Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
Glavni i odgovorni urednik: prof. dr GORDANA DEVEČERSKI

MEDICINSKI PREGLED

ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
PRVI BROJ JE ŠTAMPAN 1948. GODINE.

MEDICINSKI PREGLED izlazi dvomesečno (šest dvobroja godišnje), u tiražu od 1000 primeraka. Akontacija pretplate za pojedince sa teritorije Srbije za 2013. godinu iznosi 3.000,00 dinara (sa uračunatim PDV-om), a 4.000,00 dinara za pojedince van teritorije Srbije, a za ustanove 8.000,00 dinara (uz dodavanje PDV-a). Uplate se vrše na račun broj 340-1861-70 ili 115-13858-06, s naznakom „Dodatna članarina za Medicinski pregled".

**Rukopisi se dostavljaju sekretaru Redakcijskog odbora časopisa »Medicinski pregled« na adresu:
Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9,
Tel. 021/528-767; Tel/Fax. 021/521-096;
E-mail: dlv@neobee.net; Web: www.dlv.org.rs**

Štamparija: Uprava za zajedničke poslove pokrajinskih organa - Odsek za poslove štamparije

Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9,
Editor-in-Chief Prof GORDANA DEVECERSKI, MD, PhD

MEDICAL REVIEW

JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA

THE FIRST ISSUE WAS PUBLISHED IN 1948

UDK and descriptor prepared by: the Library of the Faculty of Medicine, Novi Sad

MEDICAL REVIEW is published two-monthly (six double issues per a year) in the circulation of 1000 copies. Advance payment for individuals from the territory of Serbia for the year 2013 is 3,000.00 dinars (the VAT being calculated in) and 4,000.00 dinars for the individuals outside the territory of Serbia, and 8,000.00 dinars (+ the VAT) for the institutions. The payments are to be made to the account number 340-1861-70 or 115-13858-06, with the remark "Additional membership fee for the Medical Review".

The manuscripts are to be submitted to the secretary of the Editorial Board of the journal "Medical Review" to the following address: Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9, Tel. 021/528-767; Tel/Fax. 021/521-096; E-mail: dlv@neobee.net; Web: www.dlv.org.rs

Printed by: Department for Joint Affairs of Provincial Authorities - Sector for Printing

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad Vase Stajića 9 Srbija

Med Pregl 2013; LXVI (5-6): 205-276. Novi Sad: maj-juni.

SADRŽAJ

ORIGINALNI NAUČNI RADOVI

PREGLEDNI ČLANCI

STRUČNI ČLANCI

PRIKAZI SLUČAJEVA

SEMINAR ZA LEKARE U PRAKSI

ISTORIJA MEDICINE

M E D I C A L R E V I E W
JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
Novi Sad *Vase Stajića 9* *Serbia*

Med Pregl 2013; LXVI (5-6): 205-276. Novi Sad: May-June.

CONTENTS

SUTENT® kapsule
sunitinib malat

TAZOCIN® IV
piperacilin/tazobaktam

Tygacil®
tigeciklin

ZYVOX® IV/Oral
(linezolid)

AROMASIN®
eksemestan tablete

EFECTIN® ER
Venlaflaksin

NEURONTIN®
gabapentin

Xanax®
alprazolam

zoloft®
(sertralin)

ZELDOX®
(ziprasidon)

Detrusitol®
tolterodin tartrat

SERMION® 30
nicergolin

VIAGRA®
(sildenafil citrat)

Genotropin®
somatropin (rbe)

Aricept® Evess
donepezil

Aricept®
donepezil

CELEBREX®
(CELEKOKSIB)

Fragmin®
dalteparin natrijum

Sortis®
atorvastatin

NORVASC®
amlodipin besilat

inspra®
eplerenon

Pfizer

IV/PO
VFEND®
vorikonazol

Conbriza

LYRICA®
PREGABALIN

Xalatan®
latanoprost

Xalacom®
latanoprost/timolol maleate

Prevenar 13
Pneumokokna polisaharidna konjugovana vakcina, adsorbovana

VIBRAMYCIN® D
doksiciklin

Radimo zajedno za zdraviji svet!

