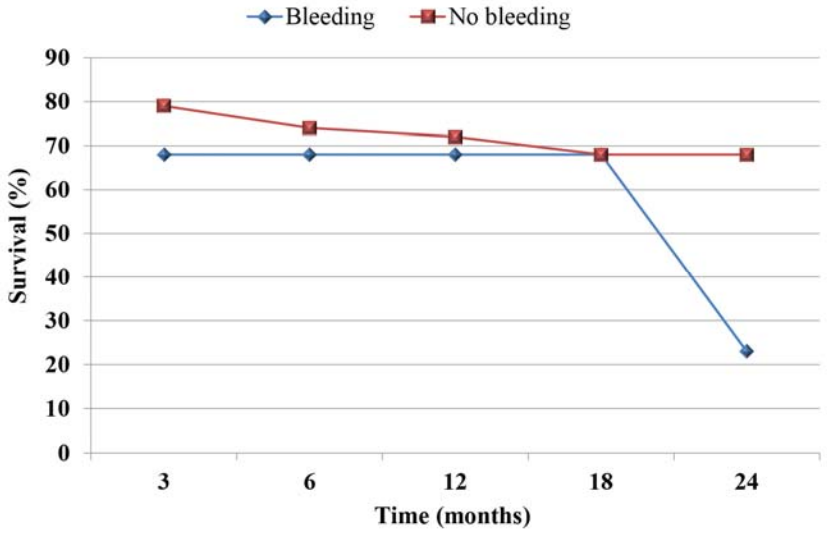

Fig. 1 – Survival in the period between 3 and 18 months of the follow-up

Table 3

Cox regression analysis – survival up to one month

Score	Complication	HR	95% CI	*p*
CTP > 10.50 +	VB	3.215	1.140–9.063	< 0.001
CTP-Crea I >10.50 +	VB	3.093	1.294–7.393	< 0.001
CTP-Crea II >11.50 +	VB	3.749	1.567–8.971	< 0.001
MELDNa > 27.50 +	VB	3.900	1.383–10.997	0.010
iMELD > 40.50 +	VB	2.838	1.303–6.183	0.009
MELD > 23.50 +	VB	3.063	1.281–7.321	0.012
UKELD > 55.50 +	VB	2.151	0.841–5.503	0.110
Updated MELD > 4.50 +	VB	2.542	0.993–6.507	0.052
MESO > 18.50+	VB	3.863	1.370–10.893	0.011

CTP – Child-Turcotte-Pugh; CTP-crea I – Creatinin-modified Child-Turcotte-Pugh I; CTP-crea II – Creatinin modified Child-Turcotte Pugh II; MELDNa – Model for End-Stage Liver Disease New Model; iMELD – Integrated Model for End-Stage Liver Disease; UKELD – United Kingdom Model for End-Stage Liver Disease; MESO – Meld-Sodium; VB – variceal bleeding; HR – hazard ratio; CI – confidence interval.

Table 4

Cox regression analysis – survival up to three months

Score	Complication	HR	95% CI	*p*
CTP > 10.50 +	VB	3.342	1.182–9.448	0.023
CTP-Crea I >10.50 +	VB	3.254	1.355–7.812	0.008
CTP-Crea II >11.50 +	VB	3.927	1.634–9.436	0.002
MELDNa > 27.50 +	VB	4.085	1.444–11.557	0.008
iMELD > 40.50 +	VB	2.999	1.369–6.568	0.006
MELD > 23.50 +	VB	3.223	1.342–7.737	0.009
UKELD > 55.50 +	VB	2.269	0.883–5.826	0.089
Updated MELD > 4.50 +	VB	2.673	1.041–6.867	0.041
MESO > 18.50+	VB	4.047	1.431–11.449	0.008

CTP – Child-Turcotte-Pugh; CTP-crea I – Creatinin modified Child-Turcotte-Pugh I; CTP-crea II – Creatinin modified Child-Turcotte-Pugh II; MELDNa – Model for End-Stage Liver Disease New Model; IMELD – Integrated Model for End-Stage Liver Disease; UKELD – United Kingdom Model for End-Stage Liver Disease; MESO – Meld-Sodium; VB – variceal bleeding; HR – hazard ratio; CI – confidence interval.

Disscusion

Among the compared prognostic scores, we found no prognostic score which, by its features, would have advantage over others in terms of predicting the occurrence of the episode of variceal bleeding.

In addition to factors that may be useful predictors of variceal bleeding in patients with terminal cirrhosis of the liver, it is also important to know predictors of outcome.

In everyday clinical follow-up, rather good predictors of outcome are certain routine parameters which we notice immediately upon the receipt of a bleeding patient. In a 5-day outcome, significant indicators of prognosis are the presence of active bleeding from varices during initial endoscopy, the presence of hemorrhagic shock and the number of units of blood transfusion which are necessary to correct shock and severe anemia in the patient. The platelet count on admission, etiology of cirrhosis and the presence of portal vein thrombosis, did not prove to be significant predictors of the outcome [7].

The results of our study, on the other hand, indicate that scores from the group of CTP scores are good predictors of a short-term survival in patients with variceal bleeding.

Patients with the values of CTP score higher than 10.50 and bleeding from the esophagus, have 3.2 times higher chance for death outcome compared to other patients. Patients with the values of CTP-crea I score higher than 10.50 and bleeding from the esophagus, have 3.1 times higher chance for death outcome than other patients. Patients with the values of CTP-crea II score higher than 11.50 and bleeding from esophagus, have 3.7 times higher chance for death outcome compared to other patients (Table 3).

The results of our study clearly support CTP scores, in particular creatinine modified CTP scores, in predicting mortality within short-term follow-up of patients with bleeding from esophageal varices**.** As we can see in Tables 3 and 4, the best results in survival prediction, in both study periods (one and three months) are affirmative for CTP crea scores.

Modified CTP scores emerged from the need to improve comprehensiveness of initial CTP score and was achieved by including creatinine into the score. The first analysis of CTP crea score was performed in 2002 by Angemayr et al. [8]. Several recent studies quite clearly confirm that creatinine modified CTP score contributed to improvement of the initial CTP score in assessment of survival [9].

If we observe the survival of patients with terminal cirrhosis independently of complications, as very affirming for CTP score and CTP-crea scores stands out the study of Papatheodoridis et al. [10]. The study points to the importance of creatinine-modified baseline CTP score and, by comparing predictability in relation to mortality, it gives priority to creatinine modified CTP score in relation to baseline CTP. Comparing CTP-crea I i CTP-crea II, the study shows that CTP-crea II is better than CTP-crea I in predicting a short-term survival [10].

A study of Huo et al. [11] compared four modified MELD scores in predicting complications of terminal cirrhosis, which significantly correlate with the patient survival. The study examined MELD, MELD Na, integrated MELD and MESO index in prediction of hepatic encephalopathy (HE), spontaneus bacterial peritonitis (SBP) and bleeding from esophageal varices. The study found that all the examined scores were higher in patients with complications.

Quite significant is the paper of Chen et al. [12], which clearly shows the importance of MELD score in prediction of outcome after the bleeding episode and endoscopic ligation of esophageal varices. The authors conclude that MELD score higher than 18 is a significant predictor of rebleeding from esophageal varices within a 5-day period after the current episode, and good predictor of mortality within 6 weeks in patients who developed repeated bleeding from varices despite endoscopic ligation.

In a very nice way, the study of Sempere et al. [13] presented the results of a research aimed at finding the best predictor of survival in patients with bleeding from esophageal varices. The study points out, as important predictors of mortality, age above 65 years, the presence of hepatocellular carcinoma in cirrhotic liver, CTP score higher than 10 and MELD higher than 18. Those indicators have proved to be essential in all statistical analysis, and in multivariate model of Cox's Regression Analysis, as independent predictors of outcome.

In addition, the study repeats the significance of MELD score in predicting short-term survival but also shows that particularly in the category of patients with variceal bleeding MELD score is more superior to CTP score both in short-term and long-term follow-up (both in 12-month and 36-month periods of follow-up). The highest difference in the compared scores (CTP and MELD) is present in 6-week and 3-month periods of follow-up where MELD score is dominant. Although the difference is still on the side of MELD score, it is lower in 12-month and 36-month periods of follow-up [13].

The first assessment of survival in the examined population we carried out 30 days after the episode of variceal bleeding. During that time period, we compared the prognostic scores in terms of predicting one-month survival. With Cox's Regression Analysis we obtained relatively similar prognostic validities for scores from the CTP group. However, the strongest predictive value in terms of one-month survival has CTP-crea II score. When in patients with variceal bleeding CTP-crea II score exceeds the threshold value of 11.50, probability of mortality increases by 3.7 times compared to patients who do not have variceal bleeding. The two other scores, CTP crea I and baseline CTP score, also behave in a quite similar way. Those three scores are predictors of one-month mortality with statistical significance ($p < 0.001$). Adding the value of serum creatinine level to the baseline CTP score significantly improved the features of this score, as it can be concluded from the results of our study.

In variceal bleeding the importance of creatinine, first of all, modified baseline CTP score, as an important prognostic factor, also helps to include weakened kidney function. Disorder of kidney function in terminal cirrhosis, in patients with bleeding from esophageal varices, may not be cau-

sed only by hepatorenal syndrome. As with other forms of bleeding in conditions of hemorrhagic shock, there may occur prerenal acute renal failure and acute tubular necrosis. Those are conditions that are associated with high mortality, so it is clear that creatinine-modified CTP score, in prognosis of survival, has a significantly improved baseline CTP score. The risk of lethal outcome initiated by weakened kidney function in patients with variceal bleeding is thus fully covered.

Among scores of the MELD group, as the best predictors of survival stood out MELD Na score and MESO index, which showed almost identical prognostic value. When patients with variceal bleeding have MELD Na score higher than 27.50 and MESO index higher than 18.50, the probability of mortality increases by 3.9 that is by 3.8 times compared to population that does not have variceal bleeding.

Those two prognostic scores are connected by one common feature, which is that both scores were created by modifying MELD score with serum sodium level. As the serum sodium level is an independent indicator of mortality in terminal cirrhosis and retention of free water and dilution hyponatremia correlate well with portal hypertension, it is clear that integration of this biohumoral indicator contributed to improving the quality of MELD score in predicting survival.

Conclusion

Survival of patients with bleeding from esophageal varices in a short-term follow-up can be predicted by following CTP score and creatinine-modified CTP scores.

Patients with bleeding from esophageal varices with CTP score and CTP-crea I score higher than 10.5 and CTP-crea II score higher than 11.5 have statistically significantly higher risk from mortality within 1-month follow-up compared to those with bleeding from esophageal varices with lower numerical values of scores of the CTP group. Among the scores of the MELD group, the best features in predicting survival of patients with bleeding from esophageal varices showed scores created by modifying baseline MELD score with serum sodium, that is, MESO index and MELD Na score.

Among the compared scores there was no any single prognostic score which could be a strong predictor of variceal bleeding episode.

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Received on July 17, 2015.
Accepted on August 25, 2015.
Online First June, 2016.

ORIGINAL ARTICLE

UDC: 617.572-089.168
DOI: 10.2298/VSP150331103S

The influence of Dupuytren's disease fingers contracture degree on surgical treatment outcome

Uticaj stepena kontrakture prstiju na uspešnost hirurškog lečenja Dipitrenove kontrakture

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Abstract

Background/Aim. Dupuytren's disease is a progressive disease of the palmar and digital fascial structures, with functional limitations. There are no clear recommendations about the optimal time of surgical repair, concerning the hand impairment. The aim of our study was to investigate the relation between finger's contracture degree and success of surgical treatment of the Dupuytren's disease. **Methods.** This prospective analysis included 60 patients operated on due to Dupuytren's contracture. According to preoperative contracture degree of proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joint, patients were divided into three groups: the group 1: < 15°, the group 2: 15−30° and the group 3: > 30°. All the patients underwent operation of partial palmar fasciectomy. Postoperative improvement was expressed with contracture reduction INDEX. **Results.** There were 60 patients with 85 fingers affected. The groups 1, 2 and 3 had 22 (37%), 37 (62%) and 26 (43%) fingers with MCP contracture and 32 (37.4%), 24 (28.2%) and 29 (34.1%) fingers with PIP contracture, respectively. Postoperative contractures of MCP joint in these groups were 0, 0.135° and 5°, and of PIP joint 0, 2.08 ° and 16.89°, respectively. After six months all MCP contractures resolved, while PIP joint contracture in the group 3 remained 13.62°. The reduction INDEX was 98.85%, 97.62% and 75.52% in the groups 1, 2 and 3, respectively. There was a statistically significant difference in the INDEX value between the groups ($p = 0.0001$). **Conclusion.** The degree of PIP joint contracture is related to the outcome of surgical treatment of Dupuytren's disease. Optimal results are achieved when contracture degree is between 15° and 30°. Surgical treatment of MCP joint contracture is successful regardless of the preoperative joint contracture degree.

Key words:
dupuytren contracture; hand; reconstructive surgical procedures; prognosis.

Apstrakt

Uvod/Cilj. Dipitrenova kontraktura (DK) je progresivna bolest palmarne i digitalne fascije sa funkcionalnim oštećenjem kao krajnjom posledicom. Za sada, ne postoje jasni stavovi o optimalnom trenutku hirurškog lečenja ovog oboljenja. Cilj rada bio je da se ispita odnos između stepena kontraktura prsta i rezultata hirurškog lečenja Dipitrenove ukočenosti. **Metode.** Ova prospektivna studija obuhvatila je 60 bolesnika operisanih zbog DK. U zavisnosti od preoperativno izmerenog stepena kontrakture u predelu proksimalnog (PIP) i metakarpofalangealnog (MCP) zgloba bolesnici su podeljeni u tri grupe: grupa 1: < 15°, grupa 2: 15−30° i grupa 3: > 30°. Svim bolesnicima učinjena je operacija parcijalne palmarne fasciektomije. Postoperativni rezultati izraženi su indeksom smanjenja kontrakture (INDEX). **Rezultati.** Kod 60 bolesnika DK zahvatala je 85 prstiju od kojih je u grupi 1 bilo 22 (37%), u grupi 2, 37 (62%), a u grupi 3, 26 (43%) prstiju sa kontrakturom MCP zgloba, kao i 32 (37,4%), 24 (28,2%) i 29 (34,1%) prstiju sa kontrakturom PIP zgloba. Postoperativna kontraktura MCP zgloba u navedene tri grupe bila je 0, 0,135°, 5°, dok je kod PIP zgloba iznosila 0, 2,08° i 16,89°. Nakon šest meseci praćenja, konktrakture na MCP zglobu bile su sanirane kod svih bolesnika, dok je kod PIP zgloba u grupi 3 opstajala prosečna kontraktura od 13,62°. Izmereni INDEX bio je statistički značajno niži u grupi 3 (75,52%) u poređenju sa grupama 1 i 2 gde je iznosio 85% i 97,62% ($p = 0.0001$). **Zaključak.** Hirurško lečenje DK kod PIP zgloba daje značajno bolje rezultate kod kontrakture od 15 do 30° nego kod kontrakture većeg stepena, te bi u tom stadijumu trebalo primeniti hirurško lečenje. Hirurško lečenje kontrakture MCP zgloba uspešno je bez obzira na preoperativni stepen kontrokture.

Ključne reči:
kontraktura, dipitrenova; šaka; hirurgija, rekonstruktivna, procedure; prognoza.

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Introduction

Dupuytren's desease is one of the most commonly acquired contractures of the hand. It is a benign palmar fibromatosis characterised by progressive shortening of the palmar fascia and often causes significant contracture of the metacarpophalangeal and proximal interphalangeal joints. This leads to significant deformity and impaired function of the hand [1]. The basic process includes a large density of fibroblasts, which increase extracellular matrix protein deposition with greater proportions of type III/type I collagen and myofibroblasts that cause wound contracture. According to pathogenesis, the ideal treatment for Dupuytren's disease in the hand would involve managing these cellular mechanisms to prevent or control the development of fibroproliferative disorder. Since there is no available method that prevents this process, contemporary therapy is based on permanent contracture resolution and prevention of the recurrence of contractures. There are two options for managing this problem: surgical and non-surgical treatment [2, 3].

Surgical treatment includes percutaneus needle fasciotomy, open fasciotomy, radical or partial fasciectomy and dermofasciectomy. Procedure selection is based on the degree and localisation of fixed flexion contracture, amount of skin involvement, patients' general health status and surgeons' individual preferences. There are no clear recommendations for the exact time of surgical repair, when functional hand impairment is concerned.

The aim of this study was to investigate the relation between finger's contracture degree and success of surgical treatment of Dupuytren's disease.

Methods

This prospective study analysed of 60 subsequent patients who had underwent surgical treatment of Dupuytren's contracture in the Clinic for Plastic and Reconstructive Surgery and Burns, Military Medical Academy in Belgrade.

Preoperatively, demographic characteristics (age, sex and profession), localisation and degree of the contracture were noted. The degree of active and passive flexion contracture of the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joint were measured with goniometer. According to the preoperative degree of the finger contracture in PIP and MCP joint, the patients were divided into three groups, with less than 15° degrees (the group 1), 15°−30° degrees (the group 2) and over 30° (the group 3).

The degree of passive flexion contracture in PIP and MCP joints was measured immediately postoperatively and after six months.

Partial palmar fasciectomy with a tourniquet in the regional intravenous anaesthesia was used as surgical technique in all the patients [1].

Controlled physical therapy was applied on fourth postoperative day while intensive physical therapy was initiated after suture removal, on 10−12th postoperative day, and lasted one month.

The degree of PIP joint contracture decreasing was represented as a numerical difference of contractures measured pre- and postoperatively (PIP-Diff.). In order to calculate the relative value of PIP joint contractures improvement, we defined the index of contractures improvement (INDEX), which represents a reduced percentage of total preoperative contracture.

That INDEX was calculated as the quotient of absolute values (PIP-Diff.) and the measured preoperative contracture of the PIP joint (PIP Pre-OP), times 100.

INDEX = (PIP-Diff.)/ (PIP Pre-OP) x 100

Fingers that were with no contracture after treatment were considered cured, while those with left contracture were considered partially cured.

Data analysis was performed using SPSS Software 11 (SPSS Inc, Chicago, Ill). All data were expressed as mean and standard deviation (SD). We used *t*-test and χ^2 test for parametric and nonparametric distributed values. Each *p* value < 0.05 was considered statistically significant.

Results

Out of 60 patients, 57 (95%) were males and 3 (5%) females with the average age of 64.26 (29−80).

Preoperative results

Clinically evident unilateral or bilateral contracture was found in 27 (45%) patients and 33 (55%) patients, respectively. Thirty five (58%) of the patients had only one finger affected, while 25 (42%) had the contracture of more than one finger. The most common contracture affected together the fingers IV and V (19 patients; 32 %). Involvement of the fingers III and IV had 5 (8%) of the patients, while only one patient (2%) had disease localized on the fingers I, III and IV.

All the patients had contracture in the MCP joint, with the average degree of 29.34°. In 22 (37%), 37 (62%), and 26 (43%) fingers contracture was less than 15°, between 15° and 30°, and over 30°, respectively. The average values of the contracture for the fingers III, IV and V were 29°, 28.55° and 28.74°, respectively.

Contracture of the PIP joint was registered in 85 fingers. Thirty two (37.5%) fingers had contracture less than 15°, 24 (28.3%) 15−30°, and 29 (34.2%) over 30°. The average degree of the contracture in the PIP joint was 30.59°. The average values of contracture for the fingers III, IV and V were 30°, 29.34° and 32.03°, respectively.

The results of postoperative and by a month follow-up

Postoperatively, all contractures of the MCP joint from the group I were completely resolved, while after 6 months patients from the groups II and III had the rest of average contracture of 0.135° and 5°, respectively. Postoperative contractures in MCP joint for the fingers III, IV and V were 2.5°, 1.18° and 1.76°, respectively. After six months all MCP contractures were completely resolved.

Postoperatively, contractures of the PIP joint in the group I of the patients were resolved, while in the groups II and III of the patients remained contracture of 2.08° and 16.89°, respectively.

After a 6 month follow-up, the weakest results of PIP joint contracture treatment were obtained in the group III (the patients with preoperative contracture greater than 30°), where the average residual contracture was 13.62°, after completing the treatment.

The average degree of the preoperative MCP and PIP articulation contracture as well as immediately postoperatively and after 6 months are shown in Tables 1 and 2, and Figures 1 and 2.

The frequency of cured and partially cured patients was statistically significantly different between the groups (χ^2 = 73.077; p = 0.0001). Detailed results are presented in Table 2.

Table 1

The average contracture of the metacarpophalangeal (MCP) and the proximal interphalangeal (PIP) joint

Affected finger (°)	Preoperatively		Postoperatively		After 6 months	
	MCP	PIP	MCP	PIP	MCP	PIP
III	29°	30°	2.5°	5.5°	0°	4°
IV	28.55°	29.34°	1.18°	6.58°	0°	4.60°
V	28.74°	32.03°	1.76°	6.35°	0°	5.40°

°contracture degree.

Table 2

Results of surgical treatment of the proximal interphalangeal (PIP) joint contractures in the group of patients

Degree (°) of the joint contracture	Number (%) of the patients	Cured, n (%)	Partially cured, n (%)
Less than 15	32 (37.5)	31 (58.5)	1 (3.1)
From 15 to 30	24 (28.3)	22 (41.5)	2 (6.3)
Over 30	29 (34.2)	0 (0)	29 (90.6)
Total (n)	85	53	32

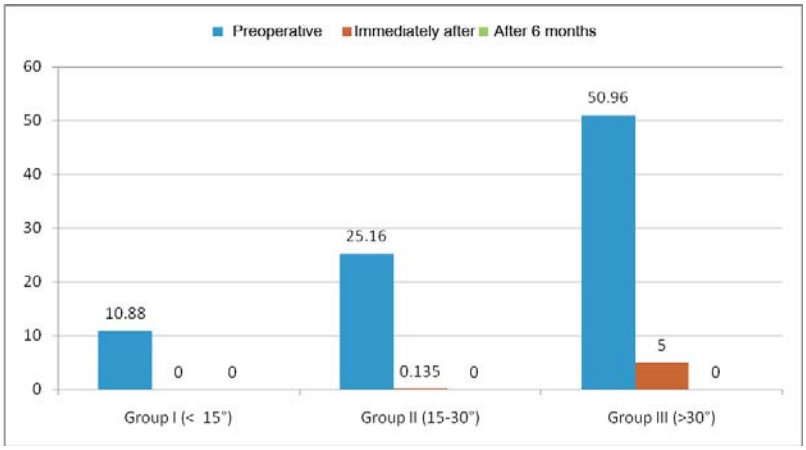

Fig. 1 − The average metacarpophalangeal (MCP) joint contracture (°) in all the three groups before, immediately after and 6 months after operation.
(y axis- contracture degree; x axis- preoperative, postoperative and 6 months follow-up contracture degree in three groups of patients).

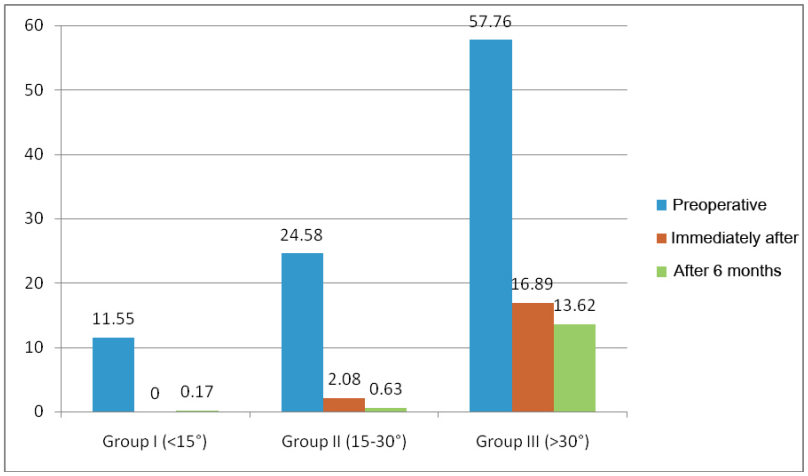

Fig. 2 – The avarage proximal interphalangeal (PIP) joint conctracture (°) in all three groups before, immediately after and 6 months after operation.
(y axis − contracture degree; x axis − preoperative, postoperative and 6-month follow-up contracture degree in the three groups of the patients).

Relation of pre- and postoperative PIP joint degree of contracture

Average reduction of contracture degree ranged from 5° to 80° with an average value of 26.65°. The group 3 had the greatest reduction in the degree of contracture, on the average of 44.14°. The average values of contracture decreasing are shown in Table 3.

Table 3

The average values of contracture decreasing

Degree (°) of joint contracture	Number (%) of the patients	Average values of contracture decreasing (degree °)
Less than 15	32 (37.5)	11.38
From 15 to 30	24 (28.3)	23.96
Over 30	29 (34.2)	44.14

The PIP joint contracture INDEX ranged from 66% to 100%, with the average of 90.68%. The greatest reduction in the degree of contracture we had in the group I of the patients (98.85%), while in the groups II and III INDEX was 97.62% and 75.52%, respectively. There was statistically significant difference in the INDEX values among the three groups, (ANOVA – $p = 0.0001$; OR=100.877).

Discussion

This study demonstrates that surgery of Dupuytren's disease at the MCP joint is likely to provide full correction of joint contracture of any degree. Unlike MCP, contracture of the PIP joint is surgically best reduced when the degree of contracture is between 15° and 30°. Since the PIP joint rather than the MCP joint correction correlated better with hand function, the above-mentioned interval might be one of the main indications for surgery.

Dupuytren's disease has certainly affected people for hundreds of years. A large number of important scientific studies over the last decade contributed to understanding the process of formation, clinical presentation and treatment of Dupuytren's contracture. Nowadays, it is well defined that myofibroblasts play a key role in the pathogenesis of this disease. These cells induce wound contraction, but their origin is not clear yet. So, the ideal treatment for Dupuytren's disease in the hand would involve managing these cellular mechanisms to prevent or control the development of fibroproliferative disorder. The ideal treatment would provide permanent contracture resolution and prevent the recurrence of contractures and diseased fascia. Historically, non-surgical management, generally, was found to be ineffective or not suitable for clinical use [2–4]. Recently, treatment with collagenase *Clostridium histolyticum* has been approved for use in the United States of America and Europe in adult patients. Despite the huge popularity of this "surgical drug", many surgeons across the world still perform surgery as the first and the best option for this kind of disease.

The decision to start surgical treatment of Dupuytren's contracture is based on functional issues that illness brings. One of the basic and clearly established principles is that surgical treatment should not be used before the onset of contracture of the fingers. The presence of palmar nodules that do not restrict movement of the fingers is not an indication for surgical treatment. Hueston [5] thought that surgical treatment should be started when "table top" test is positive test. According to Hurst [6], each MCP joint flexion contractures greater than 30° and/or any kind of PIP joint contracture is an indication for surgical treatment. McFarlane [7] reported that MCP joint contractures can be successfully surgically corrected regardless of the duration of the disease, while PIP joint contractures greater than 30° will not be fully resolved, and will require additional procedures of the surrounding anatomic structures.

Contracture of 30° in the PIP joint is commonly referred to as the cut off value for the beginning of surgical treatment [8]. However, there are no information on whether the surgical treatment of contractures smaller or larger degree than the abovementioned, gives better functional outcome and surgeons in practice are usually guided by personal experience.

Some authors claim that MCP contracture does not affect the overall success of Dupuytren's contracture treatment, but contractures greater than 30° require a qualified physical therapy and increases the cost of treatment [9–11]. We agree with this statement because in our study all the patients with MCP contracture less than 30° (59 fingers involved) were completely resolved surgically without additional postoperative procedures. The patients with MCP contracture greater than 30° (26 fingers involved) had a minimal contracture and only after application of a qualified physical therapy, were completely cured.

Studies have also assessed the outcome of Dupuytren's surgery for PIP joint contracture. Abe et al. [12] demonstrated that those with a worse preoperative deformity were more likely to have a worse postoperative outcome. Misra et al. [13] also assessed this and supported this relationship. Our study reaffirms that preoperative degree of PIP joint contracture is a significant predictor of surgical success.

In the group of patients with PIP joint contracture less than 15° and from 15° to 30°, the contracture rest after six months was on the average 0.17° and 0.63°, respectively, while the patients with PIP joint contracture greater than 30° had improvement of 13.62°. Therefore, the greatest reduction in the degree of contracture we had in the group of patients with less than 15° (98.85%) and between 15° and 30°

(97.72%), while the reduction was the least obtained in the subjects from the group with contracture greater than 30° (76.52%). Based on these results we believe that PIP joint contracture of 15° to 30° with or without MCP joint contracture is an indication for surgical treatment. Although the treatment of PIP joint contracture less than 15° gave also good results, we believe that they do not represent an absolute indication for surgical treatment for several reasons. In our clinical material, the group of patients with contracture less than 15° did not have significantly better results compared to the patients with contractures of 15° to 30°. As we mentioned earlier, the goal of surgical treatment is not only to correct flexion contracture, but to completely preserve flexion of the affected finger. Operative treatment represents an additional trauma and does not lead to significantly better results for contracture smaller than 15°.

Conclusion

The degree of PIP joint contracture is related to the outcome of surgical treatment of Dupuytren's disease. Optimal results are achieved when contracture degree is between 15° and 30°. Surgical treatment of MCP joint contracture is successful regardless of the preoperative joint contracture degree.

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Received on March 31, 2015.
Revised on August 28, 2015.
Accepted on September 2, 2015.
Online First May, 2016.

ORIGINAL ARTICLE

UDC: 618.1-006-07-084
DOI: 10.2298/VSP150205143G

Presence of histopathological premalignant lesions and infections caused by high-risk genotypes of human papillomavirus in patients with suspicious cytological and colposcopy results – a prospective study

Prisustvo patohistoloških premalignih lezija i infekcija visokorizičnim genotipovima humanih papilomavirusa kod bolesnica sa sumnjivim citološkim i kolposkopskim nalazima – prospektivna studija

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Abstract

Background/Aim. In patients with premalignant cervical lesions, human papillomavirus (HPV) infection, at any moment, may be spontaneously eliminated, or may persist or transform cervical epithelium from a lower to a higher degree. Due to that, it is necessary to wisely select the patients who are at high risk of cancer development. The aim of the study was to establish the interdependence between a suspicious Papanicolaou (Pap) test and colposcopy with the infection caused by high-risk genotypes of human papillomavirus and the presence of premalignant cervical lesions. **Methods.** This prospective study used cytological, colposcopy, real-time polymerase chain reaction (PCR) of high-risk genotypes of human papillomavirus and histopathological analysis of cervical biopsy specimen. Out of 2,578 female patients sent to cytological analyses in Clinical Center of Montenegro, during 2012, 2013 and 2014, the study included 80 women who had to submit their biopsy specimens due to a suspicious Pap test and atypical colposcopy results. **Results.** In the group of 80 (3.1%; n = 80/2,578) of the selected female patients with suspicious Pap test and colposcopy, 2/3 or 56 (70%) of them had cervicitis, and 1/3 or 24 (30%) had cervical intraepithelial neoplasia. The most common type in cervical intraepithelial neoplasia was HPV16 in 8 female patients, *ie* 61.53% out of the number of infected, or 33.33% out of the total number of premalignant lesions. **Conclusion.** Patients with suspicious Papanicolaou test, colposcopy results and infection which is caused by high-risk HPV infection (HPV 16 in particular) often have premalignant cervical lesions. In these cases, histopathological confirmation of lesions is mandatory, since it serves as a definitive diagnostic procedure.

Key words:
papillomaviridae; uterine diseases; uterine neoplasms; vaginal smears; histology; primary prevention.

Apstrakt

Uvod/Cilj. Kod premalignih lezija grlića materice infekcija visokorizičnim genotipovima humanih papilomavirusa (HPV) može spontano biti eliminisana, opstajati ili dovesti do transformacije epitela grlića nižeg u viši stepen. Zato je važno pravilno odabrati bolesnice koje su u visokom riziku od obolevanja od karcinoma. Cilj studije bio je da se ustanovi međuzavisnost sumnjivog Papanikolau testa i kolposkopskog nalaza sa infekcijom visokorizičnim genotipovima HPV i prisustvom premalignih lezija grlića materice. **Metode.** U ovoj prospektivnoj studiji korištena je citološka, kolposkopska, lančana reakcija polimeraze (PCR) u realnom vremenu visokorizičnih genotipova HPV, kao i patohistološka analiza bioptata grlića materice. Istraživanje je obuhvatilo 2 578 žena u Kliničkom Centru Crne Gore, koje su upućene na citološku analizu tokom 2012, 2013, i 2014. godine. Posmatrano je 80 žena kojima je indikovana biopsija grlića

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materice zbog sumnjivog Papanikolau testa i atipičnog kolposkopskog nalaza. **Rezultati.** U grupi od 80 (3,1%; n = 80/2 578) odabranih bolesnica sa sumnjivim Papanikolau testom i kolposkopijom, njih 2/3 ili 56 (70%) bilo je sa cervicitisom, a 1/3 ili 24 (30%) sa cervikalnom intraepitelnom neoplazijom. Najčešće zastupljeni pojedinačni tip kod bolesnica sa cervikalnom intraepitelnom neoplazijom bio je HPV16 kod 8 bolesnica, tj. 61,53% od broja inficiranih ili 33,33% od ukupnog broja premalignih lezija. **Zaključak.** Kod bolesnica koje imaju sumnjiv Papanikolau test i kolposkopski nalaz i infekciju visokorizičnim genotipovima HPV (posebno HPV16) česta je pojava cervikalnih intraepitelnih neoplazija. U tim situacijama, obavezna je patohistološka provera lezije, kao odlučujući dijagnostički postupak.

Ključne reči:
papilloma virus, humani; materica, bolesti; materica, neoplazme; vaginalni brisevi; histologija; preventivno-medicinska zaštita.

Introduction

Premalignant phase of planocellular cervical cancer is a phase-continuous process of epithelial change, from low degree lesions, classified as low-grade squamous intraepithelial lesion – LGSIL, to lesions of more severe degree, classified as high grade squamous intraepithelial lesion – HGSIL, caused by persistent human papillomavirus (HPV) infection. Carcinogenesis of cervical cancer is a process spanning more years. In this period it is possible to detect infection, virus type, degree of epithelial lesion and apply an appropriate patient treatment. HPV infection of cervical epithelium is a sexually transmitted disease which is highly contagious. At any moment, infection may be spontaneously eliminated, persist or lead to the transformation of cervical epithelium of a lower to a higher degree, due to which it is necessary to wisely select the patients who are at high risk of cancer development [1].

The highest incidence of premalignant intraepithelial cervical lesions is in women aged between 25 and 35. The average life expectancy with diagnosed carcinoma *in situ* is 35 years, and with invasive carcinoma between 48 to 52 years. It has been proven that HPV is the main cause of cervical cancer, but there are a number of contributing factors, such as: smoking, promiscuous behaviour, other sexually transmitted diseases (*Chlamydia trachomatis*, *Herpes simplex* virus type 2, *Cytomegalovirus*), partners' sexual behaviour, socioeconomic status, genetic, hormonal and immunological status of a woman [2].

The majority (80%) of fatal outcomes happens in developing countries which is chiefly due to the lack of preventive programmes for timely detection of premalignant cervical lesions [3]. The preventive programmes include different screening methods: cytology [Papanicolaou (Pap test)], colposcopy, diagnostics of cervical infection by HPV, and pathohistological biopsy specimen. The sensitivity of these methods is different and their combination provides for timely diagnostics of premalignant lesions and cervical cancer prevention [4].

Even though cytological examination of cervical epithelium is primarily used as a primary screening method for the detection of premalignant lesions, today current researches are directed towards finding an optimum screening method to make it possible to assess cervical cancer risk. Some researches show it could be done by combining diagnostic cytopathology and verification of cervical HPV DNA or RNA.

Modern medicine can cure premalignant intraepithelial lesions, therefore, timely diagnostics of intraepithelial lesions is of crucial importance. Use of different diagnostic procedures and their mutual combination increases sensitivity of diagnostics of cervical epithelium changes. With the combination of different diagnostic procedures it is possible to detect 98% of pathological cervical lesions [4].

The aim of this study was to determine the importance of cytological examination (Pap test) in relation to the detection of premalignant cervical lesions, determine the association of HPV DNA diagnostics (high risk) and of premalignant cervical lesions, establish the interdependence between suspicious Pap test and the presence of premalignant cervical lesions, and establish the interdependence between HPV DNA (high risk) and the presence of premalignant cervical lesions, and determine what is the most common type of high-risk HPV DNA in cervical precancerous lesions.

Methods

This prospective study used cytological, colposcopy, HPV DNA (high risk) diagnostics and histopathological analysis of cervical biopsy specimen.

The female patients were made familiar with the proposed diagnostic procedures and gave their consent. Then, they completed a questionnaire containing the questions about age, marital status, menarche, the first intercourse, number of partners, use of contraception and its type, and social status.

This research included 2,578 female patients who had cytological analyses during 2012, 2013 and 2014, and then selected 80 women who had to submit their biopsy specimens due to a suspicious Pap test – atypical squamous cells of undetermined significance (ASCUS; *ie* Pap III A and B) and atypical colposcopy results. All women, apart from Pap test and pathohistological examination, went through HPV DNA diagnostics. The included women were of all ages.

Pap test was performed in such a way that we took a swab prior to bimanual examination and microbiological analysis of the swab, since blood and lubricants must not contaminate the sample. While taking cytological swab, the whole cervix must be visible. If there is excessive secretion, it is necessary to remove it by physiological saline and if there are no signs and symptoms of cervical lesions, a swab should be taken between 10 and 16 days from the beginning of menstrual cycle. A patient is placed in a position typical for gynecological examination. Speculum is cleaned with

physiological saline, lighting should be good, and with an appropriate endocervical brush we collect cells form ectocervix, then from cervical canal with relatively subtle rotations, taking into account that rotations do not cause bleeding, which would contaminate the swab and make further analysis of cytological results more difficult. Swab content should be immediately placed on a Petri dish, within a couple of seconds. It must not be allowed for the swab to dry up in the air, since cytological readings will be compromised. The smear on a petri dish shoud be completely soaked in 95% alcohol and sprayed with polyethylene glycol. A Petri dish should be adequately labelled together with a form which contains: patient's name and family name, last menstruation cycle date, regularity of menstrual cycle, the number of given births, miscarriages and if there were any previous abnormal swabs or treatments. The form should also contain information on using contraceptive pills or intrauterine device [4].

HPV DNA infection diagnostics was performed by real time polymerase chain reaction (RT PCR). In order to take a swab for the diagnostics of HPV infection, a patient assumes the lithotomy position, vaginal wall is spreaded, middle part of the brush with longer bristles (used for cervical swabs specimen, single use only) is put deep into the cervical canal and the rest of the brush with shorter bristles is in contact with the external part of the cervix. The brush is rinsed in a specialised solution – PreservCyt-Solution, which is located in a sampling bottle, the brush is dipped 10 times in the solution and then rotated on the bottom of the bottle. The brush is then removed from the bottle and the lid placed so that the marked line of the lid passes the marked line of the bottle. The bottle is then labelled, the label contains name and family name of the patient, and then all data are inserted into medical documentation of the patient [5].

The swabs taken in such manner are used to detect high-risk HPV genotypes (Abbott High Risk HPV DNK test, Abbott Molecular, USA) in the specimen by PCR method. This analysis is performed on Applied Biosystems 7500 Real-Time PCR System.

Cervix tissue biopsy specimen is taken with a patient in the lithotomy position. External gynaecological organs and the vagina should be cleaned and then vaginal wall spread. Cervix is grasped by a tentaculum and pulled in the direction of vaginal axis which enables cervical tissue biopsy specimen to be taken. Biopsy specimen should be stored in a dish with formalin together with a document form for a specialist of histopathological medicine. The form contains cytological status of the patient and an obligatory information on a possible, previous premalignant lesion of the patient with date and treatment manner. The form was contains patient's personal data: name, family name, age. The cervix tissue biopsy specimen is used for the histopathological diagnostics [6].

Statistical data were analysed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA). Due to small sample size, only descriptive statistics for scores was performed (medians and percentages). The processed data and the results were presented in tabular and graphical forms. Data processing and analysis used the following statistical methods: descriptive statistics, χ^2 test and Fisher's exact test.

Results

Out of 2,578 female patients who had cytological analyses during 2012, 2013 and 2014, this study included 80 (3.1%) who had to submit their biopsy specimens due to an abnormal Pap test and atypical colposcopy results. All the women, apart from Pap test and pathohistological examination, went through HPV DNA diagnostics. The included women were of all ages, the youngest patient was 19, and the oldest one 74 (Figure 1).

In the group of 80 of the selected female patients with abnormal Pap test, 2/3 or 56 (70%) had cervicitis, and 1/3 or 24 (30%) had cervical intraepithelial neoplasia (CIN) (Figure 2).

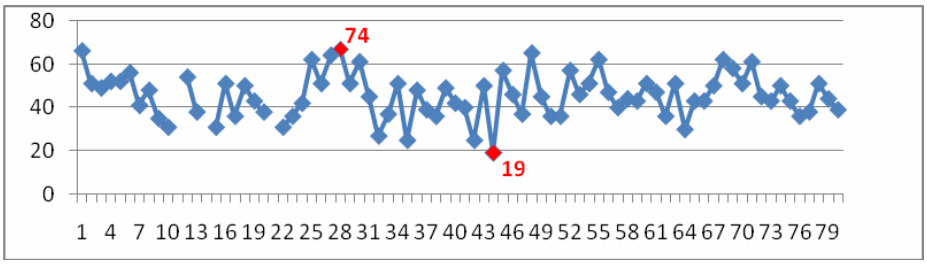

Fig. 1 – Age range of all the patients.

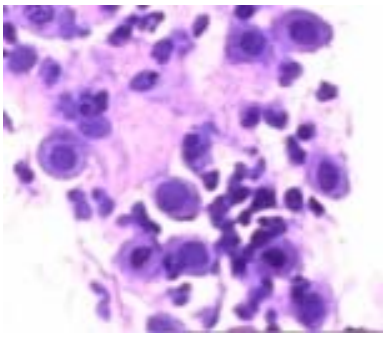

Fig. 2 – Suspicious cytological findings (Papanicolaou, ×400).

CIN I was present in 12 (15%) patients, CIN II in 3 (3.75%), and CIN III in 9 (11.25%) of patients. LGSIL and HGSIL lesions were present in 15%.

Of 80 examined female patients, HPV infection was present in 32 (40%). Combined HPV types were verified in 11 (13.75%) patients, out of the total number of the patients and 39.39% out of the total number of the infected (Table 1, Figure 3).

tal number of infected (16.66%) of all CIN I patients. Others were combined with other genotype.

The group CIN II contained 3 female patients, out of which 1 (33.33%) was with HPV positive genotype. This case involved the combination of HPV31, 33 and 45 genotypes.

The group CIN III contained 9 female patients, out of which 8 (88.88%) were with HPV positive genotype.

Table 1

Frequency of histopathological parameters

Histopatological variables	Frequency (n)	Percentage (%)
Suspicious findings	80/2,578	3.1
CIN I	12	15
CIN II	3	3.7
CIN III	9	11.25
CERVICITIS	56	70
LGSIL	12	15
HGSIL	12	15
CIN	24	30
HPV positive cervicitis	19	33.92
HPV positive CIN	13	54.16

CIN – cervical intraepithelial neoplasia; LGSIL – low-grade squamous intraepithelial lesion; HSIL – high-grade squamous intraepithelial lesion; HPV – human papillomavirus.

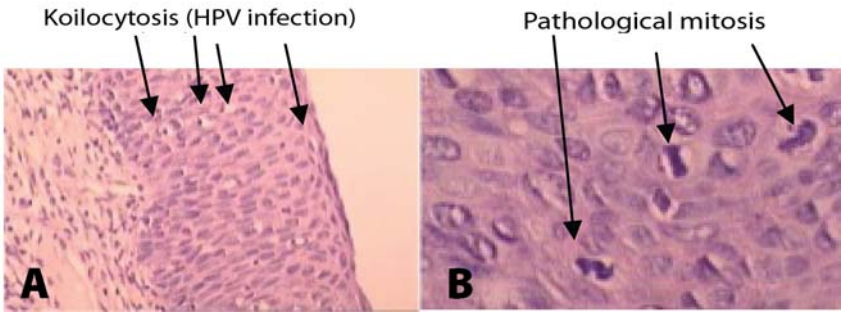

Fig. 3 –Histopathological characteristics of cervical intraepithelial neoplasm in CIN III with A) Koilocytosis (HE ×200); B) Pathological mitosis (HE ×400). CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus.

Out of 56 females with cervicitis, 19 (33.92%) had HPV infection (23.75% of the total number patients). The most commonly individual type present was HPV45 in 8 (42.10%) patients or 14.28% out of the total number of patients with cervicitis. The second individual most common type was HPV31 in 5 (26.31%) patients or 8.92% out of the total number of patients with cervicitis. Common types in cervicitis were found in 4 (21.05%) cases or 7.14% out of the total number of patients with cervicitis.

Out of 24 female patients with cervical intraepithelial neoplasm 13 (54.16%) had HPV infection. The incidence of HPV infection was higher in patients with CIN (54.16%) compared to the patients with cervicitis (33.92%).

The most common type in the CIN was HPV16 in 8 (61.53%) female patients out of the number of infected or 33.33% out of the total CIN number. Combined types in CIN were found in 7 (53.84%) cases out of the number of infected or 29.16% out of the total number of CIN.

The group CIN I contained 12 female patients, out of which 4 (33.33%) were with HPV positive genotype. The most common was HPV16 in two cases (50%) out of the to-

Fisher's test confirmed a statistically significant difference between the presence of HPV infection in patients with CIN III compared to those with cervicitis ($p = 0.002$, $p < 0.01$).

The most common genotype was HPV16 in 6 (75%) of the infected female patients or (66.66%) out of all CIN III patients. The frequency of HPV 16 infection was higher in the infected patients with CIN III (75%) when compared to the patients with cervicitis (10.52%). The second most common genotype was non-existent.

Fisher's test confirmed a statistically significant difference between the presence of HPV16 infection in the patients with CIN III, in comparison to those with cervicitis ($p = 0.026$, $p < 0.05$).

Discussion

Out of all the patients with Pap test for cytological analysis, 3.1% had ASCUS findings. Such percentage is the golden mean of all reports. Namely, Rinku et al. [7] described the presence of ASCUS in 5.3% of Pap tests during the screening procedure. Their data correlate to the results found in

other studies [8]. When it comes to the neighbouring countries of the West Balkan Region, one of the studies conducted in the Republic of Serbia by Ravić [9] found that out of 17,350 women which participated in the screening procedure, 1,038 (5.98%) had suspicious/positive cytological and/or colposcopy result which led then to further histological diagnostics. In one earlier research in the town of Karlovac screening encompassed 2,076 women and, due to suspicious/positive cytological and or colposcopy results in 14.3% of them, biopsy procedure was performed [10]. Additionally, in the 70s and 80s in the municipality of Šabac, 399,203 gynecological exams were performed in order to have organised screening of female genital organs cancer. All the women went through Pap test and colposcopy. Due to suspicions changes indicative of *portio vaginalis uteri* (PVU), biopsy specimens were taken from 2.21% of women [11]. Generally speaking, published data on the percent of pathological-cytological results after the conducted screening procedures is very different and it ranges from 2% to 3% [12–21], 5% to 6% [22–24], 7% to 8% [25–29]. In 2003, France, Luxembourg and Finland reported percentage which is lower than 1.2% [30–32]. Very high percentage, from 10% up to even 25%, was reported from Ibadan, Nigeria, and Taiwan [33, 34]. Interesting data come from France, since different parts of France reported diametrically different data. Namely, they conducted pilot studies on organised screenings. The Isère Department reported only 1.2% of abnormal Pap tests, the Bouches-du-Rhône department reported 4.94%, and the Doubs department as much as 15.11% [35]. Multiple factors influence the number of suspicious/positive Pap tests within screening. One of the most fundamental reason is health of the population. Certainly, this numbers shall be lower in countries which systematically organise cervical cancer screening. One of the most important factors is the quality of cytological laboratory.

The percentage of cases with chronic cervicitis, 56 (70%), is close to the percentage in the study. In the study conducted by Zhang et al. [36], out of 875 female patients with ASCUS, 553 (63.2%) were diagnosed with chronic cervicitis, and Ravić [9] reported that out of 1,038 biopsy specimens, taken on the basis of suspicious and positive Pap and/or colposcopy results, 612 (58.9%) were benign [9]. Massad et al. [37] found lower percentage of benign histological results (45%).

There were 24 (30%) CIN cases, CIN I was present in 12 (15%) of the cases, CIN II in 3 (3.75%), and CIN III in 9 (11.25%). To sum up, LGSIL lesion was present in 15% of the patients and the same percent (15%) was related to HGSIL. Ravić [9] explains that in biopsy specimens, taken on the basis of suspect and positive Pap tests and/or colposcopy results, there were 37.57% of CIN. LGSIL was verified in 268 (25.82%), HGSIL in 122 (11.75%) of the patients. In some studies the percentage of patients diagnosed with LGSIL ranges from 13% to 22%, HGSIL from 26% to 27% [37–39]. Massad et al. [37] stated that there were 33% of cervical dysplasia. Similar distribution and total percentage as in our research can be found in the study of Zhang et al. [36], (33.02%) with cervical intraepithelial neoplasia, out of which 165 cases were with CIN I (18.9%), 45 (5.1%) cases with CIN II, 79 (9.0%) cases with CIN III. Lower percentage is found in the ASCUS-LSIL Triage Study (ALTS) Group. During a two-year monitoring with ASCUS 26% were diagnosed with CIN, out of which LGSIL was present in 15%, and HGSIL in 11% of the cases (6% CIN; 2.5% CIN3) [40]. Higher incidence of CIN I-III (40–66%) than in our research can be found in some other studies [41–43]. Patel et al. [41] in his retrospective study which included 19,215 Pap smears, conducted in the Gujarat Oncology Hospital, found that the presence of CIN III in cytologically detected ASCUS was 38.89% [42]. Similar distribution to found in our study can be found in Rinku et al. [7] with 23% for LGSIL in comparison to 7%–25% in other studies [44]. Rinku et al. [7] found that HGSIL incidence is 11.7% and other authors [45] from 4%–17%.

Out of 80 examined female patients, high risk HPV infection was present in 32 (40%) of them. Higher incidence can be found in a study Jordan et al. [45] (in 41%–50% cases of ASCUS, HPV test was positive). Also, higher percentage can be found in the paper written by Planinić et al. [46]. In women with ASCUS, HPV DNA of high-risk genotypes was detected in (46%) of samples (n = 19/41). Out of 56 female with cervicitis, 19 (33.92%) had HPV infection, or 23.75% of the total number of those with HPV infection. Higher percentage than this can be found in a study of Planinić et al. [46] where HPV DNA was detected in 62 (36.9%) out of 168 of women with cervicitis, and the most frequently detected was DNA of other high-risk genotypes (36/168; 21.4%) and HPV-16 DNA (11/168; 6.5%). Out of 24 female patients with cervical intraepithelial neoplasm, 13 (54.61%) had HPV infection. Much higher percentage can be found in a study of Crum et al. [47] where HPV sequence was detected in 85% of all biopsies and it contained precancerous changes.

In our research most common type in CIN was HPV16 in 8 (61.53%) female patients out of the total number of infected or 33.33% out of the total CIN number. CIN III group contained 9 female patients, out of which 8 (88.88%) were with HPV positive genotype. The most common was HPV16 in 6 (75%) infected female patients or 66.66% of all CIN III patients. In a study of Insinga et al. [48] the most present types of high-risk HPV16 and/or HPV18 were present in 52% of detected CIN2 lesions, 61% for CIN**.** Moscicki et al. [49] presented results, and stated that HPV16 was present in 50% of high-grade CIN [49, 50]. Similar data can be found a paper of in Arbyn and Dillner [51], and they state that HPV 16 and 18 cause half of high-grade cervical squamous intraepithelial lesions and 25% of low-grade cervical squamous intraepithelial lesions. Much higher incidence was reported in a paper of Huang et al. [52], who, in paraffin-embedded biopsy specimen, found HPV-16 in 5 (83.3%) out of 6 cases of CIN I and in 10 (90.9%) out of 11 cases of CIN II/III. Lungu et al. [53] study confirmed that LGSIL changes were exceptionally heterogeneous and out of them any of 40 HPV genotypes can be extracted.

Conclusion

The percentage of suspicious results of Pap tests shown in this study is the golden mean of all reports. We deem it to be the result of quality work performed by the cytological laboratory. Synchronous determination of Pap test and HPV is obligatory,

especially after a suspicious Pap test and abnormal colposcopy. This approach enables classification of women into groups with higher or lower risk of premalignant lesion. One method cannot go without the other. The incidence of HPV infection is higher in patients with cervical intraepithelial neoplasm compared to patients with cervicitis. HPV16 is the most common single cause of cervical intraepithelial neoplasm (especially CIN III). Patients with suspicious Papanicolaou test, colposcopy results and infection caused by high-risk HPV infection (HPV 16 in particular) often have premalignant cervical lesions. In these cases, pathohistological confirmation of the lesion is mandatory, as a definitive diagnostic procedure. This is the only way to make quality diagnostics and provide adequate monitoring and valid treatment to our female patients.

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Received on February 5, 2015.
Accepted on July 30, 2015.
Online First June, 2016.

ORIGINAL ARTICLE

UDC: 577.15:[616.895.8:615.214
DOI: 10.2298/VSP141202142D

Age-related changes of superoxide dismutase activity in patients with schizophrenia

Promene aktivnosti superoksid dizmutaze kod bolesnika sa shizofrenijom zavisno od starosti

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Abstract

Background/Aim. Superoxide dismutase (SOD) is the critical enzyme in the detoxification of superoxide radicals because those are the first species produced in the majority of biological free radical producing reactions. Inconsistent data are present about SOD activity in patients with schizophrenia. Numerous studies show that SOD is elevated in chronic schizophrenic patients. However, decreased SOD activity is found in neuroleptic naive, first episode schizophrenic patients, in chronic-medicated patients and in chronic-unmedicated patients. The aim of this study was to examine the influence of age, gender, age at disease onset, the duration of the disease, the number of episodes, heredity, psychopathologic symptoms and drug treatment on erythrocyte SOD activity in patients with schizophrenia. **Methods.** This study included 68 consecutive patients with schizophrenia (29 males and 39 females) ranging in age from 18 to 61 years, divided into two age groups (< 34 years and > 34 years). SOD activity was measured in erythrocyte hemolyzates by commercially available Ransod test. **Results.** In the group of patients younger than 34 years SOD levels were significantly higher (1,381 ± 273 U/gHb, $p = 0.038$) compared to the levels in the older patients (1,231 ± 206 U/gHb). Gender and heredity did not induce any significant difference in SOD activity between the groups. A significant difference in enzyme activity was found between the younger and older patient groups having the onset of the disease after 24 years of age (1,408 ± 217 U/gHb *vs* 1,252 ± 213 U/gHb, $p = 0.031$, respectively). The patients in the younger group with more than one psychotic episodes had significantly higher SOD activity (1,492 ± 298 U/gHb; $p = 0.009$) than those with only one episode (1,256 ± 177 U/gHb), as well as than the older patients with more than one episode (1,253 ± 231 U/gHb; $p = 0.014$). Although the duration of the disease did not induce any significant difference in enzyme activity between the younger and older patient groups, a significant negative correlation was obtained between SOD activity and the duration of the disease ($r = -0.511$, $p < 0.01$). No significant differences were found in SOD activity between the groups with the different positive and negative syndrome scale (PANSS) scores. First generation antipsychotics were associated with elevated enzyme activity in both groups. Simultaneous treatment of patients with first generation antipsychotics and second generation antipsychotics induced a significant decrease in SOD activity in the younger patient group. **Conclusion.** Our results show that erythrocyte SOD activity is increased in the early phase of schizophrenia, depending on age at the onset of the disease, the number of psychotic episodes, the duration of the disease and medical treatment.

Key words:
schizophrenia; superoxide dismutase; erythrocytes; age factors; antipsychotic agents.

Apstrakt

Uvod/Cilj. Superoksid dizmutaza (SOD) je važan enzim u detoksikaciji superoksid radikala, primarne reaktivne vrste u većini bioloških procesa u kojima se stvaraju slobodni radikali. Podaci o aktivnosti SOD kod bolesnika sa shizofrenijom su nekonzistentni. Mnogobrojne studije pokazale su da je SOD povećana kod bolesnika sa hroničnom formom shizofrenije. S druge strane, snižena aktivnost SOD nađena je kod bolesnika u prvoj epizodi bolesti, kod obolelih koji nikada nisu bili na terapiji antipsihoticima i kod hroničnih, lečenih i nelečenih bolesnika. Cilj rada bio je da se ispita uticaj pola, životnog doba, vremena pojave bolesti, trajanja bolesti, broja psihotičnih epizoda, herediteta, predominantne simptomatologije i klase primenjivanih antipsihotika na aktivnost eritrocitne SOD kod bolesnika sa shizofrenijom. **Metode.** Ispitano je 68 bolesnika sa

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shizofrenijom (29 muškaraca i 39 žena) starosti od 18 do 61 godine, podeljenih u dve grupe (< 34 godine i > 34 godine). Aktivnost SOD merena je u hemolizatu eritrocita komercijalnim testom Ransod. **Rezultati.** U grupi bolesnika mlađih od 34 godine aktivnost SOD bila je značajno viša (1 381 ± 273 U/gHb; $p = 0.038$) nego aktivnost SOD u grupi starijih bolesnika (1 231 ± 206 U/gHb). Nije utvrđena značajna razlika u aktivnosti SOD među grupama u pogledu pola i herediteta. Značajna razlika u aktivnosti enzima nađena je između mlađih i starijih bolesnika kod kojih je bolest počela posle 24. godine starosti (1 408 ± 217 U/gHb prema 1 252 ± 213 U/gHb; $p = 0{,}031$). Bolesnici mlađe grupe koji su imali više od jedne psihotične epizode imali su značajno višu aktivnost SOD (1 492 ± 298 U/gHb; $p = 0{,}009$) od onih koji su imali samo jednu epizodu (1 256 ± 177 U/gHb) i od bolesnika starije grupe koja je imala više od jedne epizode (1 253 ± 231 U/gHb, $p = 0{,}014$). Mada dužina trajanja bolesti nije pokazala statistički značajnu razliku u aktivnosti enzima među grupama, značajna negativna korelacija uočena je između trajanja bolesti i aktivnosti SOD ($r = -0{,}511$; $p < 0{,}01$). Nije nađena značajna razlika u aktivnosti enzima između grupa sa različitim skorovima skale pozitivnih i negativnih simptoma (PANSS). Antipsihotici prve generacije bili su udruženi sa povišenom aktivnošću enzima u obe grupe. Simultano lečenje bolesnika antipsihoticima prve i druge generacije izazivalo je značajan pad aktivnosti SOD u grupi mlađih bolesnika. **Zaključak.** Dobijeni rezultati pokazuju da je aktivnost eritrocitne SOD povišena u ranoj fazi shizofrenije i da zavisi od godina života bolesnika na početku bolesti, broja psihotičnih epizoda, trajanja bolesti i klase primenjivanih antipsihotika.