Pfizer H.C.P. Corporation, Predstavništvo Beograd
Trešnjinog cveta 1/VI, 11070 Novi Beograd
Tel. 011/ 3630 000 • Faks 011/ 3630 033

CEL-10-13

ORIGINALNI NAUČNI RADOVI
ORIGINAL STUDIES

Klinički centar Vojvodine, Novi Sad
Klinika za infektivne bolesti
Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad[1]
Poljoprivredni fakultet, Departman za veterinu, Novi Sad[2]

Originalni naučni rad
Original study
UDK 616.981.57-085:615.246
DOI: 10.2298/MPNS1306209D

ISHOD LEČENJA ENTEROKOLITISA KOJI IZAZIVA *CLOSTRIDIUM DIFFICILE* PRIMENOM ANTIBIOTIKA UZ PROBIOTIK

OUTCOMES OF CLOSTRIDIUM DIFFICILE ENTEROCOLITIS AFTER ADMINISTRATION OF ANTIBIOTICS ALONG WITH PROBIOTIC SUPPLEMENT

Radoslava DODER[1], Nadica KOVAČEVIĆ[1], Dragica MUNĆAN[1], Aleksandar POTKONJAK[2], Branka TOMAŠEV[1] i Maja RUŽIĆ[1]

Sažetak

Uvod. Enterokolitis koji izaziva *Clostridium difficile* je potencijalno fatalna bolest sa porastom incidencije u bolničkim uslovima. Terapijski pristup u lečenju enterokolitisa predstavlja značajan problem zbog skolnosti ka relapsu i reinfekciji. Cilj rada bio je ispitivanje faktora koji utiču na pojavu enterokolitisa koji izaziva *Clostridium difficile* i ishoda enetrokolitisa nakon primene standardne antimikrobne terapije u kombinaciji sa probiotikom. **Materijal i metode.** Sprovedeno je nekomparativno, opservaciono, prospektivno ispitivanje na 42 bolesnika (22 muškarca i 20 žena) koji su lečeni na Klinici za infektivne bolesti u Novom Sadu u periodu od oktobra 2011. do aprila 2012. godine pod dijagnozom enterokolitisa koji je izazvao *Clostridium difficile*. **Rezultati.** Nastanak bolesti bio je češći kod starijih bolesnika (78,6% bilo je starije od 60 godina), kod prethodne upotrebe antimikrobne terapije (83,8%), prethodne hospitalizacije (83,3%) i komorbiditeta (85,7%). Kliničkom slikom su dominirale blaže do umerene tegobe. Na primenjenu standardnu antibiotsku terapiju (metronidazol, vankomicin) uz probiotik tokom 10 dana, broj i izgled stolica, osećaj bola u trbuhu i osećaj nadutosti pokazali su signifikantno povoljan klinički odgovor. Statistički značajne promene u laboratorijskim parametrima (broj leukocita, C-reaktivni protein) zabeležene su 5. dana bolesti. Rekurentna infekcija, nakon uspešno spovedene terapije, registrovana je kod 9,5% bolesnika. **Zaključak.** Primena probiotskih bakterija *Lactobacillus acidophilus* Rosell-52*, Lactobacillus rhamnosus* Rosell-11 *i Bifidobacterium longum* Rosell-175 u kombinaciji sa standardnom antibiotskom terapijom kod bolesnika sa entrokolitisom izazvanim *Clostridium*-om *difficile* imala je povoljan učinak na težinu kliničke slike i normalizaciju laboratorijskih parametara. Rekurentna infekcija nakon uspešno spovedene terapije zabeležena je kod manjeg broja bolesnika nego što se navodi u literaturi.

Ključne reči: Enterokolitis; Clostridium difficile; Probiotici; Ishod tretmana; Antimikrobni lekovi; Muško; žensko; Rekurentnost; Kombinovana terapija

Summary

Introduction. *Clostridium difficile* enterocolitis is a potentially fatal disease showing increasing incidence in hospital environment. Therapeutic approach in the management of *Clostridium difficile* enterocolitis is highly complex, particularly because of its tendency to relapse and reinfection. The study was aimed at investigating the factors influencing the development of *Clostridium difficile* enterocolitis and outcomes of enterocolitis after administration of standard antimicrobial therapy combined with probiotic supplement. **Material and Methods.** A *non-comparative prospective observational study* encompassed 42 patients (22 males and 20 females) diagnosed with *Clostridium difficile* enterocolitis and treated at the Department of Infectious Diseases in Novi Sad in the period October 2011 – April 2012. **Results.** Higher incidence of the disease was found in elderly patients (78.6% of them were over 60 years of age), after antimicrobial therapy (83.8%), after hospitalization (83.3%) and in comorbid conditions (85.7%). The clinical picture revealed predominantly mild to moderate symptoms. A good clinical response to the standard antimicrobial therapy (metronidazole, vancomycin) combined with probiotic given for 10 days was observed in all patients, and the improvement in parameters such as the number and appearance of stools, abdominal distension and pain was recorded. Statistically significant changes in laboratory parameters (leukocyte count, C-reactive protein level) were recorded on day 5 after the onset of disease. Recurrent infection after successful therapy was observed in 9.5% of the patients. **Conclusion.** Administration of probiotic bacteria *Lactobacillus acidophilus* Rosell-52*, Lactobacillus rhamnosus* Rosell-11 and *Bifidobacterium longum* Rosell-175 alongside the standard antimicrobial therapy in the patients with *Clostridium difficile* enterocolitis demonstrated positive effects on the severity or clinical picture and normalization of laboratory parameters. Recurrent infection after successful therapy was observed in only a small number of patients as compared with the literature data.