Ključne reči:
shizofrenija; superoksid dismutaza; eritrociti; životno doba, faktori; antipsihotici.

Introduction

Superoxide dismutase (SOD), EC 1.15.1.1 is an enzyme that catalyzes the dismutation of the toxic superoxide radical, a by-product of oxygen metabolism, into either molecular oxygen or hydrogen peroxide [1]. Hydrogen peroxide is further chemically converted by either glutathione peroxidase (GPx) or catalase into water [2, 3]. Although cells contain a large number of antioxidants to prevent or repair the damage caused by reactive oxygen species (ROS) by maintaining these species in physiologically acceptable level, SOD is primary, critical enzyme in the detoxification of superoxide radicals because these are the main ROS, primarily generated in the most biological free radical producing reactions.

Three forms of SOD are present in humans and protect the cells from superoxide toxicity: copper- and zinc-containing SOD (CuZnSOD/SOD1) localized predominantly in cytoplasmic and nuclear compartments, manganese SOD (MnSOD/SOD2) localized within the mitochondrial matrix, and copper- and zinc containing SOD predominantly found in extracellular compartments (EC SOD/SOD3). Impaired activities of these isoforms can lead to a variety of cell damage from oxidant stress to the cell death [4–6]. Meta-analysis of oxidant stress in schizophrenia shows abnormalities in first episode psychosis, suggesting that it might be independent of antipsychotic medications and erythrocyte SOD might be a trait marker for schizophrenia [7]. However, impaired oxidant stress defense has been reported in blood of both drug-naïve and antipsychotic-treated patients, suffering from schizophrenic psychosis [8]. Plasma and erythrocyte SOD activities were found increased [8–10] or decreased [11, 12], but total SOD (CuZn, Mn, and FeSOD) decreased [13] in patients with schizophrenia. Both MnSOD and CuZnSOD were found lower in patients with tardive dyskinesia (TD) than those without TD [14–16]. These data show that some controversy still exists regarding the level of SOD activity in schizophrenia. A significant reason for this discrepancy might be a large scale of patient age (18–60 years) [12] tested as a whole group.

In relation to biological variability of antioxidant enzymes, it was shown that plasma and erythrocyte SOD activity was rather stable in adults below 65 years, and did not show any significant variation according to gender [17]. Later, Inal et al. [18] noted significantly lower erythrocyte SOD activity in subjects aged 41–69 years than in younger ones, and a negative correlation between SOD activity and age. SOD levels in blood donors aged 58–65 years from the rural environment were significantly lower than those in their urban counterparts [19]. No significant differences were found in mitochondrial SOD and GPx activities in rats between 12 and 24 months of age, but age- and gender-related differences were observed in MnSOD expression [20].

The present study was designed to examine the relationship between SOD activity and a variety of demographic and clinical characteristics of patients with shizophrenia including age, gender, the onset of the disease, the duration, the number of episodes, heredity, psychopathological symptoms and drug treatment.

Methods

This study included 68 consecutive patients with schizophrenia (29 males and 39 females), mean age 32.7 ± 9.4 years, divided into two groups: the younger patient group (< 34 years, n = 44) and the older patient group (> 34 years, n = 24). They were recruited, screened and diagnosed for schizophrenia at the Clinic of Psychiatry of the Clinical Center Niš, using the diagnostic criteria of the International Classification of Mental and Behavioral Disorders (ICD-10). The patients were clinically observed, their personal history recorded, and the psychopathological evaluation and clinical management assessed using the Positive and Negative Syndrome Scale (PANSS). The groups were marked as PANSS positive score predominance – PANSS (+), PANSS negative score predominance – PANSS (-), as well as the group showing almost equally positive and negative symptoms – PANSS (+/-). The demographic and clinical characteristic of patients including age, gender, age at the onset of the disea-

se, the disease duration, the number of episodes and heredity were collected using medical documentation, as well as autoanamnestic and heteroanamnestic data obtained from the patient family members. Heredity was assessed by the presence or absence of schizophrenia and bipolar affective disorder among the first and the second degree relatives. According to drug treatment the patients of both groups (younger and older) were divided into three subgroups: the patients treated with the first generation antipsychotic (FGA) – haloperidol, the patients treated with the second generation antipsychotics (SGA) – clozapine or olanzapine, and the patients receiving haloperidol and one of the second generation antipsychotics (FGA and SGA). The exclusion criteria were: coincidental immune, inflammatory, vascular and liver diseases, any substance (except tobacco) abuse, history or present symptoms of any other psychiatric or neurological disorder.

The patients' consent to participate in the study was obtained from each patient. The study was approved by the Human Ethics Committee of the Clinical Center Niš.

Venous blood was collected in tubes with EDTA. Plasma was separated by centrifugation at 3,000 rpm for 10 min and the buffy coat was removed, and packed cells washed three times with physiological saline. Erythrocyte suspension was used for hemolysate preparation in which the enzyme activity was measured.

SOD activity was measured by Ransod commercially available test (Randox Lab., Crumlin, UK) on the autoanalyzer AU-680 (Beckman Coulter International SA, Nyon, Switzerland) according to the instructions of the manufacturer. This method is based on superoxide inhibition to react with 2-(4-iodphenil)-3/4nitrophenol)-5-feniltetrazolium chloride and form colored formazan in a xanthine/xanthine oxidase system. Enzyme activity was calculated according to SOD standards and expressed in units *per* gram (g) of hemoglobin (Hb). The reference range of Ransod method is 1,092–1,817 U/gHb.

Statistical analysis

Data analysis was performed using the SigmaStat computer program. The results are reported as $\bar{x} \pm SD$ and as median (interquartile range). The difference between the groups was tested by the One Way Analysis of Variance followed by Tukey or Dunn's post-hoc tests, respectively, as appropriate. $p < 0.05$ was considered to indicate statistical significance. Correlations between enzyme activity and demographic, clinical and drug treatment characteristics of patients were assessed using Spearman's coefficient.

Results

Table 1 shows demographic and clinical characteristics of the patients with schizophrenia. There was a statistically significant difference in age ($p < 0.001$) and duration of psychiatric disease ($p < 0.001$) between the two age groups (below 34 and above 34 years).

As shown in Table 2, in the group of patients younger than 34 years, SOD levels were significantly higher

Table 1

Demographic and clinical characteristics of the patients with schizophrenia

Characteristics	Groups of patients	
	< 34 years	> 34 years
Male/Female, n	19/25	10/14
Age (years), $\bar{x} \pm SD$	26.6 ± 5.1***	41.4 ± 7.0
Heredity (+/-), n	12/32	12/12
Age of disease manifestation (before/after 24 years), n	29/15	8/16
Duration of psychiatric disease (years), $\bar{x}$ (range)	3(1-4.75)***	6(4.5–12.5)
Number of episodes (one/more than one), n	21/23	5/19
PANSS positive scores predominant (> 3), $\bar{x} \pm SD$	9.7 ± 4.2	11.2 ± 5.7
PANSS negative scores predominant (< -8), $\bar{x} \pm SD$	13.9 ± 4.9	12.3 ± 3.5
PANSS positive and negative scores almost equally expressed (>-8< 3), $\bar{x} \pm SD$	2.6 ± 3.8	4.5 ± 3.3
PANSS general psychopathology, $\bar{x} \pm SD$	49.3 ± 8.5	47.5 ± 9.5
FGA (haloperidol treated), n	14	8
SGA (clozapine or olanzapine treated), n	14	6
FGA and SGA treated, n	16	10

***** *-p* < 0.001 *vs* older patient group.**
PANSS – positive and negative syndrome scale; FGA – first generation antipsychotics; SGA – second generation antipsychotics.

Table 2

Erythrocyte superoxide dismutase (SOD) activity in the patients with schizophrenia grouped by age

Groups of patients	SOD (U/gHb)
Whole group (n = 68), $\bar{x}$ (min–max)	1,255 (1,136–1,457)
patients < 34 years (n = 44), $\bar{x} \pm SD$	1,381 ± 273*,**
patients > 34 years (n = 24), $\bar{x} \pm SD$	1,231 ± 206

***p* = 0.038 *vs* older patient group (> 34 years);**
****p* = 0.001698 *vs* whole group.**

(1,381 ± 273 U/gHb, $p = 0.001698$) compared to the values of the patients of the whole group [1,255 (1,136–1,457) U/gHb], as well as to the values of the older patient group (1,231 ± 206 U/gHb, $p = 0.038$).

Related to gender SOD activity was insignificantly higher in the female patients than in the male ones in the younger patients group (Table 3).

Erythrocyte SOD activity in the heredity positive and heredity negative patients of the younger patient group was not significantly different compared to the corresponding older patient groups (Table 3).

SOD activity in the patients younger than 34 years was higher than in patients older than 34 year, regardless the age of patients at the disease onset (Table 3), but statistically significant difference in the enzyme activity was found only between subgroups of patients developing the disease after 24 years of age ($p = 0.031$).

In the younger patients group, the patients who had more than one psychotic episode had significantly higher SOD activity ($p = 0.009$) than those who had only one episode, as well as than the older patients with more than one psychotic episode ($p = 0.014$) (Table 3).

In the patients younger than 34 years, suffering more than five years, SOD activity was insignificantly higher ($p = 0.078$) in comparison with the SOD activities of the patients older than 34 years (Table 3). A significantly negative correlation coefficient was found between the duration of the disease and SOD activity ($r = -0.511$, $p < 0.01$). None of other studied factors significantly correlated with the enzyme activity.

No significant differences in SOD activity were found in different PANSS scores between the two age groups (Table 4).

Neither haloperidol, nor second-generation antipsychotic drugs used in the treatment of patients, caused significant differences in SOD activity between the groups. However, significantly higher enzyme activity was found in the younger patient group between those treated with FGA and those treated with FGA and SGA ($p = 0.010$) (Table 4).

Discussion

The major finding of this study is that erythrocyte SOD activity is significantly higher in the early phase of schizophrenia than in the later one which was confirmed by a significant negative correlation between the duration of the disease and SOD activity. Contrary to our findings Wu et al. [8] observed that neither age nor duration of the illness were associated with SOD activity in the first-episode or chronic patients.

Table 3

Erythrocyte SOD activity and clinical features of schizophrenia in patients grouped by age

Characteristics	SOD (U/gHb)				*p*
	n	patients < 34 years	n	patients > 34 years	
Male	19	1,367 ± 289	10	1,310 ± 127	0.591
Female	25	1,415 ± 236	14	1,329 ± 355	0.517
Heredity (+)	12	1,288 (1,202–1,434)	12	1,305(1,175–1,425)	0.926
Heredity (-)	32	1,361 ± 310	12	1,203 ± 174	0.122
Patient's age at the disease onset					
before 24 years	29	1,368 ± 297	8	1,209 ± 202	0.359
after 24 years	15	1,408 ± 217	16	1,252 ± 213	0.031
Number of episodes					
one	21	1,256 ± 177	9	1,206 ± 96	0.558
more than one	23	1,492 ± 298**	19	1,253 ± 231	0.014
Disease duration					
to one year	12	1,319 ± 188		-	-
less than 5 years	19	1,341 ± 230	7	1,378 ± 526	0.827
more than 5 years	13	1,474 ± 394	17	1,255 ± 214	0.078

****$p = 0.009$ *vs* younger patients having one episode; SOD – superoxide dismutase.**
The data are presented as mean ± standard deviation or range (min–max).

Table 4

Erythrocyte superoxide dismutase (SOD) activity in patients with schizophrenia related to the predominant symptomatology and drug treatment.

Variables	SOD (U/gHb)				*p*
	n	patients < 34 years	n	patients > 34 years	
PANSS (+)	15	1,385 (1,187–1,481)	10	1,409 ± 329	0.756
PANSS (-)	15	1,399 ± 282	6	1,171 ± 238	0.234
PANSS (+/-)	14	1,219 ± 225	8	1,208 ± 183	0.914
FGA	14	1,500 ± 277**	8	1,406 ± 352	0.486
SGA	14	1,362 (1,073–1,709)	6	1,054 (980–1,129)	0.167
FGA and SGA	16	1,210 (1,181–1,292)	10	1,283 (1,121–1,412)	0.598

****$p = 0.010$ *vs* FGA and SGA of the younger patient group.**
For abbreviations see under Table 1.
The data are presented as mean ± standard deviation or range (min–max).

In 1986 Abdalla et al. [21] showed about 60% higher SOD activity in neuroleptic-treated and untreated patients with schizophrenia than those found in normal individuals. High erythrocyte SOD activity in schizophrenia have been reported in many previous studies [10, 22] which negatively correlated with malondialdehyde (MDA) concentration [23], while some other studies noted low SOD activity in patients with schizophrenia [24, 25]. Significantly lower levels of SOD and GPx with an increased oxidative stress as indicated by high blood MDA levels were found by Dadheech et al. [12] and Zhang et al. [25]. Similar to our findings, Rukmini et al. [23] noted higher SOD activity in patients with schizophrenia in parallel with the increased catalase activity and MDA level. The increased erythrocyte SOD activity and decreased GPx activity were also found in patients with acute and chronic schizophrenia associated with lower erythrocyte reduced glutathione (GSH) [10]. In addition, a significant increase in cytosolic and mitochondrial isoenzymes of SOD were shown in frontal cortex and substantia innominata of postmortem brain tissue [26]. This discrepancy may be in part explained by our results showing increased SOD activity in younger patients, *ie* in the early phase of schizophrenic disease. This high SOD activity may be induced in response to oxidant stress and increased production of ROS [27], as confirmed by the presence of carbonyl stress [28] and other markers of oxidative cellular damage [29]. These findings indicate that oxidative stress is a primary event and that SOD activity abnormalities are its consequence. That is recently confirmed by Cabungcal et al. [30] who have shown that juvenile antioxidant treatment prevents adult deficits in the developmental model of schizophrenia. Higher conversion of superoxide might elevate hydrogen peroxide level which, in turn, could inactivate SOD [31], leading to the inhibition of the enzyme activity in the later stage of the disease.

In attempt to explain the divergency of findings related to SOD in schizophrenia, some authors have studied SOD polymorphism. Hitzeroth et al. [32] investigated the functional polymorphism (Ala-9Val) in the MnSOD gene in the Xhosa population and did not find any significant difference in either genotype or allele frequency between the schizophrenic and the control group, nor between the polymorphism and symptom severity. Another study [33] reported similar results related to the patients with schizophrenia, but it found a decrease in -9Ala (mutant) allele among patients with TD, suggesting that the -9Ala (high activity) MnSOD allele may play a role in protecting against susceptibility to TD in patients with schizophrenia.

Contrary to our results related to the SOD activity between PANSS subgroups in both groups, plasma SOD activities were found negatively correlated with positive symptoms of schizophrenia in first-episode patients [8], and Yang et al. [34] noted a significantly positive relationship between the change in SOD at pretreatment and posttreatment and the reduction in the PANSS negative subscore. There is also an assumption that the positive symptoms of schizophrenia are associated with hyperactivity of dopaminergic system and the increased production of ROS, due to auto-oxidation of catecholamines, which leads to increased oxidant stress in PANSS (+) patients [35].

Inconsistent data are present about the effects of antipsychotics on antioxidant enzymes and oxidant stress. In 2006 Zhang et al. [25] showed that the activities of SOD and GPx were decreased but the levels of MDA elevated in patients with the chronic form of schizophrenia as compared with the healthy controls. No significant differences were found in any parameters measured among all three subgroups treated with clozapine, risperidone or typical antipsychotics. Six years later, the same authors [22] showed that blood levels of SOD and plasma nitric oxide were significantly increased in patients with schizophrenia and that both risperidone and haloperidol equivalently reduced the elevated blood SOD levels. There is also evidence that chronic haloperidol treatment for both 45 and 90 days significantly decreased MnSOD, CuZn SOD and catalase activities in the rat brain, whilst risperidone, clozapine or olanzapine treatments did not produce any alterations in the activity of antioxidant enzymes [36]. These results are compatible with the study of Yao et al. [37] who observed that both SOD and GPx activities were higher in drug-free conditions than in patients treated with haloperidol. However, we found elevated SOD activity in the group of younger patients treated with FGA in comparison with the group of younger patients treated with FGA and SGA. SGA did not change SOD activity in both studied groups. In addition, Qing et al. [38] showed that atypical antipsychotics slightly up-regulated the expression of CuZn-SOD whereas haloperidol strongly increased the expression of this enzyme. These findings indicate that haloperidol could have not just a stimulatory effect on SOD activity, but could be an inducer of oxidant stress, and SGA have a potential to normalize the activity of the enzyme. The lowest activity of SOD observed in our patients simultaneously treated with FGA and SGA could be a consequence of dopamine D2 receptor antagonism and excessive dopamine auto-oxidation followed by the inhibition of enzyme activity due to overproduction of hydrogen peroxide, or could be the result of unknown biochemical mechanism.

Conclusion

Our results show that erythrocyte SOD activity is increased in the early phase of schizophrenia and that it depends on the onset of the disease, the number of psychotic episodes, the duration of the disease, and medical treatment. These findings suggest the use of antioxidants as adjuvant therapy in the prodromal and early phase of schizophrenia. Also, these data indicate that patients with schizophrenia should not be studied as the general population, but separately classified according to each factor that affects enzyme activity in a longitudinally designed study.

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Received on December 2, 2014.
Revised on May 28, 2015.
Accepted on June 23, 2015.
Online First June, 2016.

ORIGINAL ARTICLE

UDC: 616-084::613.25
DOI: 10.2298/VSP140821140G

Predictors of overweight and obesity among adults aged 50 years and above: Serbian national health survey

Prediktori prekomerne telesne mase i gojaznosti kod osoba starih 50 i više godina: nacionalno istraživanje zdravlja stanovnika Srbije

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Abstract

Background/Aim. Obesity is a complex and multifactorial condition related to morbidity, mortality, poor quality of life and many other problems. The aim of the study was to determine the prevalence of overweight and obesity and factors associated with them (demographic, socioeconomic factors and lifestyle) in adults aged 50 years and above in Serbia. **Methods.** This cross-sectional study, representative for the population in Serbia, was carried out in one-year period, including 6,932 people aged 50 and over. Individuals were interviewed and anthropometrically examined. The association between overweight and obesity with demographic, socioeconomic and behavioral factors was analyzed using multivariate logistic regression. **Results.** Age, level of education and smoking were significantly associated with overweight and obesity, regardless of gender. Marital status was significantly associated with obesity, regardless of gender and with overweight only in women. Breakfast consumption habit was significantly associated with obesity only in men. There was no significant association of overweight and obesity with the type of settlement, alcohol consumption and physical activity, regardless of gender. **Conclusion.** The results of our study indicate the need for more intensive implementation of measures affecting the factors which contribute to overweight and obesity. Emphasis should be put on the population-based policies and programs that support environmental changes.

Key words:
obesity; overweight; prevalence; age factors; socioeconomic factors; risk assessment; serbia.

Apstrakt

Uvod/Cilj. Gojaznost je kompleksno i multifaktorijalno stanje povezano sa obolevanjem, umiranjem, lošim kvalitetom života i mnogim drugim problemima. Cilj ovog rada bio je da se utvrde prevalencija prekomere telesne mase i gojaznosti i faktori povezani sa njima (demografski i socioekonomski faktori i stil života) kod odraslog stanovništva Srbije, starog 50 i više godina. **Metode.** Istraživanje je sprovedeno kao studija preseka na reprezentativnom uzorku stanovništva Srbije i obuhvatilo je 6 932 osobe stare 50 i više godina. Ispitanici su bili intervjuisani i mereni su im antropometrijski pokazatelji. Povezanost između prekomerne telesne mase i gojaznosti sa demografskim, socioekonomskim i bihejvioralnim faktorima analizirana je primenom multivarijantne logističke regresije. **Rezultati.** Starost, nivo obrazovanja i pušenje bili su značajno povezani sa prekomernom telesnom masom i gojaznošću, nezavisno od pola. Bračni status je bio značajno povezan sa gojaznošu i kod muškaraca i kod žena, dok je povezanost sa prekomernom telesnom masom utvrđena samo kod žena. Redovnost uzimanja doručka bila je značajno povezana sa gojaznošću kod muškaraca. Nije utvrđena značajna povezanost prekomerne telesne mase i gojaznosti sa mestom stanovanja, konzumiranjem alkohola i fizičkom aktivnosti, bez obzira na pol. **Zaključak.** Rezultati naše studije ukazuju na potrebu intenzivnije primene mera za suzbijanje faktora rizika od prekomerne telesne mase i gojaznosti. Posebno su značajne populacione strategije i programi koji podržavaju promene u okruženju.

Ključne reči:
gojaznost; telesna masa, prekomerna; prevalenca; životno doba, faktori; socioekonomski faktori; rizik, procena; srbija.

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Introduction

Excess body weight poses one of the serious public health issues of the 21st century [1]. The World Health Organization (WHO) emphasizes that the world is in a grip of a global epidemics, and it is estimated that by 2020 obesity (OB) will be the single biggest cause of death on the planet [2]. In countries of the European Region overweight (OW) prevalence varies from 32% to 79% among men, and from 28% to 78% among women. In addition, the prevalence of OB ranges from 5% to 23% among men and from 7% to 36% among women [3]. Epidemiological studies show that OB is associated with increased risks of morbidity, premature mortality, negative effects on health related quality of life [4, 5] and reduced life expectancies [6]. Obese people are at the higher risk for a number of chronic diseases, including metabolic and cardiovascular disease, musculoskeletal problems, lower physical function and some cancer [7]. Those conditions often underlie disability among older population and contribute significantly to the total health burden [8]. OW and OB are a reflection of the combination of a variety of factors including a range of demographic, socioeconomic factors and lifestyle [9–14].

In Serbia, the concern about OB among adults is growing. The results obtained from the National Studies on Health of the Population of Serbia, aged 20 years and above which were carried out in 2000 and 2006 did not show any significant changes in the prevalence of OB and OW. But, the changes were noticed in a survey conduced in 2013 showing a statistically significant increase of OB compared with 2006 (21.2% *vs* 17.3%, respectively) but also no significant changes in the prevalence of OW. Current findings also reveal that OW is more present in men than in women (42.2% *vs* 29.5%, respectively) while there are no significant differences in OB, regardless gender. The similar trend was noticed in 2013 [15]. A significant increase in OW and OB is recorded in the age 45 and over, with the highest proportion in the age 55–74 years [16, 17].

The disease burden attributable to OB in Serbia increases with age and the highest rates are at the age 55–64 in both males and females [18]. At the same time, Serbia goes through a rapid ageing of the population. Current projection estimates that the participation of each 5 years of age group after 55 years in women and 50 years in men in total population will continue to increase [19]. It is expected that ageing of the population of Serbia combined with the increase in OB is likely to result in an increase of older obese population followed with sociomedical and economic consequences.

The focus of this study is on adults aged 50 years and more. According to our knowledge, we do not have studies in which the association of demographic, socioeconomic status and lifestyle with OW and OB at the age 50 years and above was surveyed and evaluated whether they could explain the difference in Serbia. The main reason to select this age group is that a large number (67%) of adults aged 50 years and over have body mass index (BMI) $\geq$ 25 kg/m^2. Every fourth of them (25.8%) have BMI $\geq$ 30.0 kg/m^2. This age group is also interested as many today's obese are in their 50's and 60's and its health effects are more likely to develope in the middle age [20]. This is the age of a significant increase in the number of chronic diseases [21, 22]. The increase in OB and OB-related chronic diseases in the current context of population ageing is likely to increase disability among older population in the future [23]. On the other hand, the generalizations from the total population may be inaccurate for predicting health consequences of OB in elderly adults [22]. Population trends regarding adults can mask considerable differences within age groups and such sorts of information are important for planning and evaluating preventive and management strategies.

The aim of this study was to analyze the prevalence of OW and OB in the population aged 50 years and above and its association with demographic and socioeconomic factors and lifestyles.

Methods

The 2006 National Health Survey of the population of Serbia database was analyzed. The study was cross-sectional and nationally representative for health examination of noninstitutionalized population aged $\geq$ 50. A stratified two-stage sample of the population was used. A total sample of people aged $\geq$ 50 was 7,522. For this purpose, we analyzed data for 7,036 persons (93.5%) to whom weight and height were measured. A number of underweight subjects (n = 104; 1.5%) was excluded due to the small number of measured persons, which could affect analysis and results (sample contamination). Therefore, the finall sample included 6,932 adults aged 50 and over.

Measures

The hight was measured to the nearest 0.1 cm, without shoes, using a mounted metal cm ruler. Body weight measurement was performed using a decimal scale in kg with accuracy of 100 g, after the removal of shoes and excess clothing.

BMI was calculated as weight in kg, divided by height in m squared. BMI classification of WHO was used: normal weight (NW) (18.5–24.9 kg/m^2), OW (25.0–29.9 kg/m^2) and OB ($\geq$ 30.0 kg/m^2) [1].

Demographic and socioeconomic variables

Individuals were grouped by age: 50–59 years, 60–69 years and 70 years and above. The level of education was categorized as primary, secondary and postsecondary, marital status as married and single (unmarried, divorced or widowed). In order to present data by the type of settlement, were used the so-called administrative-legal criteria, according to which settlements were divided into “urban” (those that have obtained this status through a legal act of the respective local self-government unit) and into “other” (rural). Socioeconomic status was measured by Demographic and Health Survey Wealth Index (Wealth Index). Its calculation included variables related to examinees assets. According to the Wealth Index, respondents were classified into five soci-

oeconomic groups or quintiles with the same number of individuals in each: poorest (first level), poor (second level), middle class (third level), wealthy (fourth level) and wealthiest (fifth level) [24].

Behaviours

Smoking status included and determined in 3 categories – non-smoker, former smoker and current smoker. Alcohol intake was determined by three categories: non-drinker (no alcohol use or former drinker), no risk drinker and heavy drinker. Two criteria were used to identify risky drinkers (heavy drinkers): an average daily consumption that exceeds the upper limit of two alcoholic beverages for men or one alcoholic beverages *per* day for women, and reporting ≥ 12 binge drinking episodes (consumption of five or more alcoholic beverages in a single day) during the previous year [25]. Physical activity during leisure time was graded in three levels based on questionnaire designed by Saltin and Grimby [26] with minor modifications. More vigorous and highly vigorous activity were combined into one category – vigorous activity, so the level of physical activity was defined as follows: sedentary (reading, watching television, etc.); light physical activity (walking, biking, fishing, etc.) for at least 4 h *per* week; vigorous activity (running, swiming, playing ball, heavy gardering, compettitive sports, etc.) for at least 4 h *per* week. Level 1 was defined as physical inactivity (lack of physical activity). Breakfast consumption, fruits and vegetables intake were classified in two categories: everyday and less than seven times *per* week.

Statistical analysis

The obtained data were statistically processed using SPSS version 17.0. Differences in frequency were tested by χ^2 test. Any variable whose univariate test has a *p*-value < 0.05 was candidate for the multivariate model. Multivariate analysis of logistic regression was used to assess the association between BMI and potential risk factors. All analyses presented were performed separately for OW as dependent variable (Model 1: OW = 1, NW = 0) and OB as dependent variables (Model 2: OB = 1, NW = 0) for men and women. The final model was obtained using forward selection. The importance of each variable included in the model was verified by examination of the Wald statistics. In interpreting these associations we applied the odds ratio (OR), with 95% confidence interval (CI). All reported *p*-values are two-tailed.

Results

The prevalence of OW and OB according to sociodemographic characteristics in men and women were presented in Table 1. Out of 6,932 analyzed people aged 50 and over, 3,216 (46.4%) were men and 3,716 (53.6%) were women. The prevalence of OW and OB were 44.3% and 19.7% in men and 38.6% and 31.0% in women, respectively. The prevalence of OW and OB among men and women, according to their lifestyle choices were presented in Table 2. The results of univariate analysis indicate that breakfast consumption habit was significantly associated with OW and OB only

Table 1

Prevalence of overweight and obesity among males (M), and females (F) according to the demographic and socioeconomic characteristics

Characteristics	Total (n) M/F	Normal weight (%) M/F	Overweight (%) M/F	Obesity (%) M/F	$p^{\dagger}$-values
Age (years)					
50–59	1,343/1,430	31.1/28.9	45.5/41.3	23.4/29.8	< 0.001/0.001
60–69	967/1,116	34.6/24.9	44.5/39.2	20.9/35.8	
70 and over	906/1,170	44.6/37.4	42.3/34.5	13.1/28.0	
Type of settlement					
urban	1,546/1,929	33.5/30.5	46.4/39.3	20.1/30.2	0.016/0.481
rural	1,670/1,787	38.3/30.3	42.3/37.8	19.4/32.0	
Marital status (n = 3,207/3,702)					
married	2,635/2,247	33.9/27.2	45.2/40.3	20.9/32.5	<0.001/<0.001
unmarried	572/1,455	45.5/35.1	40.0/36.1	14.5/28.8	
Educational level					
primary	1,465/2,480	42.9/29.0	39.5/37.6	17.5/33.5	<0.001/<0.001
secondary	1,234/927	30.1/30.9	46.8/41.4	23.1/27.7	
postsecondary	517/309	30.4/40.5	51.6/37.9	18.0/21.7	
Household wealth					
poorest	843/951	47.2/33.6	37.1/35.5	15.7/30.8	< 0.001/0.001
poor	719/777	35.5/29.7	43.0/38.5	21.6/31.8	
middle	692/822	33.2/25.3	44.4/40.1	22.4/34.5	
wealthy	503/597	28.6/30.0	49.9/38.5	21.5/31.5	
wealthiest	459/569	28.3/33.6	53.2/41.5	18.5/25.0	
Total					
n	3,216/3,716	1,157/1,129	1,424/1,433	635/1,154	
%	100.0/100.0	36.0/30.4	44.3/38.6	19.7/31.0	

$p^{\dagger}$ – values calculeted by χ^2 test.

Table 2

Prevalence of overweight and obesity among males (M) and females (F), according to the lifestyle risk factors

Parameters	Total (n) M/F	Normal weight (%) M/F	Overweight (%) M/F	Obesity (%) M/F	$p^{\dagger}$-values
Everyday breakfast consumption					
no	524/747	33.6/28.6	39.7/40.3	26.7/31.1	
yes	2,679/2,965	36.5/30.8	45.1/38.1	18.4/31.1	< 0.001/0.451
total	3,203/3,712	36.1/30.4	44.2/38.5	19.7/31.1	
Everyday fruits intake					
no	1,962/2,055	36.5/31.6	43.8/37.7	19.7/30.7	
yes	1,236/1,641	35.2/28.8	45.2/39.4	19.6/31.8	0.697/0.181
total	3,198/3,696	36.0/30.4	44.3/38.4	19.7/31.2	
Everyday vegetables intake					
no	1,382/1,520	37.9/33.0	43.1/36.8	19.0/30.2	
yes	1,834/2,196	34.5/28.6	45.2/39.8	20.3/31.6	0.137/0.016
total	3,216/3,716	36.0/30.4	44.3/38.6	19.7/31.0	
Physical activity					
lack	2,193/2,916	36.5/30.2	43.9/38.5	19.7/31.3	
light	627/491	31.4/29.9	48.2/42.4	20.4/27.7	0.055/0.106
vigorous	377/289	40.3/31.5	40.8/33.2	18.8/35.3	
total	3,197/3,696	35.9/30.3	44.4/38.6	19.7/31.1	
Smoking					
non-smoker	1,131/2,072	30.9/26.5	49.0/40.5	20.2/33.0	
former smoker	688/252	25.3/28.2	48.1/38.5	26.6/33.0	< 0.001/< 0.001
regular or periodical smoker	884/553	44.5/40.5	38.2/34.7	17.3/24.8	
total	2,703/2,878	33.9/29.3	45.2/39.2	20.9/31.5	
Alcohol drinking					
non-drinker	1,040/2,204	34.3/28.9	46.3/38.5	19.4/32.7	
no risk drinker	1,150/504	33.5/32.1	46.4/41.5	20.1/26.4	0.088/0.091
heavy drinker	388/44	34.8/29.5	39.9/43.2	25.3/27.3	
total	2,578/2,752	34.0/29.5	45.4/39.1	20.6/31.4	

***$p^{\dagger}$* – values calculated by χ^2-test.**

in men. Fruits intake was not associated with OW and OB regardless of gender, while vegetables intake was significantly associated with OW and OB only in women. Data revealed that smoking was significantly associated with OW and OB in male and female. Drinking habit of men and women were not associated with OW and OB. Contrary to expectation, there was no statistically significant difference in body weight according to the level of physical activity regardless to gender.

Independent variables that were significantly associated with OW and OB in univariate analysis, were included in multivariate logistic regression (Table 3), with the dependent variable OW (Model 1) and OB (Model 2). Models were analyzed separately for men and women. Age, level of education and smoking were significantly associated with OW and OB, regardless gender. Men were less likely to be OW if they are 70 years and older compared with those who are under 60 years old (OR = 0.71; 95% CI, 0.56–0.89), similar as women of the same age (OR = 0.66; 95% CI, 0.51–0.86). Additionally, marital status was significantly associated with OB, regardless of gender and it was significantly associated with OW only in women. Single men and women were less likely to be obese compared to married ones and single women were also less likely to be OW. Women with higher levels of education were less likely to be OW (for postsecondary level of education OR = 0.62; 95% CI, 0.46–0.84) or OB (OR = 0.42; 95% CI, 0.30–0.59), contrary to obtained results in men. Men with no breakfast consumtiom everyday were more likely to be obese (OR = 1.74; 95% CI, 0.1.31–2.31). Men and women smokers are less likely to be OW or obese, compared with non-smokers. Male former smokers were more likely to be obese compared to non-smokers (OR = 1.46; 95% CI, 1.11–1.93).

Discussion

The results of this study reveal the magnitude of the problem of OW and OB in Serbian population of 50 years and above. Nearly two-third of this population were OW or obese. Obesity affect every fifth of men and almost every third of women aged 50 years and over. Among men, 44.3% and among women 38.6% were OW. A recent study carried out in 10 European countries indicate that among males, the prevalence of OW is 49.8% and 16.2% of OB. For females, the prevalence of OW is 36.1% and 19.8% of them are obese [22].

Multivariate analysis revealed a strong association between OW and OB and age. The analyses show that the risk to be OW and obese decreases with age, regardless gender. These findings are in accordance with the results of various other studies [15, 22]. The literature states that weight loss is due to reduction in appetite and food intake, changes in body composition, loss of skeletal muscles. The most obvious changes associated with ageing concern body composition. Ageing is associated with decrease in total and lean body mass. It is known that body weight increases until 60 years of age and decreases progressively thereafter. Muscle mass

Table 3

Adjusted odds ratio (OR) for overweight – OW (Model 1) and obesity –OB (Model 2) among adults aged 50 and over

Explanatory variables	Men		Women	
	Model 1‡, OR (95% CI)	Model 2§, OR (95% CI)	Model 1‡, OR (95% CI)	Model 2§, OR (95% CI)
Age				
50–59	1.00	1.00	1.00	1.00
60–69	0.83 (0.67,1.03)	0.70 (0.54, 0.91)**	0.90 (0.72, 1.13)	1.07 (0.85, 1.36)
70 and older	0.71 (0.56, 0.89)**	0.41 (0.30, 0.56)**	0.66 (0.51, 0.86)**	0.68 (0.52, 0.89)**
Marital status				
married		1.00	1.00	1.00
single		0.65 (0.47, 0.88)**	0.79 (0.65, 0.97)*	0.81 (0.65, 0.99)*
Educational level				
primary	1.00	1.00	1.00	1.00
secondary	1.43 (1.17, 1.75)**	1.42 (1.11, 1.81)**	0.91 (0.73, 1.12)	0.74 (0.59, 0.93)*
postsecondary	1.55 (1.21, 2.00)**	1.10 (0.79, 1.52)	0.62 (0.46, 0.84)**	0.42 (0.30, 0.59)**
Everyday breakfast consumption				
yes		1.00		
no		1.74 (1.31, 2.31)**		
Smoking				
non-smoker	1.00	1.00	1.00	1.00
former smoker	1.11 (0.88, 1.39)	1.46 (1.11, 1.93)**	0.91 (0.65,1.28)	1.10 (0.77, 1.56)
smoker	0.47 (0.38, 0.58)**	0.44 (0.34, 0.58)**	0.53 (0.42,0.67)**	0.53 (0.41, 0.69)**

†NW – normal weight; CI – confidence interval; ‡Logistic regression model. Dependent variable was overweight (OW = 1, NW = 0); §Logistic regression model. Dependent variable was obesty (OB = 1, NW = 0); *$p < 0.05$, **$p < 0.01$.

declines with age and is gradually replaced by fat mass. Furthermore, fat location changes over time, with fat mass tending to increase around the abdomen as we age, which can often lead to serious metabolic consequences [10, 27].

There have been opposing reports about the association of marital status and OB. Some studies show a positive association [28] although some others do not find any association [29]. We observed that married men and married women were more likely to be obese than those who were single. The exact mechanism linking OB and marital status is not fully understood. Some longitudinal studies explain that married couples eat more regular meals, richer and denser foods and that married couples, especially women, are no longer concerned about attracting a partner. Marital role obligations often discourage exercise [30].

Review of the literature show that a higher socioeconomic status in developed countries is directly associated with OB among men and women [31], while in developing countries there is an increased association between socioeconomic status and OB, where the highest rate of obesity and type 2 diabetes are being observed among the most disadvantaged groups, notably the poor and minorities [32]. Although the results of the univariate analysis indicate that household wealth and education are associated with OB and OW, we decided to include only education in multivariate logistic regression. The first reason for this was that education and socioeconomic status are highly correlated, so that those with greater wealth are more likely to have higher education. The second reason was that while the level of education could be considered a fixed category because it can only increase, wealth status is variable, particularly in our country with a high unemployment and social stress [33].

We found that educational level has been associated with body weight. Men with higher level of education were more likely to be obese or OW compared to men with lower level of education. However, we observed that in women OW and OB were inversely associated with educational level. Women with higher levels of education are less likely to be OW or obese, contrary to the obtained results in men. Our results are in consonance with other epidemiological studies [28, 31], although some studies found the inverse association in both genders [34]. Reasons for the association between OB and education level in women could be explain by the fact that women with a higher education level express a higher interest in caloric intake and OB. Higher educational attainment through increased knowledge enables an individual to make healthy choices and integrate healthy behavior into a coherent lifestyle, giving them the sense of control over their health [35]. Social pressure to be slim is probably more pronounced in educated women than men [28]. When we look at type of settlement we notice no association of the prevalence of OW and OB with the type of settlements. The explanation could be found in the fact that Serbia is faced with unfavorable socioeconomic situation expressed through the low rate of employment, poverty, especially among children and people aged 60 and over, and low gross domestic product (GDP) [36]. We hypothesize that it have an impact on less protective health behavior and its impact on OW and OB among people, regardless the type of settlements. In survey carried out in ten European countries on those aged 50–79 years, the authors explain that high GDP of this European countries diminishes the differences between urban and rural areas [37].

We observe that men and women who were smokers are less likely to be OW and OB compared to non-smokers, while men who were former smokers are more likely to be obese compared to non-smokers. The association between

cigarette smoking and BMI is not completely understood. It was believed that mean BMI tended to be lower in current smokers than in non-smokers, but recent data do not report so [38]. In current smokers, nicotine speeds up human metabolism, which could explain why smokers tend to have lower body mass. When the person quits smoking, his\her metabolism slows down and weight is gained even though a person is not eating more food. When someone quits smoking, they can usually feel more hungry and food has better flavor and taste [39]. On the other hand, it has been reported that heavy smokers have greater body weight than do light smokers and non-smokers. One of the explanations could be that heavy smokers are more likely to adopt behaviors contributing weight gain (*eg* unhealthy diet, physical inactivity, high alcohol intake). There is, also increasing evidence that smoking affects body fat distribution and that is associated with central obesity [40]. Nevertheless, further research in this field should be conducted.

Previous epidemiological studies revealed association between alcohol consumption and OB [41]. Some studies describe positive association in men and null association in women [13]. Data from the present analyses showed no significant association between alcohol consumption and OB, regardless of gender. The exact relationship should be elucidated, but in assessing the association between alcohol consumption and OB drinking frequency and drinking pattern should be taken into account [42]. As the relationship between OB and alcohol consumption is complex and may be confounding with other types of behavior like smoking, dietary intake, and levels of physical activity more studies are needed to describe their association.

The findings from our study show that skipping the breakfast is associated with the increased likelihood of OB in men. One of the hypotheses is that individuals who do not eat early in the morning tend to be hungry later on and that they may consume a greater number of calories during the evening hours than individuals who eat consistently through the day. Greater energy intake may result in greater fat storage and this may be one of the factors leading to increase in body weight [43].

Changes in dietary habits and physical activity have been implicated as potential cause of OB. But, we did not find any association between physical activity and OW or OB in men and women engaged in this study. These findings are in line with the literature [44]. The problem in interpretation of our obtained data is that self-reported physical activity is not very precise measure of physical activity. Besides that, our study included only leisure time physical activity, and not work related and transportation physical activity, so we had no insight into overall physical activity. Such sort of information requires application of tests for more precise measurement of physical working capacity which is difficult to implement in national representative cross-sectional study.

Some limitations must be considered in interpreting our results. First, our study was cross-sectional, not longitudinal. Thus, no conclusion could be drawn about causal relationships of OW and OB and socioeconomic factors and lifestyle. Second, OW and OB are assessed using BMI as a measure of overall adiposity, although, the waist circumference is more appropriate anthropometric index of abdominal OB. But, waist circumferences were not included in the survey. Despite the fact that BMI is not ideal method for assessment of nutritional status, there is still much controversy which requires more research in this field to define specific cut-off points for elderly. Our results are based on self-reported data about sociodemographic status and health behaviors. Some of them, do not always reflect the real situation, as alcohol abuse which is negatively valued in our society, especially in women or self-reported financial situation.

The baseline information obtained from the pooled data from the Serbian Health Survey, 2006 is used to look at the prevalence of OW and OB at targeted population and to understand factors associated with them. The obtained information should be used as a base for increase investments in effective-based OB-prevention programs, especially regarding the fact that the 2013 Survey points to a statistically significant OB increase. Emphasis should be put to health promotion strategies for adults – middle aged and older population.

Conclusion

The health of adults aged 50 years and over in Serbia presents an important medical, social and economic challenge. Ageing of the population of Serbia in combination with the increase in obesity is likely to result in an increase of older obese population followed with its negative effects on health status of the population and social and economic consequences. This study revealed the prevalence of overweight and obesity in Serbian adults aged 50 years and over and its association with demographic, socioeconomic status and lifestyle. Based on body mass index (BMI) measurements, one fifth of adults over 50 were obese and more than two fifths were overweight. Higher proportion of women were obese than men, while more men than women were overweight. Age, level of education and smoking were significantly associated with overweight and obesity, regardless gender. Marital status was significantly associated with obesity, regardless gender and with overweight only in women. Breakfast consumption habit was significantly associated with obesity only in men. There was no significant association of overweight and obesity with the type of settlement, drinking alcohol and physical activity, regardless gender.

Acknowledgements

This work was supported by the World Bank, World Health Organization Regional Office for Europe (country office Serbia); Institute of Public Health of Serbia "Dr Milan Jovanović Batut"; Ministry of Education, Science and Technological Development, Serbia, through contract No. 145084 (2006-10).

On this occasion we would like to express our gratitude to the Ministry of Health of the Republic of Serbia which allowed the use of the data base of the project "Investigation of Population Health in Serbia, 2006", and therefore enabled realization of this study.

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Received on August 21, 2014.
Revised on August 31, 2015.
Accepted on September 3, 2015.
Online First June, 2016.

SHORT COMMUNICATIONS

UDC: 615.03:615.33]:616-022.7(497.1)
DOI: 10.2298/VSP150626146S

Relationship between outpatient antibiotic use and the prevalence of bacterial infections in Montenegro

Odnos vanbolničke upotrebe antibakterijskih lekova i prevalencije bakterijskih infekcija u Crnoj Gori

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Abstract

Background/Aim. The overuse of antibiotics unnecessarily exposes patients to risk of side effects, encourages reconsultation for similar problems and enhances antimicrobial resistance. The use of antibiotics in the year 2011 in Montenegro was high (39.05 Defined Daily Dose – DDD/1,000 inhabitants/day), but it was not considered in relation to the frequency of bacterial diseases. The aim of our study was to determine the degree of conformance between the amount of outpatient antibiotic consumption and the reported prevalence of outpatient bacterial infections in the Republic of Montenegro. **Methods.** Data on the use of antibacterial drugs was obtained from the Agency for Medicines and Medical Devices of Montenegro for the year 2012. The amount of antibiotics was calculated using the Anatomic Therapeutic Chemical (ATC) DDD methodology. Data on the prevalence of outpatient infective disease was obtained from the Health Statistical Yearbook 2012 of Montenegro and it was expressed *per* 1,000 inhabitants. **Results.** A total of 30.34 DDD/1,000 inhabitants/day of antibiotics in outpatients were prescribed in Montenegro in 2012, with penicillins being most frequently prescribed. Amoxicillin and amoxicillin with clavulanic acid were the most frequently used antibiotics. The prevalence of outpatient bacterial infections was 6,745 cases or 10.87/1,000. The most frequent infections were respiratory tract infections. Less than 50% of the prescribed amount of antibiotics were prescribed in accordance with national guidelines on treatment of bacterial infections. **Conclusion.** Use of antibiotics in Montenegro in 2012 was more than double than necessary according to prevalence of bacterial infections and average duration of treatment. The structure of antibiotics was not in full compliance with the national good practice guidelines, but it was in accordance with data on bacterial antibiotic resistance in outpatient practice. It is necessary to initiate measures to rationalize the use of antibiotics both in terms of quantity and in terms of the structure of the most used antibiotics.

Key words:
bacterial infection; anti-bacterial agents; outpatients; prevalence; montenegro.

Apstrakt

Uvod/Cilj. Prekomerna upotreba antibiotika izlaže bolesnike riziku od pojave neželjenih dejstava, uzrokuje ponovne posete lekaru i dovodi do pojave rezistencije bakterija na antibiotike. Upotreba antibiotika u Crnoj Gori u 2011. godini bila je visoka [39,05 definisanih dnevnih doza (DDD)/1 000 stanovnika/dan)], ali nije razmatrana u odnosu na učestalost vanbolničkih bakterijakih infekcija. Cilj ovog rada bio je da se ispita usklađenost upotrebe antibiotika i učestalosti vanbolničkih bakterijskih infekcija u Crnoj Gori. **Metode.** Podaci o upotrebi antibiotika dobijeni su od Agencije za lekove i medicinska sredstva Crne Gore. Upotreba je izračunata pomoću *Anatomic Therapeutic Chemical* (ATC)/DDD metodologije. Podaci o učestalosti vanbolničkih bakterijskih infekcija dobijeni su iz Zdravstvenog statističkog godišnjaka Crne Gore, a učestalost je izražena brojem slučajeva na 1 000 stanovnika. **Rezultati.** Vanbolnička upotreba antibiotika u Crnoj gori u 2012. godini iznosila je 30,34 DDD/1000 stanovnika/dan, a najčešće korišćeni bili su penicilini. Amoksicilin sam i u kombinaciji sa klavulanskom kiselinom bili su najčešće korišćeni antibiotici. Bakterijske infekcije bile su registrovane kod 6 745 bolesnika, odnosno kod 10,87 bolesnika/1 000 stanovnika. Najčešće zabeležene bile su respiratorne infekcije. Manje od 50% od upotrebljene količine antibiotika korišćeno je u skladu sa nacionalnim preporukama za lečenje bakterijskih in-

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fekcija. **Zaključak.** Vanbolnička upotreba antibiotika u Crnoj Gori u 2012. godini bila je više nego dvostruko veća od potrebne, ukoliko se u obzir uzme učestalost vanbolničkih bakterijskih infekcija i prosečna dužina lečenja. Struktura upotrebljenih antibiotika nije bila u potpunosti u skladu sa nacionalnim preporukama dobre kliničke prakse, ali je bila u skladu sa podacima o bakterijskoj rezistanciji u vanbolničkim uslovima. Potrebno je sprovesti mere sa ciljem racionalizacije upotrebe antibiotika u Crnoj Gori, kako u pogledu količine, tako i u pogledu izbora najčešće korišćenih antibiotika.

Ključne reči:
infekcija, bakterijska; antibiotici; bolesnici, vanbolničko lečenje; prevalencija; crna gora.

Introduction

According to current pharmacotherapeutic guidelines, antibiotics should be used for treatment of bacterial infections when clinical signs clearly indicate bacterial infection, or based on susceptibility testing. However, it often happens that antibiotics are used for treatment of viral infections, particularly in outpatient institutions which are less able to obtain antibiogram, and when self-medication is present in the community [1, 2].

Overuse, which is most common deviation in antibiotic use, unnecessarily exposes patients to risk of side effects, encourages reconsultation for similar problems and enhances antimicrobial resistance [3–5]. High use can significantly overload health care budget.

Agency for Medicines and Medical Devices of Montenegro cooperates with European Center for Disease Prevention Network (ESAC –NET). Data on antibiotic use in the year 2011 in Montenegro was published in The Lancet, where consumption of antibiotics in Montenegro of 39.05 Defined Daily Dose (DDD)/1,000 inhabitants/day occupied second place among 42 countries involved [6]. Although the authors concluded that the use was unjustifiably high, the consumption of antibiotics was not considered to the frequency of bacterial diseases, which could confirm or deny this statement.

The aim of our study was to determine the degree of conformance between the amount of outpatient consumption of antibiotics and the reported prevalence of outpatient bacterial infections in the Republic of Montenegro, and, based on this, to estimate if the consumption of antibiotics is in agreement with the prevalence of infective diseases in Montenegro.

Methods

The study was performed in Montenegro, a country with 620,029 inhabitants, for the year 2012.

Data on the use of antibacterial drugs was obtained from the Agency for Medicines and Medical Devices of Montenegro for the year 2012. They referred to total consumption of antibiotics – those obtained by prescription and those purchased in retail pharmacies. The amount of antibiotics was calculated using the Anatomic Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology [7].

Data on the prevalence of outpatient infective disease was obtained from the Health Statistical Yearbook 2012 of Montenegro [8]. The prevalence was expressed *per* 1,000 inhabitants. Data on the use of antibiotics and the prevalence of reported outpatient bacterial diseases in Montenegro was compared in order to get conformance between the number of bacterial infections and the amount of prescribed antibiotics.

Results

A total of 30.34 DDD/1,000 inhabitants/day of antibiotics in outpatients were prescribed in Montenegro in 2012, with penicillins being most frequently prescribed. Macrolides occupied the second place, with cephalosporins holding the third position (Table 1).

Amoxicillin and amoxicillin with clavulanic acid were the most frequently used antibiotics, followed by azithromycin, ciprofloxacine and cefalexin. Pipemidic acid was also among the top 10 antibiotics (Table 2).

The prevalence of outpatient infective diseases reported to the Institut of Public Health for the year 2012 was 8,679 cases, or 13.99 cases/1,000 inhabitans (1.4%) (Table 3). The most frequent infections were respiratory tract infections, intestinal infections and urinary tract infections.

When total amount of outpatient use of antibacterial drugs was considered in relation to the prevalence of outpatient bacterial infections in Montenegro in 2012, it becomes obvious that less than 50% of the prescribed amount of antibiotics was prescribed in accordance with national guidelines on treatment of bacterial infections (13.86 out of 30.34 DDD/1,000 inhabitants/day).

Disscusion

The use of antibiotics is now in the spotlight for several reasons: it has been significantly increased during recent decades, they were often administered for the treatment of a viral infection, and unclear cases of fever [1, 9]. This resulted in an increase in pathogen resistance, with consequent narrowing of choice of antibiotics and often the lack of therapeutic success [10, 11]. That is why an international network such as ESAC was created, which aimed to monitor and compare the use of antibiotics among the countries, and to start with educational or administrative measures in case of excessive use of antibiotics [12–14]. Another option to assess the appropriateness of antibiotic prescribing is a comparison with morbidity statistics.

Data on the prevalence of outpatient bacterial infections published by the Institute of Public Health of Montenegro indicate that bacterial infections occurred in 722 persons *per* 1,000 inhabitants *per* year, or 1.98 persons *per* 1,000 inhabitants *per* day [8]. Assuming that all bacterial infections were treated with antibiotics, and that the therapy lasted 7 days, the amount of antibiotics used should be 13.86 DDD/1,000 inhabitants/day. The use of antibiotics in our study was 30.34 DDD/1,000 inhabitants *per* day, which means that the amount of antibiotics used was more than two times higher than it is optimal. Although the number of bacterial infections in

Table 1

Total amount of antibacterial drugs for systemic use Anatomic Therapeutic Chemical (ATC) group J01 at ATC level 3 and/or 4 in Montenegro in 2012 expressed as Daily Defined Dose (DDD) 1,000 inhabitants/day

ATC code	Antibiotics	DDD/1,000 inhab/day
J01A	Tetracyclines	1.13
J01C	Beta lactam antibiotics – penicillins	15.08
J01CA	Broad-spectrum penicillins	9.49
J01CE	Narrow-spectrum penicillins	1.47
J01CR	Combination of penicillins and enzyme inhibitors	4.12
J01D	Other beta-lactam antibacterials	3.60
J01DB	First-generation cephalosporins	1.93
J01DC	Second-generation cephalosporins	0.19
J01DD	Third-generation cephalosporins	1.48
J01E	Sulfonamides and trimethoprim	1.02
J01F	Macrolides, lincosamides, and streptogramins	4.62
J01FA	Macrolides	4.60
J01G	Aminoglycosides	0.66
J01GB	Other aminoglycosides	0.66
J01M	Quinolones	3.66
J01MA	Fluorinated quinolones	2.38
J01MB	Other quinolone derivatives	1.28
J01X	Imidazole derivatives	0.58
Total		30.34

Table 2

The 10 most often used antibiotics in Montenegro in 2012

ATC code	Antibiotic	DDD/1,000 inhab/day
J01CA04	Amoxicillin	8.75
J01CR02	Amoxicillin and clavulanic acid	4.12
J01FA10	Azithromycin	2.76
J01MA	Ciprofloxacine	2.29
J01DB01	Cephalexin	1.93
J01FA01	Erythromycin	1.82
J01DD08	Cefixime	1.32
J01MB04	Pipemidic acid	1.28
J01EE01	Cotrimoxazole	1.02
J01A	Doxicycline	0.94

ATC – Anatomic Therapeutic Chemical; DDD – defined daily dose.

Table 3

Prevalence of outpatient bacterial infections in Montenegro in 2012

Diagnosis	No	No of cases / 1,000 inhabitants / year
Respiratory infectious diseases	6,381	10.29
Intestinal infectious diseases	1,170	1.89
Parasitic infectious diseases	942	1.52
Anthropozoonic infectious diseases	33	0.05
Sexually transmitted infectious diseases	35	0.06
Transmissive infectious diseases	14	0.02
Other infectious diseases	74	0.12
Carriers	28	0.05
Total number of bacterial infections	6,745	10.87
Total	8,679	13.99
No/1,000 inhabitants/day		1.98

No – number.

Montenegro population was probably higher than reported, as not all of the patients visited doctors for the treatment, the obtained ratio of antibiotic use/prevalence of infection shows a disproportion between the amount of antibiotics and the number of people with bacterial infections. Even more, according to national pharmacotheraputic guidelines, many bacterial infections should not be routinely treated with antibiotics, which makes the results even worse [15]. This practice of high use of antibiotic was common in the former Yugoslavia, which has traditionally been at the top among the European countries according to the use of antibiotics [16]. Data from Serbia show that the use of antibiotics remains

high [6]. Available studies from southern regions of Serbia report an increase in outpatient use of antibiotics and a pretty high amount of antibiotics used (22.83 DDD/1,000 inhabitants/day in 2005 to 25.96 DDD/1,000 inhabitants/day in 2007) [17]. Only in certain cases, where the administrative measures were taken, their use in some parts of Serbia was significantly reduced [2, 18]. According to some sources consumption of antibiotic even higher than in Montenegro was detected in Croatia with 33.28 DDD/1,000 inhabitants/day in 2012. However consumption in Croatia shows decreasing trend (37.38 DDD/1,000 inhabitants/day in 2008) [19]. To the contrary some papers report consumption of antibiotics in Croatia of approximately 24 DDD/1,000 inhabitants/day in 2011, and approximately 20 DDD/1,000 inhabitants/day in Bosnia and Herzegovina [6].

Besides the tradition, one of the reasons for high consumption of these drugs is the possibility to obtain antibiotics without a prescription, as it is the case in Greece or Turkey, and, until a few years ago, in Serbia [9, 20]. In Montenegro during 2012 there was also a possibility to buy antibiotics without a prescription. Studies carried out in Montenegro and in Serbia have showed that more than a half of the total antibiotics used in outpatient practice was bought without a prescription [2, 10]. Restriction of the free sale of antibiotics through administrative measures is one of the most effective measures for the reduction of antibacterial drugs use.

The most commonly used antibiotics in outpatient practice in Montenegro in 2012 were amoxicillin and amoxicillin with clavulanic acid. Similar results are available from studies in Croatia as well [19]. According to the national guidelines of good clinical practice, issued by Ministry of Health of Montenegro, semisynthetic penicillins and/or macrolides are the drugs of first choice in the treatment of respiratory infections, which were most frequently reported [15]. When resistance to amoxicillin is high, amoxicillin/clavulanic acid is recommended instead. According to studies performed in Montenegro in 2009, the most frequent isolate from the throat of outpatients (beta haemolitic streptococcus) was sensitive to amoxicillin. The second isolate, *Staphylococcus aureus* was completely resistant to amoxicllin. The most frequent isolate from urinary tract infections, *Escherichia coli*, was resistant to amoxicillin, and sensitive to amoxicilin clavulanic acid [10]. This fact could explain the empirically more frequent use of amoxicillin clavulanic acid, despite the current national recommendations [21, 22].

Conclusion

This study estimated an association of the prevalence of outpatient bacterial infections among the population of Montenegro with the use of antibiotics in outpatients. We found that the use of antibiotics is more than twice as needed when taking into account the number of people with bacterial infections and the average duration of treatment of 7 days. The structure of antibiotics is not in full compliance with the national good practice guidelines, but it is in accordance with the situation of antibiotic resistance in outpatient practice. It is necessary to initiate measures to rationalize the use of antibiotics both in terms of quantity and in terms of the structure of the most used antibiotics.

Acknowledgements

The study was financially supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant number III 41012).

Conflict of interest

The authors of this manuscript have no conflicts of interest to declare.

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Received on June 26, 2015.
Revised on August 26, 2015.
Accepted on September 1, 2015.
Online First June, 2016.