Key words: Enterocolitis; Clostridium difficile; Probiotics; Treatment Outcome; Anti-Infective Agents; Male; Female; Recurrence; Drug Therapy, Combination

Adresa autora: Prof. dr Radoslava Doder, Klinika za infektivne bolesti,
21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: radoslavadoder@yahoo.com

Skraćenice

CD − *Clostridium difficile*
AB − antibiotik
CRP − C-reaktivni protein
ALT − alanin-aminotransferaza
AST − aspartat-aminotransferaza

Uvod

Infekcija koju izaziva *Clostridium difficile* može se razviti nakon kolonizacije crevnog trakta sporama koje su unete ingestijom. Germinacijom iz spora nastaju vegetativne bakterijske forme, sposobne da produkuju toksine. Normalna flora sprečava kolonizaciju CD kompeticijom za nutrijente i receptorska mesta na enterocitima. Upotreba antibiotika je najvažniji faktor rizika za nastanak infekcije CD, ali veliki značaj imaju i prolongirana hospitalizacija, komorbiditet, različita imunodeficijentna stanja, stariji uzrast, inflamatorna bolest creva, skorašnji operativni zahvat, upotreba nekih lekova (antineoplastici, imunosupresivi, inhibitori protonske pumpe) ili prisustvo nazogastričnog tubusa [1−3]. Klinička simptomatologija je različita, od dijareje do po život opasnog toksičnog megakolona. Lečenje peroralnim vankomicinom (125−250 mg/6 h) ili ekonomski prihvatljivijim, a podjednako efikasnim peroralnim metronidazolom (400 mg/8 h) tokom 10 dana je standardna terapijska opcija [3]. Izbor terapijskih režima u prvoj epizodi infekcije CD zavisi od težine kliničke slike (zapažena je bolja efikasnost vankomicina u odnosu na metronidazol kod težih formi bolesti) [3,4]. Terapijski pristup u lečenju CD enterokolitisa predstavlja značajan problem zbog pojave rekurentne infekcije. Nakon prvog relapsa, 50−60% bolesnika razvija ponovljene epizode eneterokolitisa [5]. U nekoliko nedavno objavljenih studija pokazano je da upotreba *Lactobacillus* GG sprečava relaps gastroenteritisa nakon upotrebe antibiotika [5−7].

Probiotici su živi mikroorganizmi koji doprinose zdravlju bolesnika poboljšavanjem mikrobiološke ravnoteže gastrointestinalnog trakta. Mogu sadržati jedan soj bakterija ili njihovu kombinaciju (*Lactobacillus, Bifidobacterium i Saccharomyces)* [8−11].

Cilj našeg rada bio je ispitivanje faktora koji utiču na pojavu enterokolitisa čiji je uzrok *Clostridium difficile* i ishoda enetrokolitisa nakon primene standardne antimikrobne terapije u kombinaciji sa probiotikom.