SHORT COMMUNICATON

UDC: 617.3-089::617.581-089.168
DOI: 10.2298/VSP150514145M

First experiences with the Fitmore® hip stem – Early results of the 16-month monitoring

Prvo iskustvo sa Fitmore® stemom kuka – rezultati 16-mesečnog posmatranja

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Abstract

Background/Aim. Fitmore® hip stem belongs to the group of short stem prostheses with the metaphysar stabilization, with its shape and form that protects the bone mass in the greater trochanter region and the distal part of the femur. The aim of this paper was to present the early postoperative results in patients with implanted Fitmore® hip stem and point out some of the advantages. **Methods.** A series of 10 patients with implanted Fitmore® hip stem, was included in this study. The average age of the patients was 54.5 (48–65) years. There were 5 women and 5 men. The total monitoring time was 16 months. To rate the condition of the hip joint we used The Western Ontario and Mc Master Universities Arthritis Index (WOMAC) score. We also monitored the degree of hip pain, hip flexion, heterotopic ossification and indentation in the stem of the prosthesis. **Results.** After 12 months of monitoring 9 (90%) of the patients had no pain in the thigh region, and only 1 (10%) experienced mild pain. The hip flexion rose from the average 89° to postoperative 114°. WOMAC score rose as well, from 49 to 94 average points. Indentation in the stem was registered 3 months after the operation in 2 (20%) of the patients – in one of the patients the indentation was 3 mm and in the other patient 5 mm. After the 16-month monitoring, the results were excellent. The monitoring period was short though it should be continued and the results should be presented after 5 and then after 10 years. **Conclusion.** Early results of the implantation Fitmore stem showed good bone ingrowth with excellent functional result.

Key words:
arthroplasty, replacement, hip; orthopedic procedures; postoperative period; recovery of function.

Apstrakt

Uvod/Cilj. Fitmore® *hip stem* pripada grupi proteza kratkog stema sa metafiznom stabilizacijom, a svojim oblikom i formom štedi koštanu masu u regionu velikog trohantera i u distalnom delu femura. Cilj rada bio je da se prikažu rani operativni rezultati kod bolesnika sa ugrađenim Fitmore® stemom kuka i da se ukaže na neke prednosti. **Metode.** Prikazana je serija od 10 bolesnika kojima je ugrađen Fitmore® stem kuka. Prosečna starost bolesnika, pet žena i pet muškaraca, bila je 54.5 (48–65) godina. Ukupno vreme praćenja iznosilo je 16 meseci. Za ocenu stanja zgloba kuka koristili smo *The Western Outario* and *Mc Master Universities Arthritis Index* (WOMAC) skor. Pratili smo i stanje bola u butini, fleksiju kuka, heterotopne osifikacije i slegnuće stema proteze. **Rezultati.** Posle 12 meseci praćenja, 9 (90%) bolesnika nije imalo bolove u butini, a samo jedan (10%) imao je slabe bolove. Fleksija u kuku porasla je od 89° u proseku, na 114° posle operacije. WOMAC skor takođe je porastao, od 49 na 94 poena u proseku. Nalegnuće stema registrovano je posle tri meseca od operacije i to kod dva (20%) bolesnika: kod jednog tri, a kod drugog 5 mm. Posle praćenja od 16 meseci rezultati su bili odlični. Period praćenja bio je kratak i trebalo bi ga nastaviti i prikazati rezultate posle 5 i 10 godina. **Zaključak.** Rani rezultati primene Fitmore® stema kuka pokazuju dobro urastanje stema uz odličan funkcionalni rezultat.

Ključne reči:
artroplastika kuka; ortopedske procedure; postoperativni period; funkcija, povratak.

Introduction

Osteoarthrosis is a very common chronic disease. It is detected in 60% of the population aged over 65, and hip osteoarthrosis is detected in 5% of the population aged over 55 [1]. Etiology of coxarthrosis is complex and depends on multiple factors, all of these factors, individually or combined, can cause a degenerative hip disease.

Replacement of the natural hip joint with an artificial one restores the function of the diseased joint and establishes a painless and satisfactory locomotion. There are a number of cemented and uncemented prosthetic models used in

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everyday practice. One of the models is Fitmore hip stem by Zimmer.

This particular system has a short uncemented stem which with its shape and curve restores the anatomy of the proximal part of the femur and allows adjustment of the prosthetic offset, *ie* it offers the possibility of adjusting the distance between the acetabulum and body of the stem. The transection of the stem has a trapezoid form, which allows the primary rotational stability. It belongs to the group of short stem prostheses with metaphysar stabilization and therefore it spares the bone mass in the greater trochanter region and the distal part of the femur [2]. With its curve, the stem of this prosthesis protects the lateral cortex of the femur, and directs its contact and the transmission of the mechanical forces and loads in the hip, towards the small trochanter. The greatest part of body weight is transferred through the medial part of the prosthesis towards the small trochanter, to the medial part of the resected femoral neck which has the shape of the letter U – this is *calcar femoris*. The surface of the cortical bone part of the resected femoral neck in the region of the small trochanter, which is used for the transfer of weight, is about 1.29 cm [2, 3].

The short and curved prosthetic stem spares the distal femur part, this maladjustment of the proximal and distal part is avoided, which is one of the reasons for the loosening of the long prosthetic stem. Additionally, it spares the femur canal for the revision stem; it reduces the intraoperative bleeding and spares the soft tissue due to the reduced surgical exposition [4]. Fitmore® prosthesis has a narrower indication area, *ie* it is used in younger patients, vital and good physical shape with a small degree of osteoporosis.

The aim of this study was to present the early postoperative results in patients with the implanted Fitmor® hip stem and point out some of its advantages.

Methods

In the period from December 25, 2013 to February 15, 2014 in the Clinic for Orthopedic Surgery the Niš, Serbia, ten hip endoprostheses of the Fitmore stem type were implanted.

Total hip arthroplasty was performed in 5 female and 5 male patients. The average age was 54.5 years (57.4 in male and 50.4 in female patients). The average weight was 81 kg in male and 69 kg in female patients.

The patients were monitored after 3, 6, 12 and 16 months following the operation.

The main diagnosis was osteoartrosis – 7 (70%) patients, followed by avascular necrosis – 2 (20%) patients and rheumatoid arthritis – 1 (10%) patient.

We used the intermediate calcar radius stem in 8 patients, and in the remaining 2 a larger calcar radius stem A family (Figure 1).

To rate the state of the hip joint, prior to and after the operation, we used WOMAC score [5].

It is critical with the use of the Fitmore® stem to use radiological templating to determine the appropriate stem family preoperatively, as medial metaphyseal/diaphyseal contact cannot be visualized intraoperatively. Templating is needed to assess the center of femoral head, leg length, offset, level of femoral neck osteotomy and stem size. The neck osteotomy must be at an angle of 50° of the long axis of the shaft and also preservation of 5–10 mm of the lateral neck cortex.

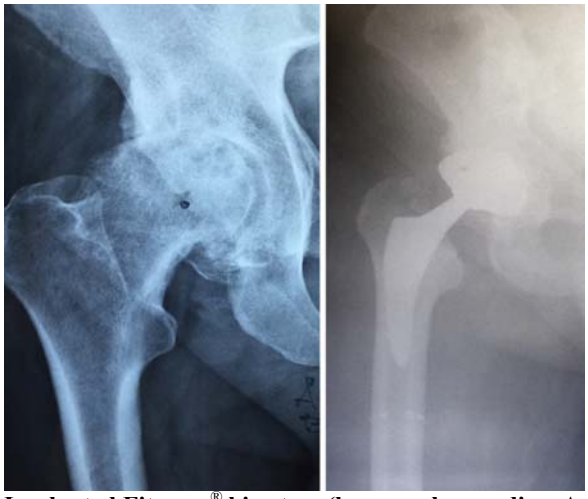

Fig. 1 – Implanted Fitmore® hip stem (larger calcar radius, A family).

Subsidence was defined as vertical stem movement of more than 5 mm according to Callaghan et al. [6].

Heterotopic ossification was classified according to Brooker et al. [7].

Results

Three months after the operation, in 5 (50%) patients thigh pain disappeared, and in 9 (90%) after 12 months. Only one (10%) patient had mild pain 12 months after the operation.

The range of motion (the degree of flexion) increased significantly from 79° (40°–120°) preoperatively to 114° (95°–150°) at the time of the last monitoring ($p < 0.001$).

The mean duration of the surgical procedure was 75 (38–125) minutes and the mean length of hospitalization was 9 (5–15) days.

Radiological results after 16 months of monitoring were in 2 (20%) of the patients hipertrophy of the femoral cortex at the height of the prosthetic stem was registered, but without clinical symptomatology. In 1 (10%) of the patient heterotrophic ossification gradus 1 according to Brooker et al. [7] was registered, in 2 (20%) of the patients there was an indentation in the stem up to 5 mm, registered 3 months after the operation.

Discussion

Total hip arthroplasty is one of the most successful orthopedic procedures. The use of short stems is growing. With short stems good and permanent fixation is achieved and clinical results are good.

Joint Implant Surgery and Research Foundation (USA) has formed a classification system for the short stem uncemented prosthesis: head stabilized, neck stabilized, metaphyseal stabilized and conventional (metaphyseal/diaphyseal) stabilized [8]. Fitmore® hip stem by Zimmer that we used in our patients belongs to the group of metaphyseal stabilized, and its characteristics are the following: it spares the bone mass in the area of greater trochanter and diaphysis of the femur, crossection is trapezoid and provides excellent stability, it has different curves in order to renovate the hip joint anatomy and achieve a good offset of the femoral neck [4, 8, 9].

Radiological templating is mandatory to determine the position of the prosthesis, its size, offset center of the rotation and leg length [10].

A long prosthetic stem can be implanted in the varus position. Berend et al. [11], Khalily and Lester [12] mention the varus of prosthetic stem from 4° to 8° as well as the fact that Fitmore® stem has a small potential to take the varus position. Additionally, sometimes a fracture of the long stem can occur.

Loosening of the stem did not occur in our series, perhaps due to the short monitoring period, although other authors do not list it either. This phenomenon occurs in prostheses with long stem due to different factors [13].

The stem of the Fitmore® prosthesis can cause remodeling of periprosthetic bone structure. Pepke et al. [14] has found that both Fitmore® and long stem prostheses have proximal stability. Fitmore® stem also has rotational stability, so its rigidity is higher, which is the reason why the remodeling process of the bone is more prominent in this type of prostheses. Guske [2] as well, in his work reports cortical hypertrophy in 29% of the patients in the series of 100 patients. In our series, this phenomenon was present in 2 (20%) of the patients.

Indentation in the Fitmore® stem up to 5 mm was present three months after the operation. We had 2 (20%) patients – in one the indentation in the stem was 3 mm, and in the other 5 mm. In the series of 100 patients, Guske [2] reported indentation in 34% of the patients.

Conclusion

The early results of Fitmore® stem implantation showed good bone ingrowth with excellent functional result in our patients. The number of published series of patients with implanted Fitmore® hip stem is small, so as in our study of the early results of the implantation of Fitmore® stem in 10 patients. Further monitoring of the patients and reporting the results 5 and 10 years after the operation are needed. Monitoring in our group of patients was 16 months.

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Received on May 14, 2015.
Revised on September 7, 2015.
Accepted on October 8, 2015.
Online First June, 2016.

GENERAL REVIEW

UDC: 616.61-053.2-08-06::616-008.9]::616.1
DOI: 10.2298/VSP150418144S

Risk factors for cardiovascular disease in children on chronic hemodialysis – Uremia-related (non-traditional) risk factors, part II

Faktori rizika od nastanka kardiovaskularnih bolesti kod dece na hroničnoj hemodijalizi – Uremijski (netradicionalni) faktori rizika, deo II

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Key words:
renal insufficiency, chronic; cardiovascular diseases; risk factors; renal dialysis; child.

Ključne reči:
bubreg, hronična insuficijencija; kardiovaskularne bolesti; faktori rizika; hemodijaliza; deca.

Introduction

As among adults with chronic kidney disease, cardiovascular disease has recently emerged as a significant source of morbidity and mortality even among children with chronic kidney disease. Both traditional and non-traditional cardiovascular risk factors are present among children with chronic kidney disease, and many of these risk factors are closely intertwined with the development and progression of chronic kidney disease. Although few pediatric data are available, management of children with chronic kidney disease, as well as management of adults, should probably include treatment of these risk factors to avoid the development of early cardiovascular disease. In addition to the traditional risk factors, there are a lot of non-traditional or uremia-related risk factors. Non-traditional risk factors are marked as uremic toxins and sometimes it is difficult to separate them from the metabolic disturbances induced by chronic renal failure.

Anemia

Anemia is the second most common non-traditional risk factor for cardiovascular disease (CVD) in children and adolescents with chronic kidney disease (CKD). Unlike the other uremic risk factors, anemia occurs relatively early in CKD due to chronic renal failure [1, 2]. The etiology of anemia is multifactorial: shortened lifespan of erythrocytes, chronic blood loss and inadequate erythropoiesis. It was found that erythrocytes in dialysis patients are sensitive to mechanical, osmotic and oxidative factors; therefore the reason for shortening of the lifespan of red cells should be sought in the corpuscular factors. Also, these patients are prone to chronic blood loss, usually during the act of dialysis; and also because of occult bleeding from the gastrointestinal (GI) tract, as well as due to taking of blood for various laboratory analyses. The most important cause of anemia in patients with CKD is the lack of erythropoietin (EPO). Also the following contributes to the onset of anemia: decreased resorption of iron from the GI tract, lack or loss of folate and vitamin B12, as well as the development of fibrosis of the bone marrow due to the secondary hyperparathyroidism which compromises erythropoiesis [3].

Despite of the widespread use of recombinant erythropoietin as a stimulating agent, recent data from the Chronic Kidney Disease in Children (CkiD) Study [2] show that when the glomerular filtration is reduced below the value of 43 mL/min/1.73 m^2, every subsequent drop of 5 mL/min/1.73 m^2 leads to a decrease in the concentration of hemoglobin by 0.3 g/dL [2].

According to the CKiD study [2], the prevalence of anemia in CKD patients (stages 2–4) is 38–48%, and in patients on HD 40–67% (Table 1). Until recently, the occurrence of anemia after kidney transplant was not given great importance; however, recent studies have shown that due to immunosuppressive therapy administered after the transplantation, the prevalence of anemia is in the range 61–86% [4].

Malnutrition and inflammation

As of recently, oxidative stress, chronic inflammation and malnutrition are defined as new risk factors in adult patients on hemodialysis HD. High levels of the same

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Table 1

Nontraditional risk factors for the cardiovascular disease (CVD) in children with chronic kidney disease (CKD)

Uremic patients risk factors	CKD (%)	HD (%)	Transplant (%)
Anemia	38–48	40–67	32–64
Raised Ca × P	30–40	53–85	
Hyperparathyroidism	30–45	50–60	
C-reactive protein		76	16
Hyperhomocysteinemia		87–92	25–98
Hyperalbuminemia		76	16

Data from the Chronic Kidney Disease in Children (CkiD) study [2]; HD – hemodialysis.

inflammatory markers have been identified in children undergoing treatment with hemodialysis (HD) [5, 6]. There is strong evidence that confirms that inflammation is a leading risk factor for CKD in children, although Goldstein et al. [7] showed a reduction of proinflammatory cytokines in children with end stage renal insufficiency, whose therapy also contains aspirin. The quality of water for dialysis, biocompatibility of the dialysis membrane and the vascular access are the key factors that can trigger the inflammatory cascade and which are maintaining the low grade chronic microinflammation. Panichi et al. [8] have discovered that C-reactive protein (CRP) levels are high in 25% of pediatric patients with CKD and in 50% of patients on HD. Patients on HD, whose concentration of CRP is > 15.8 mg/L have a 2.4 times bigger risk of a cardiovascular death compared to patients whose CRP is < 3.3 mg/L. Malnutrition is an important problem in children with terminal renal insufficiency. Hypoalbuminemia is an important marker of malnutrition. Failure to correct the hypoalbuminemia through the diet, suggests that other factors are responsible for the reduced concentration of albumin in these patients. It is certain that systemic inflammation is associated with malnutrition. Moreover, the increased CRP along with the decreased levels of albumin has been recognized as a powerful predictor of mortality in patients on dialysis. A significant inverse correlation between the proteins of the acute phase of inflammation (CRP and ferritin) and markers of malnutrition (albumin) has been shown. Thus, inflammation is closely associated with malnutrition in children with terminal renal failure. In patients on hemodialysis, malnutrition occurs due to the loss of appetite, lack of nutrition, increased loss of nutrients during the HD, the presence of uremic toxins, increased metabolism, the presence of comorbidities (diabetes mellitus, infection, sepsis, congestive heart failure), increase of oxidative stress and the use of a biocompatible dialysis membrane [9–11].

Natriuretic peptides

Natriuretic peptides are a well-described family of hormones, which play the main role in the homeostasis of salt and body volume. The synthesis and release of these natriuretic peptides are generally stimulated by an increase of the extracellular fluid volume, which is observed through the atrial and ventricular stretch receptors. Their main role is to induce the natriuresis by effecting the renal hemodynamics and tubular function. This role of induction of the natriuresisis is limited in patients with CKD and end stage renal disease (ESRD). Brain-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP are predominantly excreted in the kidneys and have a significant potential for clinical use in this population [9, 10].

There is a small number of publications on the values of natriuretic peptide in children with CKD. Rinat et al. [12] followed the BNP and NT-proBNP in 75 children with CKD (24 of which were treated with HD) and correlation with echocardiographic parameters. In their conclusion, they have published that the levels of BNP and NT-proBNP are significantly elevated in patients with terminal renal failure who are treated with HD. It was even observed that the value of BNP and NT-proBNP is increased in asymptomatic patients in the early stages of CKD. Despite the fact that the levels of these peptides are strongly dependent on the glomerular filtration rate, hemoglobin levels, left ventricular hypertrophy, diastolic dysfunction and diastolic blood pressure, the authors believe that monitoring of natriuretic peptides can help in the assessment of asymptomatic cardiac damage in children with CKD [9, 10].

Homocysteine

Mild to moderate hyperhomocysteinemia is observed in approximately 60–70% of patients with CKD and in more than 90% of patients treated regularly with hemodialysis [2]. Renal function is an important determinant of the concentration of homocysteine in the plasma, therefore through all stages of CKD, between the levels of homocysteine and glomerular filtration, an inverse relation is maintained which is independent from the primary renal disease. The etiology of hyperhomocysteinemia in CKD is unclear. Since there is no significant renal excretion of homocysteine, it is considered that the cause of hyperhomocysteinemia is the deterioration extrarenal metabolism of homocysteine [13]. It is considered that hyperhomocysteinemia occurs as a consequence of the reduced activity of key enzymes involved in the metabolism of homocysteine (methionine synthase, N5, N10-methyl tetrahydrofolate reductase, cistation β-synthase and betaine-homocysteine methyltransferase). Hyperhomocysteinemia blocks the degradation of asymmetric dimethylarginine (ADMA), it also contributes to the accumulation of ADMA in the endothelium of blood vessels and it activates the onset of atherosclerosis. According to the results of observational studies conducted in this group of patients, the high level of homocysteine is a risk factor for the cardiovascular mortality and vascular disease. Pathological mechanisms by which

hyperhomocysteinemia promotes atherosclerosis are still unclear. Experimental evidence supports a number of options, including the damage to endothelial cells, increased oxidation of LDL, increased platelet aggregation mediated by thromboxane, inhibition of protein C anticoagulant and stimulated smooth muscle cell proliferation. In this way, hyperhomocysteinemia potentiates the endothelial dysfunction and oxidative stress, it manifests the prothrombotic effects and impairs the coagulation status. Although it is proven that the therapeutic use of folic acid and the vitamin B reduce plasma homocysteine levels in this population, so far it is unknown whether it also reduces the mortality [9].

Asymmetric dimethylarginine

A high concentration of asymmetric dimethylarginine (ADMA) is a risk factor for the onset of cardiovascular complications in children on hemodialysis. High concentrations of ADMA (> 2.22/mol/L) are caused by the reduced activity of the enzyme of dimethylarginine dimethylaminohydrolase (DDAH). Microinflammation, diabetes mellitus, hyperhomocysteinemia and oxidative stress significantly reduce the activity of this enzyme and increase the concentration of ADMA. ADMA blocks the production of nitrogen oxide (NO) in the endothelial cells and contributes to the onset of the atherosclerosis. The absence of biologically active NO is associated with leukocyte-platelet aggregate adhesion. These mechanisms contribute to the onset of acute atherothrombotic events which increases the rate of cardiovascular mortality [13, 9].

Oxidative stress and adiponectin

Increase of oxidative stress is a risk factor for the onset of atherosclerotic cardiovascular complications in patients on hemodialysis. Oxidative stress and elevated concentrations of oxy-LDL block the activity of DDAH and reduce the degradation of ADMA. As it was said before, accumulation of ADMA disrupts functioning of the L-arginine/NO system in endothelial cells, which leads to the reduced levels of NO and the development of atherosclerosis. The use of L-arginine, vitamin E and N-acetylcysteine significantly reduces the level of oxidative stress and it reduces the risk of cardiovascular complications in patients on HD [11, 14].

Adiponectin is a product of the fat tissue which is involved in the lipid metabolism and the regulation of the glucose metabolism. Low levels of adiponectin are associated with the known cardiovascular (CV) risk factors such as dyslipidemia, insulin resistance and chronic inflammation. Some studies suggest that the elevated levels of adiponectin have a protective effect on the onset of CVD [15, 16]. Several studies on children and adults also show a link between the low levels of adiponectin, hypertension and left ventricular hypertrophy (LVH) [16, 17]. In chronic kidney disease, however, despite the increased risk for CVD, the levels of adiponectin were actually higher than physiological. The manner in which this increased level of circulating adiponectin is correlated (interacts) with the cardiovascular risk factors is not clear. Published studies estimate that the relationship between adiponectin and CV risk factors in patients with CKD show inconsistent and sometimes contradictory results. The aforementioned CKiD study [16] monitored the levels of adiponectin in serum as well as the relationship of adiponectin and other anti-inflammatory cytokines which are involved in the regulation of the lipid and glucose metabolism. This is the first study that by the use of the high resolution (HR) gel filtration test, recently discovered, allowing us to analyze the adiponectin in the form of all three complexes. The study shows that the high molecular weight (HMW) complex accounts for about half of the total adiponectin. These studies, along with the studies on adult patients confirm that serum levels of total adiponectin are increased in children with mild to moderate CKD, compared with previously published normal values in healthy children, and it is inversely correlated with the renal function. This increase is accompanied by the elevation of HMW and reduction of the high molecular weight (LMW) complex in the circulation, while the trimmer part remained unchanged. Adiponectin can also be found in urine and its levels are inversely related to the glomerular filtration rate (GFR). The mechanism of these changes in fractions of adiponectin could be caused by the relatively low clearance for HMW oligomers compared to the LMW form. Recent animal studies featuring the fluorescently-labeled recombinant adiponectin indicate that adiponectin is primarily metabolized in the liver, but also through the kidneys. What is the role of the liver in comparison to the kidney in the detection of adiponectin complexes in patients with reduced renal function is not known. The fact remains that the level of adiponectin is significantly decreased after kidney transplantation [15].

Disorders of calcium and phosphorus metabolism and hyperparathyroidism

Disorder of calcium (Ca) and phosphorus (P) metabolism is specific for patients at chronic hemodialysis and presents the most important cause for the onset of the cardiac and vascular diseases in their case. Hyperparathyroidism affects 30–45% of children with CKD in phases 2–4 and almost 60% of children on hemodialysis [18–20]. Among the Turkish children with chronic renal insufficiency, almost 30% have increased levels of calcium-phosphorus products, while 40% of them have the increased levels of the parathyroid hormone [18]. The relationship between the disturbances of the mineral metabolism and the structural vascular changes in children with CKD has been confirmed, and documented in many papers [2, 15, 19]. Although administration of vitamin D supplements in terminal renal insufficiency is the basic therapy for the control of secondary hyperparathyroidism, there is evidence that vitamin D has a direct effect on the deposition of calcium in vascular smooth muscle cells [20, 21].

Structural and functional changes in the left ventricle

Long-term maintenance of the increased pressure and fluid, combined with other risk factors (anemia and hyperparathyroidism) in children on HD may lead to structu-

ral changes in the myocardium, such as accumulation of collagen, fibrosis and calcification [22].

Myocardial fibrosis leads to the decreased compliance of the left ventricle. The pathogenesis of myocardial fibrosis includes: angiotensin II, chronically increased parathyroid hormone, increased sympathetic activity, disturbance of the metabolism of phosphorus, a high level of Ca × P product, chronic inflammation, anemia, and other CV risk factors [15, 5].

In children at the stage 2–4 of CKD, the prevalence of LVH is 20–30%, while in patients on HD, the prevalence is 60–85%. Data of the European Dialysis and Transplant Association (ERA-EDTA) [23] shows that in 29% of children on peritoneal dialysis and in 59% of children on hemodialysis has LVH that is proven by echocardiography. In our study the LVH was 60% [24]. Children on HD usually have the eccentric (asymmetric) form of left ventricular hypertrophy and the normal relation between left ventricular mass/left ventricular volume (LVM / LVV) [25, 26].

Unlike adults with CKD, whose early heart failure is associated with systolic dysfunction, in children the systolic function is usually preserved longer, which we have confirmed in our results [26].

In children on HD the diastolic dysfunction precedes the systolic cardiac dysfunction. The prevalence of the diastolic dysfunction is increased in patients who are on chronic HD [2, 22]. One of the reasons for the increased prevalence is the emergence of new Doppler techniques, which allow detection of the diastolic dysfunction at an early stage. Tissue Doppler (TDI) in combination with a conventional (PW) Doppler can provide the additional information about the pressure of left ventricular filling (E/Em) in children on HD, which can facilitate risk stratification and making of the diagnosis [22, 27, 28].

Conclusion

Early recognition of risk factors and treatment of patients with asymptomatic cardiovascular changes is the key for the reduction of the mortality and morbidity in dialysis patients with the developed cardiovascular disease during childhood. By influencing risk factors, including aggressive monitoring and control of blood pressure, dyslipidemia, metabolism of Ca and P, anemia, malnutrition, chronic inflammation and other, it is possible to significantly postpone and improve the cardiovascular outcome of these patients.

Individual assessment of the condition of the cardiovascular system in hemodialysis patients can significantly postpone and improve the cardiovascular outcome and bring about the improvement of the living condition of each patient individually.

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Received on April 18, 2015.
Accepted on July 30, 2015.
Online First June, 2016.

PRACTICAL ADVICE FOR PHYSICIANS

UDC: 616.21-06:617.7
DOI: 10.2298/VSP141118141J

Silent sinus syndrome – one more reason for an ophthalmologist to have a rhinologist as a good friend

Sindrom tihog sinusa – još jedan razlog za oftalmologa da ima rinologa kao dobrog prijatelja

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Key words:
maxillary sinus; syndrome; enophthalmos; diagnosis; ophthalmologic surgical procedures; otorhinolaryngologic surgical procedures; treatment outcome.

Ključne reči:
maksilarni sinus; sindrom; enoftalmus; dijagnoza; hirurgija, oftalmološka, procedure; hirurgija, otorinolaringološka, procedure; lečenje, ishod.

Introduction

Silent sinus syndrome (SSS) is a rare condition involving the maxillary sinus, characterized by unilateral collapse of the maxillary sinus and orbital floor, associated with negative antral pressure in the absence of sinus symptoms [1, 2]. It is also known as imploding antrum syndrome and typical radiological findings are ipsilateral depression of the orbital floor and opacification of a collapsed maxillary sinus [1, 2]. There has been some more than 105 cases of SSS published in English literature so far (1). The largest case series with 22 patients was published by Kass et al. [3] in 1997.

SSS is characterized by spontaneous and progressive enophthalmos ("sunken" eye-eye recession into globe) and hypoglobus (globe displaced downward; a drop in the pupillary level), so it is common that these patients first present to ophthalmologist [1, 2, 4]. Its development is gradual and progressive, so after a few months up to a few years may become symptomatic [1]. Since patients present with ophthalmological complains, without any nasal or sinus symptoms, with painless course and slow development, the term "silent sinus" was introduced [5].

The first report of this entity was in 1964 in a paper written by Montgomery [6]. His report was about patients who had diplopia and enophthalmos associated with collapse of the maxillary sinus. Wilkins and Kulwin [7], in their paper published in 1981, emphasized that there was no orbital trauma in patients as a cause of the clinical simptoms and signs, although up till then it was known it happens only as a consequence of orbital trauma. Soparkar et al. [5], in their paper published in 1994, introduced the term silent sinus syndrome. They described a large group of 14 patients with spontaneous, unilateral enophthalmos and hypoglobus associated with "asymptomatic, bone thinning, maxillary sinus disease" [seen on computed tomography (CT) scans].

Imploding antrum syndrome can be primary or secondary. Primary or spontaneous (SSS) is idiopathic, whereas secondary may arise from mid-face trauma (including surgery), rhinosurgery, chronic rhinosinusitis and has also been reported in less than 1% of patients after orbital decompression in Graves ophthalmopathy (thyroid eye disease) [1, 5, 8, 9].

SSS most commonly presents unilaterally, although there are reports on it being bilateral [4, 10]. It occurs exclusively in maxillary sinus (there is one report about it in the frontal sinus) [1, 11]. SSS presents in the third to forth decades of life and seems to affect both genders equally [9]. The incidence of SSS is similar in the left and right maxillary sinuses (there might be a slight predominance for presenting on the right side – (57%) [4, 9]. The average duration of the progressive, characteristic orbitopathies until presentation is 3 months (range 10 days – 2 years) [5, 9]. Average enophthalmos at presentation is 2,96 mm (± 0.16 mm), average hypoglobus at presentation is 2.78 (± 0.25 mm) [5, 9, 12]. Although mostly observed in adults, there have been reports on SSS in children [9, 13, 14].

The syndrome's typical constellation of symptoms and signs are: spontaneous, gradual and progressive enophthalmos and hypoglobus (ocular asymmetry – a drop in the pupillary level, deep upper lid sulcus), so patients have a various

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degree of facial asymmetry (esthetic problem) [1, 2, 8, 15–17]. The eye is retracted into the orbit (one more prominent) and downward placed (Figure 1). There is normal ocular motility and vision, with no reccurent infections, pain or pressure. But, diplopia (usually in up gaze), cheek pressure, (intraorbital) facial pressure or mild pain, mild dental pain can also be the symptoms. Some other ophthalmological signs that can occur are abnormal eyelid signs (retraction, ptosis, absent crease), lid lag, and dry eyes from lagophthalmos [1, 2, 8, 15–17].

Fig. 1 – Typical ocular (facial) asymmetry in silent sinus syndrome (SSS) – hypoglobus and enophthalmos (3 mm) on the left side; upper-lid retraction, deepened upper-lid sulcus.

Pathophysiology

SSS has two main theorized mechanisms: maxillary sinus atelectasis (MSA) which could be idiopathic, posttraumatic, or post-surgery, and maxillary sinus hypoplasia (MSH) [4].

The exact pathophysiology of SSS is unknown, and so far, there are three main theories [1, 3, 5, 9, 15, 17].

The first theory is associated with prolonged negative pressure (continued negative pressure within the sinus) [3, 5, 15, 17–19]. A complete obstruction of the MS ostium results in hypoventilation and accumulation of secretion. In this enclosed cavity subsequent gas resorption leads to subatmospheric pressure that creates vacuum, thus creating a suction effect of negative pressure within the maxillary sinus, vacuum may induce osteopenia, bone remodeling and sinus walls retraction (like eustachian tube dysfunction causing retraction in the middle ear) [15]. The chronic negative pressure in the sinus slowly retracts the orbital floor, altering orbital anatomy and affecting the function of orbital contents. Continued negative pressure within the sinus activates the osteoclasts; in turn, these make the sinus walls thinner. The enophtalmos and hypoglobus are induced because the thinned orbital floor cannot support the pressure from the overlying orbital content, which gradually expands into the sinus [3, 5, 15, 17–19].

There is a hypothesis suggesting that lateralized middle turbinate may act as one-way pneumatic valve, leading to progressive reduction of air in the antrum and subsequent collapse of the maxillary sinus [1, 16].

However, given the rarity of SSS and the very high prevalence of maxillary sinus ostiumobstruction, Hourany et al. [20] has placed this first theory explanation under question. The prolonged negative pressure theory also fails to offer an explanation for the exclusive involvement of the maxillary sinus, so he supposed that some other compounding factors such as trauma or anatomic predisposition play a role [20].

The second theory of SSS pathogenesis is inflammatory erosion [15]. Chronic inflammation could induce the erosion of the orbital floor. Inflammatory cells can produce cytokines that inhibit the replication of osteoblasts and collagen synthesis, thus favoring the osteopenic process. Subclinical inflammatory process can induce osteopenia, resulting in maxillary bone loss, but the negative pressure in the maxillary sinus must also take part in the mechanisms.

The third theory involves hypoplasia [15]. SSS is supposingly the result of an infection in a congenitally hypoplastic maxillary sinus, but one third of the patients have no history of sinus disease in childhood and SSS occurs in normal and well-developed maxillary sinus.

Diagnosis

The diagnosis of SSS is made by typical clinical features – gradual onset of enophthalmos and/or hypoglobus, in the absence of orbital trauma (including surgery) or sinus disease, nasal endoscopy and CT scans of the nose and paranasal sinuses [1, 9].

Nasal endoscopy will show either a completely normal finding, or one of the two typical pictures: firstly, widened middle meatus on the affected side with inward retraction of the uncinate process [15] and secondly, middle turbinate lateralized (middle meatus obscured due to lateral displacement of the middle turbinate toward the uncinate process) [9, 15, 21].

Imaging of the choice for SSS is CT [16, 22–24]. CT finding is typical and definitely confirms the diagnosis [1, 4, 16, 20, 22–24]. At coronal CT scans, we shall see the uncinate process and medial sinus wall retracted laterally; medial meatus enlarged, orbital floor retracted into sinus lumen, increased orbital volume, inward retraction of medial and superior walls of the MS, decrease in the MS volume and its total opacification (Figure 2). The maxillary sinus can be normally developed or hypoplastic, but is opacified, and the infundibulum is always occluded [1, 20]. Occlusion is usually caused by lateral retraction of the uncinate process with the uncinate process being retracted against the inferomedial aspect of the orbital wall. The middle meatus is correspondingly enlarged with varying degrees of lateral retraction of the middle turbinate. The most characteristic imaging feature of the silent sinus syndrome is the inward retraction of the sinus walls into the sinus lumen, with associated decrease in sinus volume, which can be nicely seen on axial CT scans. The orbital floor (maxillary roof) is always retracted and commonly thinned, demineralized [1, 4, 20]. Axial CT scans will show maxillary sinus opacity with inward bowing ("implosion") of the maxillary sinus walls and associated lateral displacement of the middle turbinate (Figure 3). Maxillary sinus "implosion" means ret-

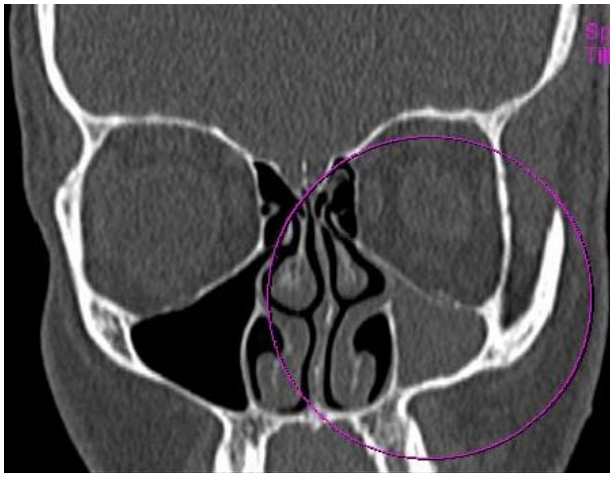

Fig. 2 – Coronal computed tomography (CT) scan: lateralized left uncinate process and medial maxillary sinus wall, enlarged left middle meatus, completely opacified left maxillary sinus, and its volume decreased.

Fig. 3 – Axial computed tomography (CT) scan: inward retracted walls of the left maxillary sinus, left maxillary sinus completely opacified, and its volume decreased.

raction of anterior, posterior and medial wall into sinus lumen. There is also patchy loss of mineralisation. Typically, all 4 walls of the sinus are retracted, though one of the medial, anterior, or posterolateral walls may be spared [20].

The orbital floor is always retracted, commonly thinned, while the other walls may be thinned, normal, or slightly thickened [1, 4, 20, 25]. Orbital floor thickening is also a possibility. Considering the meaning of the thinned or thickened sinus walls in SSS, Hourany et al. [20] discused the issue in their paper, illustrating it with the case that supports the notion that SSS is an aquired condition, since thickening of the sinus walls is probably related to chronic inflammation and not to underlying developmental hypoplasia [20].The opacification of the MS can be complete or near complete (total or near total) [16, 18]. Sanchez et al. [25] described an image of a "pseudo-pneumo-orbit" that can also be seen due to air trapped under the upper eyelid.

The cases of lateralized uncinate process and increased orbital volumes observed on CT scans, but lacking clinical enophthalmos and hypoglobus exist, and are a matter of discussion if it is, or it is not the SSS. Wise et al. [26] in their paper published in 2007 conclude that it potentially represents early SSS, before the development of clinical orbital findings, so such cases should be considered and treated as an early stage of SSS.

Differential diagnosis

The changed architecture of maxillary sinus seen in SSS should be differentiated from the MSH and chronic maxillary atelectasis (CMA) [27].

Maxillary sinus hypoplasia or failure of development (arrested pneumatisation), is an infrequent congenital anomaly, and can occur in the absence of disease or surgery [27]. This is often accompanied by hypoplasia of the uncinate process. The prevalence of 10.4% has been described [4], with a proposed classification of the degree of hypoplasia based on CT appearances in three types [4, 27].

The distinction between the imaging appearance of hypoplastic maxillary sinus and silent sinus syndrome is not well understood. Some authors believe that a congenital underdevelopment of the maxillary sinus is responsible for the development of SSS, but the acquired nature of this condition is now more readily apparent [20].

Chronic maxillary atelectasis is the term that describes a persistent decrease in the sinus volume from inwardly bowing antral walls [4, 12]. CMA was also differentiated in 3 stages based on the observed anatomical changes on CT scans. Stage 3 CMA (clinical deformity) is diagnosed when enophthalmos, hypoglobus, and/or midfacial deformity is noted. The presence of sinus-related symptoms distinguishes CMA stage III from SSS. Brandt and Wright [12] are some of the authors that support the concept that SSS and CMA are the same clinical entity, because SSS fits within the staging classification of CMA. They suggested abandoning the term SSS and recommend universal adoption of the CMA staging system, which uses nomenclature that more accurately portrays the pathophysiology and natural history of this condition [12].

A clinician treating a patient presenting with enophthalmos and hypoglobus, must also consider a wide range of diseases [9]. The differential diagnosis for SSS includes trauma to the orbit (especially blow out fracture), prior orbital decompression for Graves orbithopathy, chronic rhinosinusitis, osteomyelitis, Wegener granulomatosis, orbital metastasis, human immunodeficiency virus (HIV) lipodystrophy, and prior orbital radiation therapy [9, 17, 18, 28]. There are also some really rare conditions to consider like orbital fat atrophy, Recklinghausen disease (the absence of the sphenoid wing), linear scleroderma, Parry-Romberg syndrome (progressive hemifacial atrophy) and pseudoenophthalmos [9, 17, 18, 20, 28].

Treatment

The treatment of SSS has objectives to restore the eye position and orbital floor height, prevent progression of enophthalmos, restore ventilation and drainage of sinus and

avoid infection [1, 14, 17]. These objectives are achieved in single- or two- stage surgery.

The treatment of SSS is surgical, performed by a rhinologist [14]. The general agreement is that sinus pathology should be treated as the first stage of the treatment. It is the functional endoscopic sinus surgery (FESS) that should be performed in patients with SSS, because it restores sinus drainage with no or minimal collateral damage [1, 9, 12, 29, 30]. The procedure must be done with extreme caution, since unintentional entry into the orbit happens much more often. Surgery starts as usually with uncinectomy which should be performed with extra care, as the inward implosion of the antral walls, in combination with a depressed orbital floor, places the orbital contents at particular risk of injury [1, 9, 30]. Then, a wide meatalantrostomy must be made, which provides aeration to the maxillary sinus. Antrostomy typically results in the release of negative sinus pressure and re-expansion of the collapsed cavity leading to the reduction of enopthalmos. A wide antrostomy prevents future reobstructions, and good reaeration of the sinus helps to avoid recurrent enophthalmos [4, 16, 29]. So, a rhinosurgeon should perform a complete uncinectomy, anterior ethmoidectomy (adds exposure of the hiatus semilunaris and medial orbital wall), trimming of the inferior third of the middle nasal turbinate with gentle medial displacement (if it is lateralized)to prevent reocclusion of the natural maxillary ostium and wide middle meatal antrostomy [1, 16, 29, 30]. In some cases an inferior meatal antrostomy with even endoscopic medial maxillectomy are done [9]. Inside the maxillary sinus with SSS, the mucus secretion (thick glue like) is often found, and removed [15, 30].

Besides the described traditional sinus treatment with FESS in SSS, there is a report on succesfull ball treatment with balloon sinuplasty [31].

The second stage in the treatment of SSS is a surgical procedure done to restore orbital volume and symmetry [1]. Should an orbital wall repair be performed at the same time with sinus surgery (FESS), depends on the severity of diplopia, the degree of cosmetic alterations, and the postsurgical evaluation of the sinus [4, 32]. Actually, the timing for management of the orbital floor is still under debate. As suggested by some authors, orbital floor reconstruction should be performed simultaneously with sinus treatment [4, 32]. Most other authors think that drainage of the sinus as a single step should be enough [1, 4, 16, 29, 30, 32]. The maxillary sinus usually remodels after FESS, so it is rarely necessary to do the secondary repair of the orbital floor for aesthetic reasons. Orbitopathies (enophthalmos and hypoglobus – cosmetic or symptomatic) improve over 6 months after surgery [1, 9], so a natural resolution of orbital findings and subjective complains happen. The recommendation today is to do the two-stage approach to orbital repair, as described, and do the second operation, if necessary, after at least 6 months [1, 9]. If a clinically significant and symptomatic enophthalmos or hypoglobus persist at 6 months after sinus surgery, the orbital floor repair is absolutely indicated [1, 9].

Conclusion

Silent sinus syndrome is a rare entity of spontaneous progressive asymptomatic collapse of the maxillary sinus. The diagnosis is based on the gradual onset of enophthalmos and/or hypoglobus, in the absence of orbital trauma (including surgery) or prior symptoms of sinus disease. Treatment is surgical, meaning functional endoscopic sinus surgery as the first and necessary step, and orbital floor repair performed in some cases, as the second step.

Silent sinus syndrome describes a constellation of ocular and sinonasal findings, so both otorhinolaryngologists and ophtalmologists should be familiar with it.

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Received on November 18, 2014.
Accepted on October 16, 2015.
Online First June, 2016.

CASE REPORTS

UDC: 612.017.1:616.329
DOI: 10.2298/VSP150723148V

An enigma of eosinophilic esophagitis

Enigma eozinofilnog ezofagitisa

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Abstract

Introduction. Eosinophilic esophagitis is a chronic immunogenic-antigen mediated disease of the esophagus, characterized by symptoms related to esophagus dysfunction, histologically defined by over 15 eosinophil counts seen in high-power microscopic field, without gastroesophageal reflux disease. In adults, the most common clinical manifestations are dysphagia, reflux, chest pain, regurgitation and bolus impaction. **Case report.** We presented the case of a female patient, hospitalized for a serious form of pancreatitis with complications, which required artificial ventilation and enteral feeding, after the initial esophagoscopy verified reflux esophagitis. Further treatment cured the primary illness, and peroral feeding was reintroduced. However, dysphagia with regurgitation occurred, and endoscopic and radiological tests verified esophagus stenosis, which histopathologically corresponded to erosive esophagitis. Two months of treatment by a double dosage of proton pump inhibitors led to no regression of disorders, and the repeated biopsies from the stenotic segments resulted in over 30 eosinophil counts in the high-power microscopic field, which histologically corresponds to eosinophilic esophagitis. Subsequent therapy included fluticasone 880 μg/day orally for a period of eight weeks, which led to complete regression of disorders, and endoscopic and histopathologic remission. **Conclusion.** In case of irresponsiveness to the conventional therapy by proton pump inhibitors, repeated esophagoscopy and histopathological analyses of esophagus mucosa biopsy can point to the diagnosis of eosinophilic esophagitis, and a good therapeutic response to topical corticosteroids can be regarded as the clinical confirmation of the diagnosis.
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Key words:
eosinophilic esophagitis; diagnosis, differential; endoscopy, gastrointestinal; esophageal stenosis; biopsy; histological techniques; gastroesophageal reflux; treatment outcome.

Apstrakt

Uvod. Eozinofilni ezofagitis je hronična imunogena antigenom posredovana bolest jednjaka, koju karakterišu simptomi povezani sa disfunkcijom jednjaka, a histološki se definiše sa više od 15 eozinofila viđenih u mikroskopskom vidnom polju velikog povećanja, uz odsustvo gastroeozofagealne refluksne bolesti. Kod odraslih osoba, najčešće kliničke manifestacije su disfagija, refluksni simptomi, retrosternalni bol, regurgitacija i zaglavljivanje (*impaction*) bolusa hrane. **Prikaz bolesnika.** Prikazana je bolesnica, hospitalizovana zbog teškog oblika pankreatitisa sa komplikacijama, koje su zahtevale veštačku ventilaciju i enteralnu ishranu putem nazojejunalne sonde, kojoj je inicijalnom ezofagoskopijom verifikovan refluksni ezofagitis. U daljem toku, osnovno oboljenje je izlečeno i uvedena je peroralna ishrana. Međutim, došlo je do disfagije sa regurgitacijom, a endoskopski i radiološki verifikovana je stenoza jednjaka. Patohistološkom analizom utvrđeno je da se radilo o erozivnom ezofagitisu. Nakon dva meseca lečenja duplom dozom inhibitora protonske pumpe nije došlo do poboljšanja. Ponovljenim biopsijama sa stenotičnog segmenta prebrojano je preko 30 eozinofila u mikroskopskom vidnom polju velikog povećanja, što histološki odgovara eozinofilnom ezofagitisu. U terapiju je uveden flutikazon 880 μg dnevno oralno, u trajanju od osam nedelja, nakon čega je došlo do potpune regresije tegoba, kao i endoskopske i patohistološke remisije. **Zaključak.** U slučaju izostanka odgovora na konvencionalnu terapiju inhibitorima protonske pumpe, ponavljane ezofagoskopije i patohistološke analize bioptata sluznice jednjaka mogu usmeriti dijagnozu u pravcu eozinofilnog ezofagitisa, a dobar terapijski odgovor na kortikosteroide za lokalnu primenu može se smatrati kliničkom potvrdom dijagnoze.

Ključne reči:
ezofagitis, eozinofilni; dijagnoza, diferencijalna; endoskopija, gastrointestinalna; jednjak, stenoza; biopsija; histološke tehnike; gastroezofagusni refluks; lečenje, ishod.

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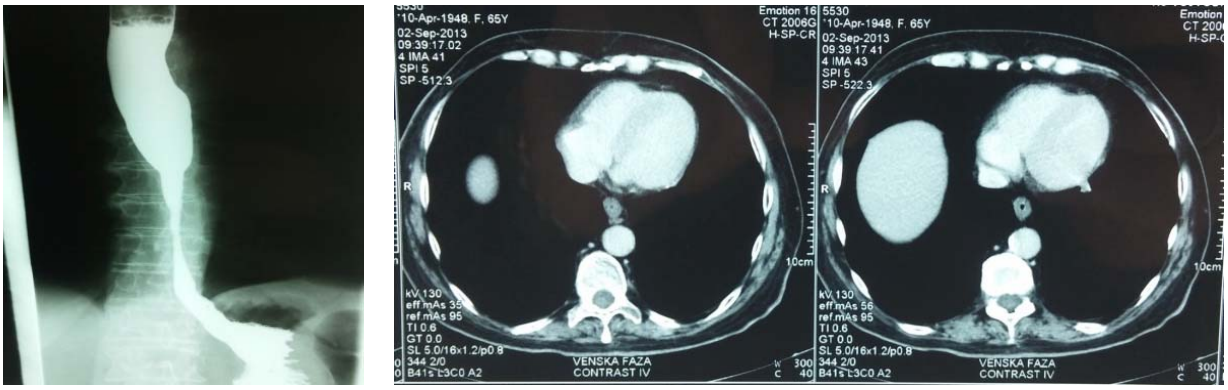
Introduction

Eosinophilic esophagitis (EoE) is a chronic immunogenic/antigen-mediated disease of the esophagus, clinically characterized by the symptoms of esophagus dysfunction, and histologically as predominantly eosinophil inflammatory infiltration, without gastroesophageal reflux disease (GERD) [1]. Due to its clinical and pathophysiological features, it is often referred to as asthma of the esophagus in the literature [2]. The precise etiology and pathophysiology of the disease is not entirely known, but it is assumed to be an allergic (Th2 mediated) disease. In healthy persons, due to constant exposure to foods, allergens and pathogens, eosinophils, which have protective function, are normally found within the whole digestive tract, except in the esophagus [3]. In EoE, Th2 lymphocytes mediated by IL-5, IL-13 and eotaxin 13 mobilize eosinophils in the mucosa of the esophagus. The activated eosinophils secrete proinflammatory and profibrotic mediators, causing damage to the local tissue and attracting other inflammatory cells (mastocytes and fibroblasts), thus increasing the inflammatory response and leading to the remodeling of the esophagus [4]. Histopathologically, EoE is defined by > 15 eosinophils seen in the high-power microscopic field (HPF) in at least one biopsy sample [1, 5]. The prevalence is as high as in 50 persons *per* 100,000 in some parts of the world; the disease usually affects males and is diagnosed between the ages 32 and 52. In adults, the most frequent clinical manifestations are dysphagia, reflux symptoms, retrosternal pain, regurgitation and bolus impaction, while the most common endoscopic findings include linear furrows, whitish exudate, vulnerable mucosa and fibrostenotic changes in the form or rings, strictures and stenosis of the esophagus [1, 2]. Besides the empirical treatment with the proton pump inhibitor (IPP), EoE is also treated with diet (elementary and elimination); medications (corticosteroids, immunomodulators, biological treatment); endoscopic dilatation (in esophageal strictures and stenosis, in cases of unsuccessful application of the above mentioned therapeutic modalities) [6, 7].

Case report

A 65-year-old female patient was hospitalized on June 17, 2013 at the Clinical Center of Vojvodina for acute biliary pancreatitis. The patient reported previous history of type 2 diabetes mellitus and hypertension, and denied any allergic/atopic reactions and hazardous habits. Due to deteriorated respiration on the second day of hospitalization noninvasive ventilation was applied, and on the day 4 a nasojejunal triple lumen probe (NJS) was applied for the purpose of enteral feeding, after the first endoscopic examination confirmed the normal diameter of esophagus with no pathological changes in the mucosa. On the day 6, due to progressive deterioration the patient was intubated for controlled mechanical lung ventilation. On the same day the NJS was temporarily removed. On the day 9 the NJS was applied again, after the second endoscopy showed a number of erosive changes in the esophagus and gastric cardia, so IPP (pantoprazol 40 mg/12 h) was introduced in the therapy. Three weeks after hospitalization the NJS was removed, full liquid diet was introduced *per os*, and in the further course of the treatment acute necrotic pancreatitis and accompanying complications were healed. In the seventh week of hospitalization the patient suffered from dysphagia followed by regurgitation of solid foods. The third endoscopic examination at the 25th cm from the incisive revealed gradual stricture of the esophagus lumen up to the 32nd cm, where the lumen was circularly narrowed to 6 mm, aperistaltic and impenetrable for the endoscope, and proximally to the stenotic segment the epithelium was contact vulnerable (Figure 1). Biopsies taken for histopathology (HP), stained with the standard Hematoxylin and Eosin (HE), Periodic acid-Schiff (PAS) and Giemsa methods, consisted of necrotic detritus with an abundance of cells of inflammatory infiltrations built of lymphocytes, plasma cells and neutrophil granulocytes, containing desquamated squamous cells. The Roentgen examination (RTG) of the esophagus passage revealed a long benign stenosis of the distal esophagus, with mild dilatation of proximal parts of the thoracic esophagus, with sufficient passage with liquid barium (Figure 2a), while computed tomography (CT) of the thorax and abdomen revealed circular thickening of the esophagus wall 6 mm in diameter in the distal third (Figure 2b). Serological tests on cytomegalovirus (CMV) and herpes simplex virus (HSV) IgM and IgG excluded viral etiology of esophagitis. Three weeks following the onset of dysphagic disorders, and in the tenth week of hospitalization, the fourth upper endoscopy was performed, revealing unchanged morphological results. New

Fig. 1 – Esophagoscopy at the 25th cm from the incisive revealed gradual stricture of the esophagus lumen up to the 32nd cm, where the lumen is circularly narrowed to 6 mm, and the epithelium is contact vulnerable.



a) **b)**

Fig. 2 – a) X-ray of the esophagus passage, revealed a long benign stenosis of the distal esophagus, with mild dilatation of proximal parts of the thoracic esophagus;
b) Chest computed tomography (CT) revealed circular thickening of the esophagus wall 6 mm in diameter in the distal third.

biopsies were taken for HP, consisting of the pieces of necrotic and granular tissue originating from ulceration, pervaded by a number of neutrophil granulocytes, which corresponds to reflux esophagitis. Eleven weeks after hospitalization, following clinical, laboratory and radiological regression of necrotic acute pancreatitis, the patient was released from the hospital for home care, with recommendation of full liquid diet and double dosage of IPP. Ten weeks after the onset of dysphagic disorders, and 14 weeks after the introduction of IPP, the fifth upper endoscopy was performed, morphologically unchanged in comparison to the previous one, and the biopsies taken for HP analysis showed pieces of granulation and necrotic tissue originating from ulceration with the areas of fresh bleeding, with a lesser piece of tissue, pervaded by mixed inflammatory infiltrate abundant in eosinophilic granulocytes (over 30/HPF), which corresponded to EoE (Figure 3). Alongside IPP, topical corticosteroid fluticasone was introduced with the dosage of 880 μg/day, divided into two doses for 8 weeks, together with elimination diet. Six weeks after the introduction of topical corticosteroid therapy, the patient came to control examination, denying dysphagia or regurgitation and stating to be tolerant to solid foods. Five months after the diagnosis of esophagus stenosis, sixth upper endoscopy was performed, showing passable esophagus of normal morphology and mucosa (Figure 4). Ten months after the onset of dysphagia, and nine months after the introduction of topical corticosteroid in the therapy for the duration of two months, the seventh endoscopy was performed, showing normal morphological results of the esophagus, stomach and duodenum, while the biopsies of the esophagus taken for HP analysis had no elements of eosinophilic esophagitis, erosions or ulceration (Figure 5).

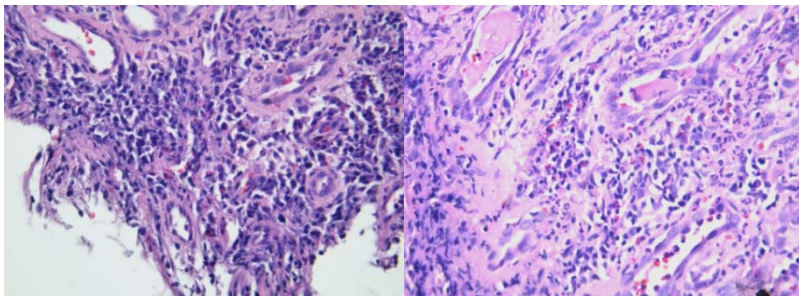


Fig. 3 – Piece of tissue, pervaded by mixed inflammatory infiltrate abundant in eosinophilic granulocytes (over 30/high-power microscopic field), which corresponds to eosinophilic esophagitis (HE, ×400).

Fig. 4 – Esophagoscopy 5 months after the diagnosis of esophagus stenosis, and 2 months after the therapy, showing the passable esophagus of normal morphology and mucosa.

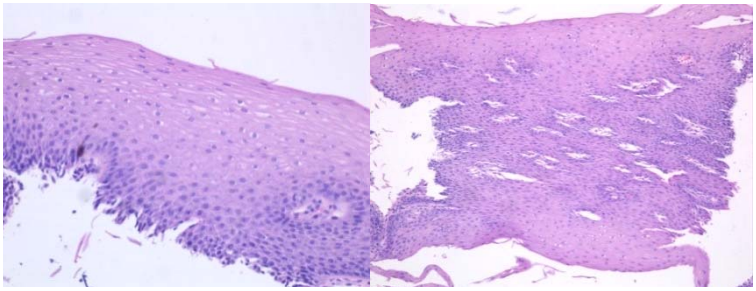


Fig. 5 – Histopathology (HP) analysis 2 months after the therapy, showing no elements of eosinophilic esophagitis, erosions or ulceration (HE, ×200).

A year after the onset of dysphagic disorder the patient was in good general condition, without dysphagia, tolerant to liquid, full liquid and solid foods. Pancreatitis was entirely cured and elective cholecystectomy planned.

Discussion

We presented the case of a female patient with esophageal clinical symptomology, with chronologically different endoscopic and pathohistological changes of the esophagus mucosa, with the final diagnosis of EoE and excellent response to the application of topical corticosteroids. Following the consensus (FIGERS, 2007), EoE is a clinical-histological entity that excludes GERD as the cause of esophageal eosinophila, either for the lack of response to therapies involving high dosage of IPP or the negative results of pH-matter [5, 8]. However, a complex interrelation between EoE, GERD and esophageal eosinophilia has been recognized. In some patients both EoE and GERD have been found, described as the entity of esophageal eosinophilia responsive to the IPP therapy (PPI-REE) [5, 8]. GERD may lead to esophageal eosinophilia, which is histologically most commonly characterized by counts lower than 10 eosinophils in HPF. Patients with GERD, not responsive to IPP therapy are regarded as resistant cases. A possible reason for GERD resistance could be EoE [3]. The efficacy of IPP in curing some cases of EoE is well-known, as well as the potential role of hydrochloric acid in the pathogenesis of EoE [6]. However, although there is overlapping between these two diseases, the interrelation between EoE and GERD remains controversial and is a motivation for further research. In the patient presented in this paper, the etiology of EoE is not entirely clear. Although allergologic tests were not performed, it cannot be positively claimed that food is the cause of EoE, since she received hypoallergenic enteral feeding while in the critical condition. Nutritional allergens, especially those from soya, milk, eggs, cereals, nuts and seafoods are a far more common cause of EoE in pediatric age [9]. Aeroallergens, as another possible cause of EoE, are less probable in the areas of intensive care units, as well as in the conditions of artificial ventilation, although they are not negligible. Attention should be paid to *Aspergillus*, as a potential aeroallergen that can be found in ventilation systems. It has been shown in animal and human research studies that this fungus may cause the infiltration of the esophagus with eosinophils [10–12]. In the case presented here the first endoscopic examinations revealed reflux esophagitis, yet the application of the full dosage of IPP led to the esophageal stenosis accompanied with dysphagia, which remained irresponsive to the extended double dosage of IPP for over two months. In the study by Foroutuan et al. [13] EoE is described in patients with refractory GERD, and it is concluded that out of 66 patients, 33.3% had endoscopic esophagitis, but that all of them had a previous history of atopy or allergy. Fujiwara et al. [14] studied the endoscopic results resembling EoE in patients with erosive esophagitis, and they concluded that there were many overlapping and common features of the two diseases, which may point to common pathogenic mechanisms. The question that arises here is whether the HP result in this case is isolated located eosinophilia, caused by GERD and reflux of hydrochloric acid above the esophagogastric (EG) junction. Abe et al. [15] describe the cases of isolated esophageal eosinophilia, in 90% above the EG juncture, which is exposed to acid reflux, which indicates that isolated EoE might be a subtype of GERD. Since in the patient presented here there was no clinical nor endoscopic improvement at double dosage and extended therapy with IPP, it was probably not a case of PPI-responsive esophageal eosinophilia. Lastly, the extended usage of NJS should not be disregarded, which could have been another potential cause of esophagitis, eosinophil infiltration and esophagus stenosis. Still, this possibility is less likely, considering the fact that modern feeding probes are made of hypoallergenic materials based on silicon or polyurethane. No similar cases have been reported in the literature.