Materijal i metode

Ispitivanjem su obuhvaćena 42 bolesnika, uzrasta od 30 do 83 godine, koji su lečeni na Klinici za infektivne bolesti, Kliničkog centra Vojvodine u Novom Sadu, u periodu od oktobra 2011. do kraja aprila 2012. godine, pod dijagnozom enterokolitisa čiji je uzrok CD. Kriterijumi za uključivanje u studiju bili su: prisutnost uobičajenih simptoma i znakova enterokolitisa: učestale vodenaste stolice (≥ 3/24 h, tokom 2 dana), povišena temperatura, bolovi, grčevi i nadutost u trbuhu, uz pozitivan nalaz stolice na CD. ELISA test na prisustvo toksina A/B CD iz uzorka tečne stolice rađen je u Institutu za javno zdravlje Vojvodine, Odsek za mikrobiologiju, u Novom Sadu. Kod bolesnika su analizirani sledeći parametri: pol i uzrast, podatak o prethodnoj hospitalizaciji i dužina hospitalizacije; prethodna upotreba antimikrobne terapije, vrsta antibiotika i dužina uzimanja; postojanje pratećih hroničnih bolesti, klinički odgovor na primenjenu terapiju kao i pojava relapsa, u periodu od otpusta iz bolnice, do kraja 2012. godine. Uobičajeni laboratorijski testovi (vrednost broja leukocita u perifernoj krvi (10^9/l), C-reaktivni potein (CRP), uree, kreatinina, ukupnih proteina, albumina, alanin-aminotransferaze (ALT) i aspartat aminotransferaze (AST) učinjeni su prvog, 5. i prema potrebi 10. dana hospitalizacije. Bolesnici su lečeni peroralnim vankomicinom ili metronidazolom tokom 10 dana, uz rehidratacionu terapiju prema potrebi i odgovarajući režim ishrane. Efikasnost primenjene terapije praćena je regresijom dijareje i simptoma entrokolitisa. Zajedno sa antibiotikom, ordiniran je i probiotik u dozi od jedne kapsule dnevno. Jedna kapsula, u trenutku pakovanja, sadržavala je najmanje 5 milijardi liofilizovanih živih probiotskih bakterija: *Lactobacillus acidophilus* Rosell-52*, Lactobacillus rhamnosus* Rosell-11 *i Bifidobacterium longum* Rosell-175.

Dijagnoza rekurentne infekcije CD postavljena je na osnovu ponovne pojave kliničkih simptoma i znakova enterokolitisa uz prisustvo toksina CD u stolici bolesnika nakon incijalne epizode i uspešno sprovedene terapije.

U radu su korišćeni parametri strandardne deskriptivne statistike (srednja vrednost, frekvencija, intervalne vrednosti (minimun, maximum), χ^2 test, t-test, p-vrednost). Statistička analiza je rađena statističkim programom SPSS. Rezultati su prikazani tabelarno i grafički.

Rezultati

U posmatranom periodu, pod dijagnozom enterokolitisa uzrokovanog CD*,* lečeno je 42 bolesnika: 22 muškarca (52,4%) i 20 žena (47,6%), uzrasta od 30 do 83 godine (najviše u kategoriji od 70 do 79 godina). Podatak o komorbiditetu (85,7%), prethodnoj hospitalizaciji (83,3%) i prethodnoj antimikrobnoj terapiji (83,8%) zabeležen je kod većine bolesnika **(Tabela 1)**.

Najčešće upotrebljavani antibiotici, pre prijema, bili su hinoloni kod 12 od ukupno 31 bolesnika (38,7%). Dužina primene prethodne antimikrobne terapije iznosila je prosečno 11,1 dan (min. 3, max. 25).

Zahvalnost

Rad je sastavni deo Republičkog projekta III- 46009. Autori zahvaljuju Ministarstvu prosvete, nauke i tehnološkog razvoja za finansiranje istraživanja prikazanih u ovom radu.

Tabela 1. Faktori rizika kod bolesnika sa entrokolitisom čiji je uzročnik *Clostridium difficle*
Table 1. *Risk factors in patients with enterocolitis caused by Clostridium difficle*

Faktori rizika/*Risk factors*	Prisutni/*Present*		Odsutni/*Absent*		Ukupno/*Total*
	N	%	N	%	N
Komorbiditet/*Comorbidity*	36	85,7	6	14,3*	42
Prethodna hospitalizacija/*Previous hospitalization*	35	83,3	7	16,6*	42
Prethodna upotreba AB/*Previous use of AB*	31	83,8	11	26,2**	42

Legenda/*Legend*: n = broj bolesnika *number of patients*; AB = antibiotici/*antibiotics;* * p < 0,01; ** p < 0,05

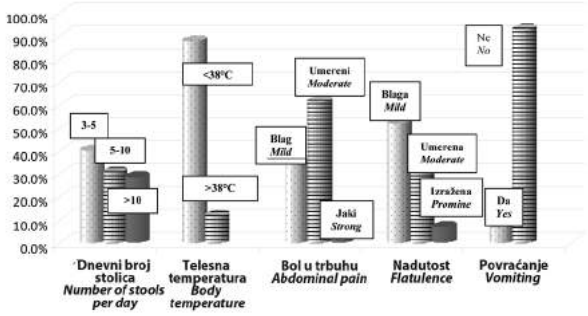
CD enterokolitis manifestovao se povišenom temperaturom do 38° C (37−88,1%); lakom dijarejom (17−40,5%), umerenim bolovima u trbuhu (26−61,9%) uz blagu nadutost (22−52,4%) **(Grafikon 1)**. Upoređivanjem navednih kliničkih paremetara pri prijemu i nakon spovedenog lečenja, zabeležen je povoljan klinički odgovor kada je u pitanju visina temperature (p = 0,012), broj i konzistencija stolice (p = 0,213), bol u trbuhu (p = 0,162) i osećaj nadutosti (p = 0,128).