Conclusion

The patient presented in this paper leads to the conclusion that despite the latest findings, eosinophilic infiltration of the esophagus is still an intriguing and complex clinical problem. Although there are common features of eosinophilic esophagitis and gastroesophageal reflux disease, their interrelation remains controversial. In case of irresponsiveness to the conventional therapy with proton pump inhibitors, repeated esophagoscopies and HP analyses of esophagus mucosa can direct the diagnosis towards eosinophilic esophagitis, and the good therapeutical response to topical corticosteroids can be taken as the clinical confirmation of the diagnosis.

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Received on July 23, 2015.
Revised on August 19, 2015.
Accepted on August 24, 2015.
Online First June, 2016.

CASE REPORT

UDC: 615.8:[616.7:616.89-008
DOI: 10.2298/VSP1508025059D

Pastoral care and religious support as a part of treatment of religious patient with the severe form of osteoarthritis

Pastirska briga i religiozna podrška kao deo lečenja religiozne bolesnice s teškim oblikom osteoartritisa

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Abstract

Introduction. Religious needs of patients are consistently being neglected in the clinical medicine. Pastoral care is a religious support which a religious patient receives from priests, chaplains, imams, rabbis or other religious authorities. Religious support, in terms of clinical medicine, is a spiritual support which religious patients obtain from religious and trained medical workers. The aim of this report was to present the effects of pastoral care and religious support in hospital treatment of a 73-year-old patient with the severe form of osteoarthritis. **Case report.** The 73-year-old, highly religious patient with severe form of osteoarthritis was admitted at the Clinic for Physical Medicine and Rehabilitation, Military Medical Academy in Belgrade, due to heterogeneous problems in the activities of daily living. The patient walked with difficulty using a stick, suffered pain, and was anxious and depressive. In order to objectively demonstrate effects of both pastoral care and religious support in this patient we performed multiple treatment with reversal design, in which the basic treatment consisting of hospital care, pharmacotherapy and physical therapy (the treatment A) was alternatively changed with the treatment that included combination of the basic treatment and religious support provided by religious physiatrist and physiotherapist (the treatment B) or combination of the basic treatment and pastoral care provided by military priest (the treatment C). The treatment A was applied three times and lasted two weeks, every time. Treatments B and C were applied once and lasted three weeks, each. The order of the treatments was: A→B→A→C→A. During the whole treatment period the patient's condition was assessed by several measuring scale: the level of depression by The Hamilton Rang Scale for Depression and The Zung Self Rating Depression Scale; the level of anxiety by The Zung Self Rating Anxiety Scale; the functional capability of patient by The Barthel Index and The Functional Independent Measure. Measuring was carried out on a daily basis. In statistical analysis two nonparametric statistic were used: the percentage of non-overlapping data (PND) and the percentage of data points exceeding the median (PEM). PND and PEM values below 0.7 reflect questionable effectiveness of the treatment. The values between 0.7 and 0.9 reflect moderate effects. The values above 0.9 are considered as a highly effective treatment. The anxiety of the patient was moderately to significantly reduced after introducing religious support (treatment B: mean and mean deviation = 50.1 ± 10.89; variability = 4.598653; mean shift = 0.219626; PND = 0.6; PEM = 0.9) and pastoral care (treatment C: mean and mean deviation = 53.5 ± 5.90; variability = 9.062591; mean shift = 0.207407; PND = 0.9; PEM = 0.9). The patient's depression was reduced after introducing pastoral care (treatment C: mean and mean deviation = 51.3 ± 4.66; variability = 10.99005; mean shift = 0.08881; PND = 0; PEM = 0.9). On the contrary, the patient's functional capability was not significantly improved. **Conclusion.** In the highly religious patient with severe osteoarthritis pastoral care and religious support, applied along with the standard medical treatment of this condition, produced some beneficial effects on anxiety and depressive mood, but with no significant effect on patient's functional capability.

Key words:
physical and rehabilitation medicine; osteoarthritis; religion; pastoral care; aged; treatment outcome.

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Apstrakt

Uvod. Religiozne potrebe bolesnika stalno se zanemaruju u kliničkoj medicini. Pastirska briga je religiozna podrška koju religioznom bolesniku pružaju sveštenici, pastori, imami, rabini i ostali religiozni autoriteti. Religiozna podrška u smislu kliničke medicine, je duhovna podrška koju religioznom bolesniku pružaju religiozni i za to obučeni medicinski radnici. Cilj rada bio je da se prikažu efekti pastirske nege i religiozne podrške u sklopu bolničkog lečenja 73-godišnje bolesnice sa teškom formom osteoartritisa. **Prikaz bolesnika.** Veoma religozna bolesnica, stara 73 godine, sa teškom formom osteoartritisa, primljena je na lečenje u Kliniku za fizikalnu medicinu i rehabilitaciju Vojnomedicinske akademije u Beogradu, zbog više problema koji su ometali njen svakodnevni život. Bolesnica se kretala otežano uz pomoć štapa, trpela je bolove i bila je anksiozna i depresivna. U cilju objektivnog sagledavanja efekata pastirske nege i religiozne podrške u lečenju ove bolesnice, sproveli smo multiplo obrtno lečenje koje se sastojalo od primene bazičnog tretmana (bolnička nega, terapija lekovima i fizikalna terapija), označenog kao tretman A, koji se naizmenično menjao sa tretmanom sastavljenim od bazičnog tretmana uz dodatak religiozne podrške koju su obazbeđivali verujući fizijatar i fizioterapeut (tretman B), odnosno bazičnog tretmana uz dodatak pastirske nege koju je pružao vojni sveštenik (tretman C). Bazični tretman bio je primenjen tri puta, svaki put u trajanju od po dve nedelje, a kombinovani tretmani sa religioznom, odnosno pastirskom podrškom, primenjivni su jedanput, po tri nedelje svaki. Redosled primenjenih tretmana bio je sledeći: A→B→A→C→A. Glavna obeležja posmatranja i merne skale bili su: nivo depresije meren Hamiltonovom skalom depresije i Cungovom skalom depresije; nivo anksioznosti, Cungovom skalom anksioznosti, a funkcionalna sposobnost bolesnika merena je indeksom Bartel i Merom funkcionalne nezavisnosti. Merenja su vršena svaki dan. U statističkoj obradi podataka korišćene su dve neparametrijske metode za kvantitativnu obradu podataka: procenat tačaka koje se ne preklapaju – (*percentage of non-overlapping data* – PND) i procenat tačaka koje prelaze nivo medijane (*percentage of data points exceeding the median* – PEM). Vrednosti PND i PEM između 0,7 i 0,9 govore o zadovoljavajućem efektu lečenja. Vrednosti od 0,9 i više govore o značajnom efektu lečenja. Uvođenjem religiozne podrške u lečenje, smanjenje anksioznosti bilo je umereno do značajno tretman (B); $\bar{x} \pm SD = 50,1 \pm 10,89$; varijabilnost = 4,598653; srednji pomak = 0.219626; PND = 0,6, PEM = 0,9). Depresija bolesnice značajno se smanjila samo nakon uvođenja pastirske brige i samo prema jednoj statistici (PEM = 0,9). Nasuprot ovome, nije došlo do poboljšanja funkcionalne sposobnosti bolesnice. **Zaključak.** Kod visoko religiozne bolesnice sa teškom formom osteoartritisa, pastirska nega i religiozna podrška, primenjeni u sklopu standardnog medicinskog lečenje tog stanja, ispoljili su određene povoljne efekte na anksioznost i depresivno raspoloženje, ali bez značajnijeg poboljšanja funkcionalne sposobnosti bolesnice.

Ključne reči:
medicina fizikalna i rehabilitacija; osteoartritis; religija; pastoralna briga; stare osobe; lečenje, ishod.

Introduction

Could we start with a rhyme? Religion and medicine – this look is broad – today are not on the same road. Religious needs of patients are consistently neglected in clinical medicine [1]. Religion is belief in the absolute power. A believer has an experience with this power. He or she knows historical shapes of this experience. This experience has an extraordinary importance for believers and their communities [2]. Man is a unity of body, soul and spirit. Spirit is a higher part of soul. Believers communicate with God through their spirit [3]. Spiritual problems of believers are not resolved by psychology [4]. Educated physicians should know the elements of psychology of religious persons [5]. This knowledge is particularly important in rehabilitation medicine.

A connection between religion and medicine was established a long time ago. Religious persons take fewer drugs in the hospital environments [6]. Believers are more capable in the activities of daily living as compared with nonreligious and less spiritual persons [7]. They have a strong motive for maintaining oral health [8]. There is a less likelihood of developing chronic pain and weakness in religious persons [9]. Daily spiritual experience and religious activities help believers with rheumatoid arthritis [9]. In patients with multiple sclerosis religion is connected with the problems of their psychological adjustment [10]. Spiritual authorities transform and strengthen psychotherapy of believers [11]. Chaplains believe that they should be active members of medical staffs [12]. Occupational therapists and the physicians of family medicine look for religious and spiritual education [13, 14]. However, there are many scientific and practical perplexities concerning the connection between medicine and religion.

Pastoral care is a religious support which a religious patient receives from priests, chaplains, imams, rabbis or other religious authorities. Religious support, in terms of clinical medicine, is a spiritual support which religious patients obtain from religious and trained medical workers. Pastoral care and religious support for believers are more an exception than the rule in western medicine, as is the case in Serbian and Russian medicine, as well [1, 15–18]. Some physicians in the United States run away from religious patients and their religious needs. The main reasons are the lack of time and the fear of crossing the professional borders [15]. There is some kind of religious medicine in Russia, so-called "Orthodox medicine" [3]. But Kostina [17], for example, claims that more physicians in this country are turning into insensitive persons with a low level of empathy. She states that in Moscow, according to one research, only 31% of patients believe physicians. Some western researches think that religious authorities are poorly trained for the work with invalids. They neither have enough experience for that nor enough money for this activity [19]. What about Serbian medicine?

In some Serbian hospitals and rehabilitation institutions there are sacral objects and clergymen. These spiritual per-

sons are mostly priests of the Serbian Orthodox Church. Unfortunately, the pastoral care in terms of active priests' participation in the medical staff does not exist. Military priests, chaplains, imams and rabbis are a part of the Serbian Armed Forces [20]. However, the results of their work are not easily perceived. According to our knowledge, so far, in Serbian medicine, particularly in rehabilitation medicine, there have not been attempts of medico-theological studies. Many questions in this sense are open. For example: can a clergyman be a useful member of a rehabilitation team; can religious medical workers, trained by priests, correctly carry out the religious support; is there a connection between pastoral care and religious support in patients with osteoarthritis? Namely, it is well-known that some kind of education is an obligatory treatment for these patients. Pastoral care and religious support are a kind of education. Education of patients with osteoarthritis could be guided by medical workers and laymen [21, 22]. There is yet one important issue. Could a single–system experimental design (n = 1) help us to obtain the answers to some of these questions?

The aim of this report was to present the effects of pastoral care and religious support in a 73-year old patient with a severe form of osteoarthritis.

Case report

The patient was a 73-year-old woman with severe form of osteoarthritis hospitalized at the Clinic for Physical Medicine and Rehabilitation, Military Medical Academy in Belgrade. Her main complaints were pain, anxiety, depression and heterogeneous problems in the activities of daily living. Osteoarthritic lesions were located on the cervical and lumbar spine, the hips and the knees. According to her medical history she earlier had lumbar disc hernia operation and non-operating treatment of rectal cancer. The patient walked with difficulty and used a stick. We performed multiple treatment with reversal design (withdrawal design) [23–25] in which the basic treatment consisting of a common hospital care, pharmacotherapy and physical therapy (the treatment A) was alternatively changed with the treatment that included combination of the basic treatment and religious support provided by religious physiatrist and physiotherapist (the treatment B) or combination of the basic treatment and pastoral care provided by military priest (the treatment C). The treatment A was applied three times and lasted two weeks, every time. Treatments B and C were applied once and lasted three weeks, each. The order of the treatments was: A→B→A→C→A. Duration of whole treatment was three months.

Within basic treatment the patient occasionally took meloxicam, ketorolac, paracetamol, metamizol and gabapentin to treat pain. Mianserin was administered to treat depression in a single evening dose of 15 mg as a continuation of the outpatient (prehospital) therapy.

Physical treatment was unified and consisted of low-level laser therapy, transcutaneous electrical nerve stimulation (TENS) and exercise. A dosage and a continuity of the physical therapy were occasionally changed.

The treatment B meant the introduction of religious support as an addition to the basic treatmant. Religious support was carried out 3 times a week. Each session took 45–60 minutes. This kind of treatment continued 3 weeks. Religious support to the patient was provided by the physiatrist and the physiotherapist who had been prepared spiritual activities by military priest. This preparation meant fasting, confession, and a prayer for the beginning of the good deed. Religious support was based on spiritual talks, reading of religious texts (the Bible in the first place), listening to spiritual music and on personal and mutual prayers.

The treatment C included combination of the basic treatment and pastoral care. Pastoral care was carried out 3 times a week. Each session took 45–60 min. This kind of treatment continued three weeks. The military priest provided pastoral care. This activity was based on religious talks with the patient, on the Communion and on the Holy Sacrament of Eucharist and Confession. Introduction of particular treatment was randomly assigned.

During the treatment periodical assessment and daily assessment of the treatment effects were performed.

Periodical assessment was performed at the start and at the end of the whole treatment. The marks of observation and the measuring scales were: the mental state of the patient – The Mini Mental State of Examination (MMSE) [26]; the activities of daily living – The Western Ontario and McMaster Universitie (WOMAC) scale, section C[21]; the level of depression – The Hamilton Rating Scale for Depression, [26] and organizational (ORA) and non-organizational (NORA) religious activity, as well as intrinsic religiosity (IR) – The Duke University Religion Index – DUREL [27].

Main assessment of the treatment effects was on a daily basis. The marks of observation and the measuring scales were: the level of depression – The Zung Self Rating Depression Scale[26]; the level of anxiety – The Zung Self Rating Anxiety Scale[26]; the functional capability of the patient – The Barthel Index and The Functional Independent Measure (FIM)[26]; the life satisfaction of the patient – The Life Satisfaction Index[26], and pain during activities and rest – Visual Analogue Pain Rating Scale [26].

Measuring was performed by the members of the healthcare team who were not engaged in pastoral care and religious support.

Nonparametric statistics were used in the quantitative analysis: the percentage of non- overlapping data (PND), and the percentage of data points exceeding the median (PEM). The PND and PEM values below 0.7 reflect questionable effectiveness of a treatment. The values between 0.7 and 0.9 reflect moderate effects. The values above 0.9 are considered as a highly effective treatment [28–30].

This treatment protocol was approved by the Ethic Committee of the Military Medical Academy, Belgrade.

Analysis of the treatment

The patient was cognitively preserved during the whole treatment (MMSE, start = 29; end = 29). She had significant problems in the activities of daily living due to pain and stiffness (WOMAC, start = 48; end = 45). At the start of the treatment some incompatibility regarding the measure of depression was perceived. According to the Hamilton's scale the

patient was moderately depressed (Hamilton, start = 20). According to the Zung's scale she was not depressed (Zung, start = 45,3). At the end of the study the patient was not depressed (the Hamilton scale = 7, the Zung scale = 46.2) . The patient was a highly religious person (DUREL, ORA, start = 5, end = 5; DUREL, NORA, start = 6, end = 6; DUREL, IR, start = 13, end = 13).

The score of depression is shown in Figure 1. It was stable during the first two-week period of the basic treatment. During the period of religious support (treatment B) and during the second period of the basic treatment (treatment A) the depression was mild to moderate. When pastoral care was introduced (treatment C), the level of depression was reduced.

The score of anxiety is shown in Figure 2. It was also stable during the first basic treatment. When the religious support and pastoral care were introduced (treatments B and C, respectively), the level of anxiety was reduced.

A life satisfaction score (Figure 3) was stable in the periods of the treatment A duration. When the religious support and the pastoral care were introduced, the life satisfaction score was not changed.

A functional capability score (FIM) is shown in Figure 4. It was stable without marked trend during periods with the basic treatment. When the religious support and the pastoral care were introduced, the patient's functional capability was not improved.

A functional capability score expressed as Bartel index (Figure 5) showed a mild instability in the second period of the basic treatment (treatment A). When the pastoral care was introduced, the functional capability was slightly improved.

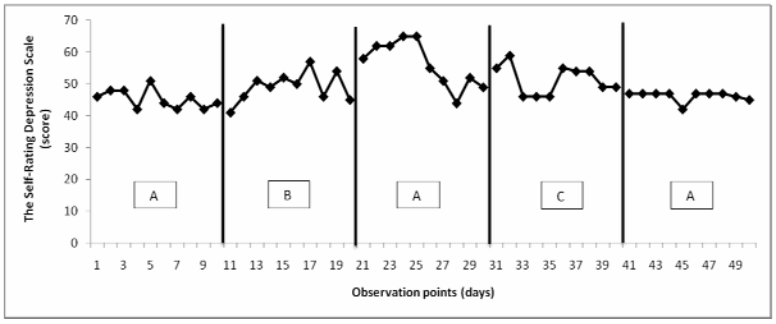

Fig. 1 – The score of depression during the tratment (The Zung Self Rating Depression Scale [26])
A – the basic treatment consisting of common hospital care, pharmacotherapy and physical therapy (the treatment lasted 2 weeks each time).
B – the treatment A + religious support (3 times a week; such session lasted 45-60 min); the treatment B lasted 3 weeks.
C – the treatment A + pastoral care (3 times a week; such session lasted 45-60 min); the treatment C lasted 3 weeks.

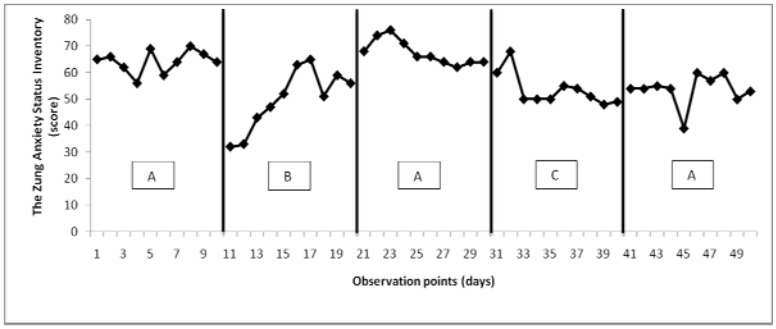

Fig. 2 – The score of anxiety during the treatment (The Zung Self Rating Anxiety Scale [26]).
(for explanation see Figure 1).

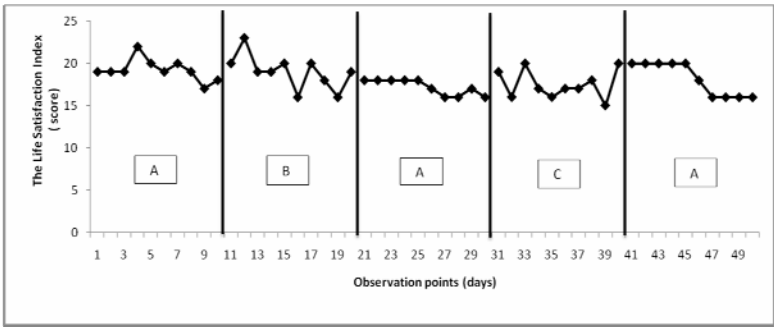

Fig. 3 – The life satisfaction score during the treatment (The Life Satisfaction Index [26]).
(for explanation see Figure 1).

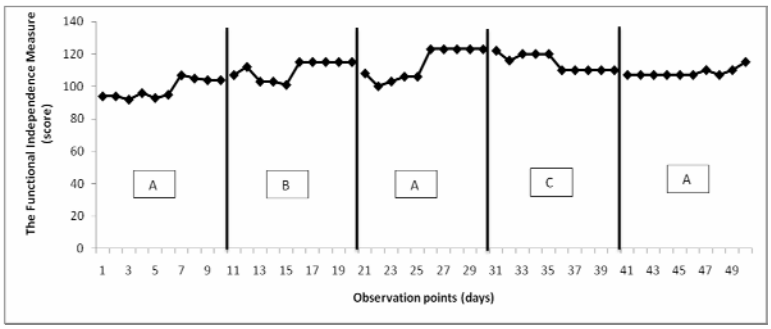

Fig. 4 – The functional capability score during the treatment (The Functional Independent Measure – FIM [26]). (for explanation see Figure 1).

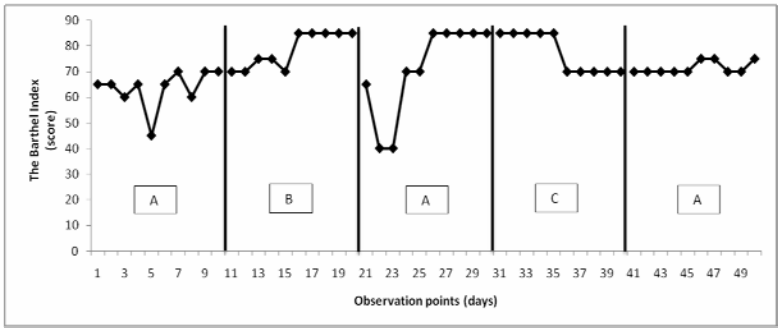

Fig. 5 – A functional capability score during the treatment (The Barthel Index [26]) (for explanation see Figure 1).

A score of pain in activity and rest (Figures 6 and 7) showed an extreme instability in the first period of the basic treatment. As a result, the estimation of the religious support and the pastoral care effects on the pain phenomenon was not possible.

Quantitative analysis demonstarated that the anxiety of the patient was moderately to significantly reduced by introducing religious support (treatment B: mean and mean deviation = 50.1 ± 10.89; variability = 4.598653; mean shift = 0.219626; PND = 0.6; PEM = 0.9) and pastoral care (treat-

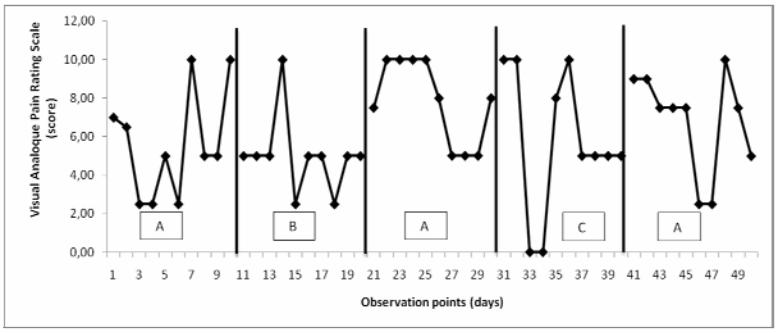

Fig. 6 – The score of pain in activity during the treatment. (for explanation see Figure 1).

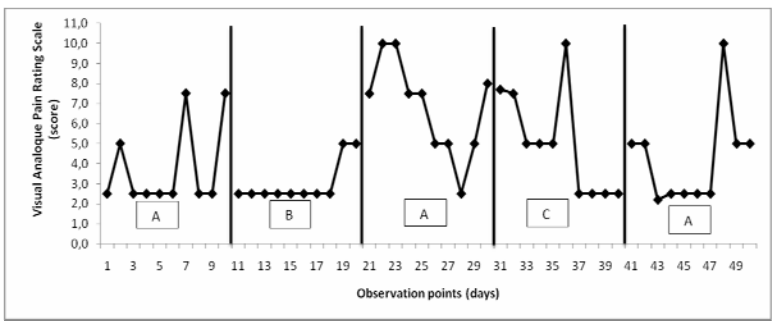

Fig. 7 – The score of pain at rest during the treatment (for explanation see Figure 1).

ment C: mean and mean dev. = 53.5 ± 5.90; variability = 9.062591; mean shift = 0.207407; PND = 0.9; PEM = 0.9). The patient's depression was reduced after introducing pastoral care (treatment C: mean and mean deviation = 51.3 ± 4.66; variability = 10.99005; mean shift = 0.08881; PND = 0; PEM = 0.9). It is worth noting that this improvement was significant according to only one statistical test (PEM). The patient's functional capability, expressed by the Barthel index, was also improved after the religious support (treatment B: mean and mean deviation = 78.5 ± 7.09; variability = 11.07087; mean shift = - 0.23622; PND = 0.7; PEM = 0.7). These results are presented in Table 1.

Table 1

The results of quantitative analysis

Scales	Design-phases	Mean	Mean dev.	Variability	Mean shift	PND	PEM
Depression Scale (score)	A	45.3	3.056868	14.81909	/		
	B	49.1	4.72464	10.39233	-0.08389	0.1	0.2
	A	56.3	7.242621	7.773429	-0.14664		
	C	51.3	4.667857	10.99005	0.08881	0	**0.9**
	A	46.2	1.619328	28.53036	0.099415	/	/
Anxiety Scale (score)	A	64.2	4.093898	15.68188	/		
	B	50.1	10.89449	4.598653	**0.219626**	0.6	**0.9**
	A	67.5	4.455334	15.15038	**-0.34731**		
	C	53.5	5.903389	9.062591	**0.207407**	**0.9**	**0.9**
	A	53.6	5.678028	9.439897	**-0.00187**	/	/
The Life Satisfaction Index (score)	A	19.2	1.316561	14.58345	/		
	B	19	2.054805	9.246621	0.010417	0.1	0.1
	A	17.2	0.918937	18.71729	0.094737		
	C	17.5	1.715938	10.1985	-0.01744	0.3	0.3
	A	18.2	1.988858	9.150981	-0.04	/	/
Independence Measure (score)	A	98.4	5.834762	16.86444	/		
	B	110.1	5.933895	18.55442	-0.1189	0.6	0.6
	A	113.8	9.919677	11.47215	-0.03361		
	C	114.8	5.266245	21.79921	**-0.00879**	0	0
	A	108.4	2.633122	41.16786	**0.055749**	/	/
The Barthel Index (score)	A	63.5	7.472171	8.4982	/		
	B	78.5	7.090682	11.07087	**-0.23622**	**0.7**	**0.7**
	A	71	18.07392	3.928312	**0.095541**		
	C	77.5	7.905694	9.803061	**-0.09155**	0	0
	A	71.5	2.415229	29.60381	**0.077419**	/	/

PND – percentage of non-overlapping data; PEM – percentage of data points exceeding the median.

Discussion

The results of this study emphasize three important facts: active collaboration between priests and medical workers is possible in the clinical setting and gives results; patient's anxiety and depression could be significantly diminished with pastoral care and religious support, and it is possible to train medical workers to provide religious support to religious patients. The patient's psychological status was improved with pastoral care and religious support. The patient was a highly religious person and these results could be expected. In medical sense, this religious-spiritual activity was important but nevertheless an additional clinical treatment. We established some improvement of the patient's functional capability during the treatment with religious support and pastoral care, as well, but these effects can not be explained by pastoral care and religious support because parameters of functional capability during periods of the basic treatment were unstable.

This case report could have both professional and practical importance.

We live in the era of technocratic medicine. It seems that a patient is an instrument today, and not the aim [31]. Jaspers diagnosed a disease of modern man yet one hundred years ago. This diagnosis has four words: hopelessness, purposelessness, loneliness and alienation [32]. Yet Heidegger claimed that losing of religion is one of the manifestations of the scientific-technical attitude to life [32]. A religious patient does not live without God. Physicians here mainly take care about a patient's body. In our profession today, with a little exception of psychiatric medicine, a patient's soul and spirit are completely in the background. Good medical workers, whether they are religious persons or not, can and should lead a patient's soul into recovery. Of course, they cannot do a priest's job, but priests and medical workers should help each other and should work together in a clinical setting

(Figure 2). This opinion should not be understood as returning to creationism: this is our obligation towards the sick and disabled believers. This is particularly important for older religious patients. It is valuable here to cite Professor Jerotić [33], who is the main authority in Serbian religious medicine. He said, ten years ago, that it is not possible to establish the state of religiosity of Serbian old people after decades of atheistic, even God-exterminating, propaganda. Professor Jerotić suggested a close cooperation between priests and physicians, especially regarding old religious patients in the hospital enviroment.

This is certainly important. However, humanism and religion differ regarding their motives [2] and "humanism" is not worth much to a religious person.

Economical factors today are more frequently the main limiting factors in psychotherapy of patients with osteoarthritis. Psychotherapists are the front line in the struggle against anxiety and depression, but their work is too expensive. Our experience shows that religious medical workers, trained by the military priest, could be good educators and spiritual advisers to the religious patient with a severe form of osteoarthritis. The psychological status of our patient was improved, in spite of the fact that pastoral care and religious support did not influence the pain phenomenon and life satisfaction. This is another proof that pain, viewed separately, must not be the main factor of anxiety and depression in patients with osteoarthritis.

In the available literature we found no similar treatment protocol which links religion and medicine using the single-case experimental design. On the other hand, there are many qualitative and quantitative studies on this topic the results of which are very interesting. Religious patients wish a spiritual contact with their physicians and are hoping for a mutual prayer [7]. Faith in secular societies is not completely denied. A study, carried out in Germany, showed that 56% of 576 patients with chronic pain believed in guardian angels [34]. Closs et al. [35] conclude that awareness of a connection between religion and chronic pain could help medical workers to communicate better with religious patients. Reynolds [36] considers that religious communities must change their attitude toward the disabled in terms of including persons with handicap in organized religion life more successfully. Patients should be actively included in the process of clinical deciding [37]. Some physicians in Russia are acquainted with the importance and the range of religious medicine [3, 5, 17, 18]. In any case, the matter in Serbia is different. Serbian society is a secular society where most medical workers are not aware religious patients and their religious needs. Religious medical workers could help religious patients if these patients were included in the process of clinical deciding.

Medicine in the future is the medicine of longevity [38]. This is particularly important for the rehabilitation medicine which is mostly the medicine of old persons and handicapped persons. However, there is no a unified attitude in the world, neither in the professional, nor in the organizational sense, regarding the religious support for religious rehabilitation patients. For example, old handicapped people do not consider that interdisciplinary home care, which possibly includes the religious support, is a better option than the common home care [39]. On the other hand, occupational therapists, as important members of the rehabilitation team, think that religious-spiritual education is necessary for their professional life and successful practice [13]. There is not a common attitude regarding the role of religious authorities in the rehabilitation team. According to Latella [40], a chaplain is an obligatory member of the rehabilitation team. On the contrary, Turk et al. [41] have also listed all members of the rehabilitation team, but have not mentioned any religious authority, not even the chaplain. When religious-spiritual support of religious rehabilitation patients is in question, there is no unity in the western rehabilitation world. Love is love if it justifies the sense of love by deeds [42]. There is little love in modern medicine. A religious anamnesis does not exist in the Serbian patient's history. How then we find a way to a religious heart?

Today it is not possible to link religion and medicine in scientific sense without a precise research methodology. A pioneer in the field of medical-theological researches in the western world, Professor Harold G. Koenig, emphasizes the necessity for serious training of researches in this scientific area [1]. Serious studies in this field commonly have large samples of patients and use a complex research methodology. These studies were projected by multidisciplinary teams of researches [43]. Randomised controlled trial is the most powerful methodology for checking the effectiveness of some kind of medical treatment. Nevertheless, some problems related to scientific methodology and the connecting of research results with practical issues in rehabilitation medicine are observed. Old people, especially aged 80 and above, are almost excluded from medical researches [44]. Most medical decisions in daily practice are not established on clear evidence-based medicine [45]. In projecting our treatment protocol a question arose: Which kind of methodology should be used to check the efficiency of the recommended religious and spiritual programs [46]? We opted for the single-system or single-case experimental design because an important element of evidenced-based rehabilitation is the tendency of medical experience originating from individual patients [23].

There are three main methodological characteristics of the single-system experimental design: studying a single person; repetition of measuring, and sequential application and withdrawal of intervention [23]. This design is only seemingly plain, actually this is a very complex research methodology. It implies a strong precision in research work and caution in statistical analyses and interpretation of results. Multiple treatment-reversal design and alternating treatment design (A-B-A-C-A) were used in different common medical and rehabilitation researches, from issues related to traumatic brain injuries and electroanalgesia to the problems in orthotic rehabilitation [21, 25]. So far, in the Serbian rehabilitation science this design has not been used. Commonly, analysis and interpretation of results of this kind of design imply a visual inspection of figures and entering data into tables according to the phases of experiment [23]. We made a step forward. The

quantitative analysis of our results was performed by the nonparametric statistics. This analysis helped us to better recognize the effects of pastoral care and religious support in the patient with a severe form of osteoarthritis.

Treatment effects presented in this case report have to be confirmed in larger studies. Limitations and shortcomings of our treatment protocol are related to the measuring scales and imperfections of the single-system design itself. Namely, the patient's religion was measured by the DUREL index. This was not the best choice because the DUREL was made for the large epidemiological studies. Besides, ethic dilemmas, problems with internal validity, the low power of generalization and complexity of statistical analyses are well-known defects of the single-system experimental design [25, 47]. All these factors limit the worth of this study.

Conclusion

The effects of pastoral care and religious support in the old highly religious patient with a severe form of osteoarthritis were good. The patient's anxiety was moderately to significantly reduced by pastoral care and religious support. The patient's depression was diminished by pastoral care.

Acknowledgements

We thank Branka Milošević, physiotherapist, for active participation in this study.

The research is supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant no. 173001).

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Received on August 25, 2015.
Accepted on October 6, 2015.
Online First April, 2016.

CASE REPORT

UDC: 617.55-053.2:616.8-053.2
DOI: 10.2298/VSP150911015M

Transverse colon *volvulus* in neurologicaly imparied patient as an emergency surgical condition – A case report

Volvulus transverzalnog kolona kao hitno hirurško stanje kod neurološki izmenjenog bolesnika

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Abstract

Introduction. Transverse colon *volvulus* is an uncommon cause of bowel obstruction in general. Predisposing factors are mental retardation, dysmotility disorders, chronic constipation and congenital megacolon. **Case report.** We presented transverse colon *volvulus* in a 16-year-old boy with cerebral palsy. Chronic constipation in neurologicaly impaired patient was a risk factor predisposing to *volvulus*. The patient was admitted to the hospital with enormous abdominal distension and acute respiratory insufficiency. A boy was emergently taken to the operating room for exploratory laparotomy. During the surgery, a 360º clockwise *volvulus* of the transverse colon was found. After reduction of *volvulus*, an enormous transverse colon was resected and colostomy was formed. In the postoperative period, despite the good functioning of stoma and intraabdominal normotension, numerous and long lasting respiratory problems developed. The patient was discharged from our institution after 8 months. **Conclusion.** Though very rare in pediatric group, the possibility of a transverse colon *volvulus* must be considered in the differential diagnosis of acute large bowel obstruction.

Key words:
intestinal volvulus; colon; cerebral, palsy; comorbidity; digestive system surgical procedures; colostomy; postoperative complications; bronchopneumonia.

Apstrakt

Uvod. *Volvulus* transverzalnog kolona je redak uzrok opstrukcije creva. Predisponirajući faktori su mentalna retardacija, poremećaji motiliteta, hronična konstipacija i kongenitalni megakolon. **Prikaz bolesnika.** Prikazali smo *volvulus* transverzalnog kolona kod dečaka sa cerebralnom paralizom starog 16 godina. Hronična konstipacija predstavljala je faktor rizika kod neurološki izmenjenog deteta i dovela je do *volvulus*-a. Bolesnik je primljen sa velikom distenzijom trbuha i akutnom respiratornom insuficijencijom. Hitno je odveden u operacionu salu radi eksplorativne laparotomije. Intraoperativno, nađen je *volvulus* transverzalnog kolona od 360º u pravcu kazaljki na satu. Nakon redukcije *volvulus*-a, jako uvećan transverzalni kolon reseciran je i otvorena je kolostoma. Postoperativno, bez obzira na dobro funkcionisanje stome i normalan intraabdominalni pritisak, razvili su se brojni i dugotrajni respiratorni problemi. Bolesnik je otpušten iz naše ustanove nakon 8 meseci. **Zaključak.** Iako je veoma redak u pedijatrijskoj populaciji, u diferencijalnoj dijagnozi akutne opstrukcije debelog creva mora se uzeti u obzir i mogućnost *volvulus*-a transverzalnog kolona.

Ključne reči:
creva, volvulus; kolon; paraliza, cerebralna; komorbiditet; hirurgija digestivnog sistema, procedure; kolostomija; postoperativne komplikacije; bronhopneumonija.

Introduction

Transverse colon *volvulus* is an uncommon cause of bowel obstruction in general [1]. Predisposing factors are: mental retardation, dysmotility disorders, chronic constipation and congenital megacolon [2]. Despite the known predisposing factors, extremely rare occurrence in pediatric population is the reason why this condition is diagnosed very often during laparotomy [3]. Contrast enema is an useful diagnostic tool, as well as computed tomography (CT) [2, 4]. Our patient had clinically subacute progressive presentation, unrecognized for a long period. At the time of admittance to our institution, his condition required emergency surgical treatment.

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Case report

A 16-year-old boy with cerebral palsy presented with extremely distended abdomen and acute respiratory insufficiency. During his life he was repeatedly hospitalized for chronic constipation. At the time of admission to the Paediatric Intensive Care Unit (PICU), beside clinical signs of severe cerebral palsy, the patient was subfebrile, anxious and diaphoretic and had severe abdominal pain. He was extremely dyspnoic with oxygen saturation of 74% measured by pulse oximetry on room air. Physical examination revealed massively distended abdomen, tympanic and without bowel sounds. The abdominal wall was tender. Rectal ampulla was empty. Electrocardiography showed sinus tachycardia (162 beats/min) followed by arterial hypertension of 210/160 mmHg. Nasogastric tube inserted initially obtained 150 mL of dark-brown content. Blood - gas analysis revealed mixed metabolic and respiratory acidosis. Conditions for urgent orotracheal intubation were provided and synchronized intermittent mandatory ventilation mode of mechanical ventilation was undertaken. Plain abdominal and chest radiography showed enormously distended bowel elevating diaphragmatic cupola on both sides, causing lung compression and almost completely disabling ventilation (Figure 1).

Fig. 1 – Abdominal and chest radiography demonstrating enormously distended bowel and elevation of both hemidiaphragms.

The intraabdominal pressure was 17 mm Hg. Intraoperative findings demonstrated a rotation of the transverse colon of 360º degrees in a clockwise direction, causing a closed loop obstruction. The transverse colon was massively dilated, but ascending colon and small bowel loops were markedly distended, too (Figure 2). After mobilization and detorsion, the enlarged transverse colon was resected and double-barrel stoma was created in the left hypochondriac region. Postoperativelly, the stoma functoned well and intraabdominal pressure was normal.

On the day of operation the patient was extubated, but on the first postoperative day he was dyspnoic, gas exchange was impaired and he was intubated again. Bronchopneumonia was diagnosed, complicated by pleural effusion requiring drainage on the left side. During mechanical ventilation, the right lung was collapsed because of pneumotorax due to airway obstruction caused by mucus, resolved by right pleural drainage. We decided to do tracheostomy and tracheostomy cannula setting was taken on. Weaning from mechanical ventilation was difficult. After 130 days the patient was discharged from the PICU 8 months following admission.

Fig. 2 – Transverse colon *volvulus* – intraoperative image of large bowel dilatation.

Discussion

Volvulus of transverse colon is a rare condition, especially in children [2, 3, 5, 6]. About 30–50% of children with transverse colon *volvulus* appear to have the history of chronic constipation, which is either idiopathic or secondary to congenital megacolon and neurological diseases [2, 3, 7, 8]. Constipation can promote elongation and chronic redundancy of the transverse colon [2]. Colon becomes more mobile, thus it can easily twist upon itself. The current case also was associated with cerebral palsy and had the history of chronic constipation. Our patient presented with subacute transverse colon *volvulus*, but delayed diagnosis and treatment resulted in progressing to the acute fulminating type with bowel infarction.

It is a great challenge to diagnose transverse colon *volvulus* [2]. In a patient with clinical deterioration, radiography may be the only, although insufficiently sensitive diagnostic procedure [2, 4]. Diagnosis is made by barium enema or CT [4]. In the presented patient there was suspicion of intestinal gangrene and ventilation was almost impossible because of enormous abdominal distension. Intra-abdominal hypertension threatened to develop into abdominal compartment syndrome. Due to the need for emergency explorative laparotomy we decided

against performing a barium enema and other diagnostic procedures.

The definitive treatment of transverse colon *volvulus* is surgical [2]. The recommended operative procedure consists of detorsion, resection of the involved segment since it is viable and primary anastomosis or stoma creation [2]. In the presented patient, at least two groups of factors contributed to pulmonary complications. Firstly, children with cerebral palsy, in general, suffer from a high incidence of repeated respiratory infections, restrictive lung disease, atelectasis and bronchiectasis and secondly, increased intra-abdominal pressure causes direct mechanical impairment of the lung, heart, renal and splanchnic function [9, 10]. Because of a threatening progress to multiorgan system failure, urgent surgical treatment was performed one and half an hour after the patient´s admittance at our institution.

Conclusion

Though very rare in the pediatric group, the possibility of a transverse colon *volvulus* must be considered in the differential diagnosis of acute large bowel obstruction. Neurologically, impaired children, apart from chronic constipation, have many associated problems that make decision for operation difficult, but any operation delay leads to high morbidity and mortality. Early surgical intervention consisting of bowel resection with primary anastomosis or with stoma, is the treatment of choice.

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Received on September 11, 2015.
Accepted on October 19, 2015.
Online First February, 2016.

C A S E R E P O R T

UDC: 616.136/.137-089:616.61-089.843
DOI: 10.2298/VSP140609139T

Aortobifemoral reconstruction and renal transplantation in a patient with abdominal aortic aneurysm and occlusion of iliac arteries: A case report

Aortobifemoralna rekonstrukcija i transplantacija bubrega kod bolesnika sa aneurizmom abdominalne aorte i okluzijom ilijačnih arterija

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Abstract

Introduction. Aortoiliac occlusive disease and abdominal aortic aneurysm in patients with renal insufficiency on hemodialysis can significantly influence the success of renal transplantation. In the recent past, advanced atherosclerosis was considered as contraindication for renal transplantation. Complicated creation of vascular anastomoses and progression of occlusive or aneurysmal disease were the main reasons. **Case report.** We presented a 52-year-old man with a 5-year history of end-stage renal disease on haemodialysis. The patient was previously excluded from renal transplantation program because of severe aortoiliac atherosclerosis and abdominal aortic aneurysm. Resection of abdominal aortic aneurysm with occlusion of the iliac arteries and reconstruction with aortobifemoral synthetic grafts was performed and followed by cadaveric renal transplantation. **Conclusion.** Advanced atherosclerotic disease in aortoiliac segment requires elective vascular surgical reconstruction, as part of preparation for renal transplantation in patients with end-stage renal disease.

Key words:
atherosclerosis; iliac artery; aortic aneurysm, abdominal; renal dialysis; comorbidity; vascular surgical procedures; kidney transplantation.

Apstrakt

Uvod. Okluzivna aortoilijačna bolest i aneurizma abdominalne aorte kod bubrežnih bolesnika na hemodijalizi mogu značajno uticati na uspešnost transplantacije bubrega. Ne tako davno, uznapredovala ateroskleroza bila je kontraindikacija za transplantaciju bubrega, jer značajno otežava kreiranje vaskularne anastomoze, a okluzivna, odnosno aneurizmatska bolest nastavlja tok. **Prikaz bolesnika.** Bolesnik, star 52 godine, sa petogodišnjom istorijom terminalne bubrežne bolesti na hemodijalizi, bio je prethodno odbijen za transplantaciju bubrega zbog teške aortoilijačne ateroskleroze i aneurizme abdominalne aorte. To je prvi slučaj vaskularne resekcije aneurizme abdominalne aorte udružene sa aortoilijačnom okluzivnom bolešću u našoj zemlji i rekonstrukcije sa aortobifemoralnim sintetskim graftom koja je prethodila kadaveričnoj transplantaciji bubrega. **Zaključak.** Uznapredovala aterosklerotska bolest aortoilijačnog segmenta zahteva elektivnu vaskularnu hirušku rekonstrukciju koja bi trebalo da prethodi transplantaciji bubrega kod bolesnika sa terminalnom bubrežnom insuficijencijom.

Ključne reči:
ateroskleroza; a. iliaca; aorta, abdominalna, aneurizma; hemodijaliza; komorbiditet; hirurgija, vaskularna, procedure; transplantacija bubrega.

Introduction

Coexistence of atherosclerosis in aortoiliac segment and renal insufficiency is not rare and arterial occlusion and stenosis can complicate renal transplantation. In the past, aneurismal lesions localized in aortoiliac segment and the use of synthetic grafts were contraindicated in transplant surgery. In recent years, large number of patients on haemodialysis (HD) and treatment cost, urged for change of inclusion criteria for renal transplantation including the presence of aortoi-

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liac aneurysms and occlusive disease. In the past few years, there were few articles on the successful kidney transplant after aortoiliac reconstruction [1–3].

Case report

A male 52-years-old patient (85 kg, 185 cm), with end-stage renal disease (ESRD), five years on HD (three times a week), with no diuresis and the serum creatinine level of 1,163 mmol/L, was rejected for renal transplantation due to the presence of severe aortoiliac atherosclerosis. Abdominal aortic aneurysm (AAA) 4.5 cm in diameter with occlusion of both iliac arteries was verified on multisliced computed tomography (MSCT) (Figure 1). The patient had simptoms of intermitent claudications in legs at the walking distance of 100 m.

Resection of AAA and aortobifemoral reconstruction with Dacron bifurcated prosthesis was performed (Figure 2). The uneventful postoperative period with symptoms withdrawal was followed by pretransplant reexamination. Abdominal ultrasonography and intravenous urography were normal.

Three months later, cadaveric renal transplantation was performed. A donor was A positive, HLA compatibility 3/6 and negative "cross-match" using complement dependant cytotoxicity (CDC) were recorded. The procedure was performed through the right Gibson incision. The left kidney proccured from cadaveric donor was inserted in the right iliac fosse. The renal artery was anastomosed with the right branch of bifurcated graft in "end-to-side" fashion with continious 6/0 polypropilene (Figure 3). Unfortunately, the renal vein was transected during procurement and reconstruction was done with a cadaveric caval vein (Figure 4). Disproportion between the caval vein and the origin of renal vein was solved with caval vein preparation using spiral sewing and lumen reduction. One end of the new vein conduit was connected with the origin of renal vein on the kidney in "end-to-end" fashion anastomosis. The opposite end of the vein conduit was connected with the iliac vein in "end-to-side" fashion anastomosis (Figure 5). Antireflux ureterocystoneostomias (UCN) with J-J stent were made.

Diuresis started after 24 h with ultrasound color Doppler exam verification of good perfusion of transplanted kidney and good flow through arterial and venous anastomo-

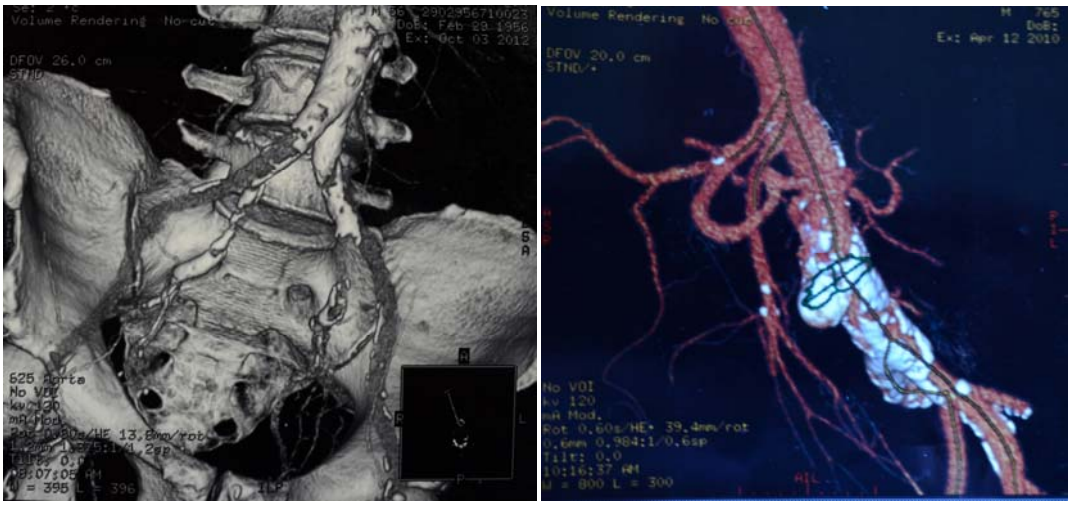

Fig. 1 – Multislice computed tomography (MSCT) angiography preoperatively.

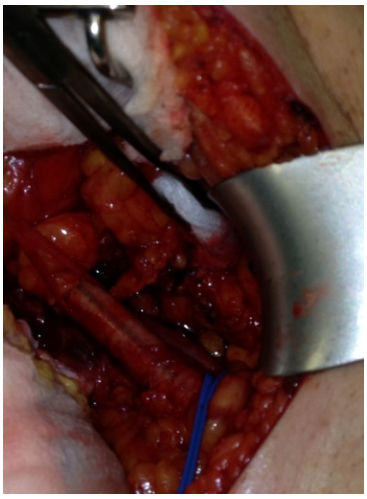

Fig. 2 – Previous reconstruction with a Dacron bifurcated prosthesis.

Fig. 3 – Renal artery anastomosed with the right branch of bifurcated graft in the "end-to-side" fashion with continuous 6/0 polypropilene.

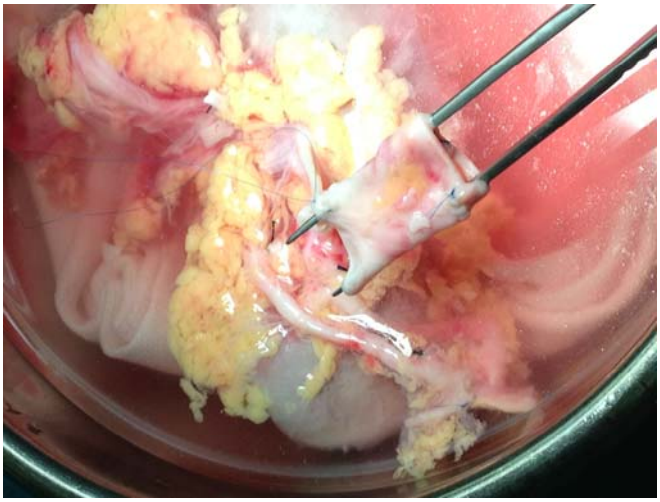

Fig. 4 – Reconstruction with a cadaveric caval vein.

Fig. 5 – Final picture – spiral sewing and lumen reduction.

sis. On the second postoperative day diuresis was 11 L *per* 24 h and creatinine level decreased to 350 mmol/L. Abdominal ultrasonography excluded hydronephrosis, perirenal or retroperitoneal collections. Anti-thymocyte globuline (ATG), methyprednisolone, mycophenolat mofetil and tacrolimus were used as immunosuppressive therapy. The patient was discharged on the 18th postoperative day after the uneventful postoperative period. On the discharge day 5 L of diuresis and creatinine 95 mmol/L were recorded. One year after the transplantation, kidney function was satisfied, with diuresis of 3 L *per* 24 h, creatinin level of 99 mmol/L and good perfusion of kidney and flow through anastomoses verified by color Doppler exam.

Discussion

The first case of anastomosis of the renal artery and the graft was described by Sterioff et al. [1] in 1974 and repeated by Ahlmén et al. [2]. The authors did not notice any complications or technical difficulties in implementing the same [1, 3]. The first simultaneous aortoiliac reconstruction and kidney transplantation was published by Cerili et al. [3] in 1977.

In modern transplant surgery it is necessary to extend criteria for renal transplantation because a large number of patients with ESRD on HD. Numerous comorbidities, including diabetes, hypertension, and severe atherosclerotic changes on all arterial vessels, contribute to increased risks for transplantation procedures.

A certain number of these patients, especially patients with aortoiliac segment atherosclerotic changes, require vascular procedures before or during kidney transplantation [4]. Based on literature data 16.7% vascular grafts were lost in the first month after reconstruction [5]. Surgical correction of aortoiliac pathology may be performed simultaneously with kidney transplantation with acceptable outcome in centers with experienced vascular surgeons [5, 6]. If these procedures must be separated it is better to perform vascular reconstruction before transplantation. On the other side, based on their results, some authors suggest separate procedures approach, as simultaneously preformed procedures are connected with higher risk of infection [7].

Matia et al. [8] suggest safe use of arterial allografts in the treatment of arterial occlusive disease or AAA simultaneously with renal transplantation. Moreover, endovascular stenting can be performed in the presence of extensive atherosclerosis before renal transplantation [9].

Numerous papers are dealing with a reconstruction works of AAA and aortoiliac segment after kidney transplantation. One of the problems is a prolonged cold ischemia time, which may jeopardize the renal transplant during simultaneous procedures.

Adequte pretransplant examination and preparation is vital for the succesfull performance of complicated vascular procedures after kidney transplantation [10–13]. The key question is whether vascular reconstructive intervention should be done preoperatively or simultaneously with renal transplantations. It is suggested that renal transplant should be performed at least 6-8 weeks after vascular intervention [10, 11].

With wider inclusion criteria for renal transplants, MSCT angiography is a routine diagnostic method in pretransplantation period, recommended in the Guidelines on Renal Transplantation from the European Association of Urology for peripheral artery disease, and cerebral occlusive vascular disease [14].

There are several surgical techniques in renal transplantation. The most frequently used technique is renal anastomosis with external iliac artery. In some cases, anastomosis with hypogastric arterery is performed. Authors of this article prefer this type of anastomosis because of good results in long period [15]. Several cases of hypogastric artery endarterectomy were performed in renal transplant patients during 17 years experience of renal transplantation in our hospital. In certain cases, CT scan interpretation was misleading and resulted in renal transplantation performance in severly changed atherosclerotic vessels. Advantages of the technique using anastomosis with the hypogastric artery are better positioning of the organ in the iliac bed and a low incidence of stenosis in anastomisos. The later, can be

explained by the similar diameter of hypogastric and renal artery [15]. The main disadvantage is wider dissection of the pelvis due to the position of hipogastric arteries.

After this successful case of aortobifemoral reconstruction and renal transplantation, we changed the protocol for renal transplant patients with inclusion of recipients with severe atherosclerotic disease. From that period, aortobifemoral bypass was performed in three pretransplant patients and they were on the waiting list.

Based on literature search, papers are mostly concentrated on aneurysm surgery after renal transplantation and a small amount of data are presented for reconstruction before renal transplantation. There is no consensus on the size of the aortic aneurysm that should be treated before transplantation. Based on our experience, all patients with AAA were rejected for renal transplant, and so far this is the first case of this reconstruction. Although AAA size of 4 cm is not an indication for aortic reconstruction, it needs to be solved as it presents contraindication for organ transplantation. Hypothetically, if aneurysm reaches diameter necessary for the reconstruction, renal transplantation will be technically difficult to perform with a high perioperative risk.

Occlusions of the iliac arteries are a strong contraindication for renal transplantation. Different degrees of iliac arteries stenosis represent a relative contraindication. Abdominal aneurysm and iliac artery stenosis in this patient did not require reconstruction *per se*, but as preparation for renal transplantation aortobifemoral reconstruction was absolutely indicated.

Conclusion

Vascular reconstruction of the aortoiliac segment with synthetic graft is the first step in preparation patients for renal transplantation. Use of synthetic graft is not contraindication for kidney transplantation. Patients with extended indications, including those with severe atherosclerosis are accepted on the waiting list.

Adequate preparation of patients with extended criteria for transplantation with severe aortoiliac disease will improve results of renal transplantation and consequently, decrease the number of patients on HD. However, multicentric studies and prolonged ”follow-ups” in the postransplantation period are needed for a definitive conclusion.

Competing interests

The authors declare that this study was not financially supported by any funds and that there are no conflicts of interests regarding the content of this article

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Received on June 9, 2014.
Revised on June 3, 2015.
Accepted on August 27, 2015.
Online First June, 2016.

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General review papers 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 as reserved for subtitles. Original articles, reviews, meta-analyses and articles from medical history should not exceed 16 pages; current topics 10; case reports 6; short communications 5; letters to the editor and comments 3, and reports on scientific meetings and book reviews 2.

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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, **Microsoft Office** (**Excel**, **Word Graph**). The use of colors and shading in graphs should be avoided.

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Preparation of manuscript

Parts of the manuscript are: **Title page; Abstract with Key words; Text; Acknowledgements** (to the authors' desire), **References**, **Enclosures**.

1. *Title page*

a) The title should be concise but informative, while subheadings should be avoided;

b) Full names of the authors signed as follows: ***, †, ‡, §, ||, ¶, **, ††, ...** .

c) Exact names and places of department(s) and institution(s) of affiliation where the studies were performed, city and the state for any authors, clearly marked by standard footnote signs;

d) Conclusion could be a separate chapter or the last paragraph of the discussion;

e) Data on the corresponding author.

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The second page should carry a structured abstract (250-300 words for original articles and meta-analyses) with the title of the article. In short, clear sentences the authors should write the **Background**/**Aim**, major procedures – **Methods** (choice of subjects or laboratory animals; methods for observation and analysis), the obtained findings – **Results** (concrete data and their statistical significance), and the **Conclusion**. It should emphasize new and important aspects of the study or observations. A structured abstract for case reports (up to 250 words) should contain subtitles **Introduction, Case report, Conclusion**). Below the abstract **Key words** should provide 3–10 key words or short phrases that indicate the topic of the article.

3. *Text*

The text of the articles includes: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

Introduction. After the introductory notes, the aim of the article should be stated in brief (the reasons for the study or observation), only significant data from the literature, but not extensive, detailed consideratuion of the subject, nor data or conclusions from the work being reported.

Methods. The selection of study or experimental subjects (patients or experimental animals, including controls) should be clearly described. The methods, apparatus (manufacturer's name and address in parentheses), and procedures should be identified in sufficient detail to allow other workers to reproduce the results. Also, 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 approval of the Ethnics Committee for the tests in humans and animals.

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 significant 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.

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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

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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 pripremaju se sa proredom 1,5 na posebnom listu. 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. 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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