Analizirane su vrednosti uobičajenih laboratorijskih parametara pri prijemu, tokom hospitalizacije i pri otpustu. Vrednosti leukocita u perifernoj krvi, CRP-a , uree i albumina su 5. dana lečenja pokazali statistički značajno poboljšanje **(Tabela 2)**.

Rekuretna infekcija CD, nakon uspešno spovedene terapije, zabeležena je kod 4 bolesnika od ukupno 42 (9,5%). U jednom slučaju, do relapsa je došlo usled ponovne upotrebe antibiotika u vezi sa lečenjem komplikacija nastalih u sklopu osnovne bolesti. Kod 3 bolesnika relaps se razvio nedelju do mesec dana nakon otpusta. U svim slučajevima spovedena je terapija vankomicinom u postepeno snižavajućim dozama tokom 6 nedelja.

Diskusija

Incidencija infekcija CD kod hospitalizovanih bolesnika je u stalnom porastu, a troškovi lečenja se u Sjedinjenim Američkim Državama procenjuju na 3 milijarde dolara godišnje [2,10,12,13]. Aberra navodi da polna struktura nije u vezi sa pojavom infekcije CD [2], što potvrđuju podaci



Grafikon 1. Simptomi i znaci enterokolitisa čiji je uzročnik *Clostridium difficile*
Graph 1. *Symptoms and signs of Clostridium difficile enterocolitis*

Kale-Pradhana [14] i naši rezultati (52,4% bolesnika muškog pola), dok je Keller u svojoj studiji uočio dominaciju muškog pola (98%) [15]. Brojna istraživanja i naši rezultati potvrđuju da se infekcija CD češće javlja kod starijih bolesnika, sa komorbiditetom, kod prolongirane hospitalizacije i prethodne upotrebe antibiotika [2,3,12,14−19].

Musher i saradnici su u prospektivnoj studiji, koja je uključila 207 bolesnika sa CD enterokolitisom, kod 53% zabeležili povišenu temperaturu (> 37,6° C), kod 83% dijareju, a kod 13% bolove u trbuhu [20]. Mi smo imali više bolesnika sa povišenom temperaturom (88,1%) umerenim bolovima (61,9%) i blagom distenzijom trbuha (52,4%), a manje sa dijarejom (40,5%). Nakon spovedene terapije zabeležen je povoljan klinički odgovor kada

Tabela 2. Laboratorijski pokazatelji kod bolesnika sa entrokoltisom čiji je uzročnik *Clostridium diffcile*
Table 2. *Laboratory findings in patients with enterocolitis caused by Clostridium difficle*

Laboratorijski nalazi *Laboratory findings*	1. dan/*Day 1* $\bar{X}$ (min-max)	5. dan/*Day 5* $\bar{X}$(min-max)	10. dan/*Day 10* $\bar{X}$(min-max)
Broj leukocita (4-10 x 10^9/l)/*Leukocytes (4-10 x 10^9/l)*	11,7 (3,41–32,6)	8,1 (9,13–15,4) *	7,9 (1,34–18,7) **
ALT (5-40 U/l)	17,3 (4–50)	24,2 (9–56)	30 (11–52)
AST (5-37 U/l)	20 (6–49)	34 (13–49)	26 (16–42)
Albumini (35-45 g/l)/*Albumins (35-45 g/l)*	31,9 (22–49)	27,6 (24–32) *	32,6 (24–41)
Ukupni proteini (60-80 g/l)/*Total proteins (60-80 g/l)*	57,5 (38–77)	51,3 (38–71)	56,5 (41–69)
Urea (2,5-7,5 mmol/l)	6,6 (1,2–33,8)	7,03 (1,7–19,8) *	7 (1,7–25,2)
Kreatinin(30-127 μmol/l)/*Creatinine (30-127 μmol/l)*	82,3 (32–256)	99,2 (36–194)	106,6 (47–213)
CRP (0,0-5,0 mg/l)	92,4 (3,4–307,8)	54,8 (3–116,9) *	27,4 (4,1–56,4)

Legenda/*Legend*: 5. dan/day * p<0,05 ; 10.dan/day ** p<0,05

je u pitanju visina temperature, broj i konzistencija stolice, bol u trbuhu i osećaj nadutosti ($p < 0,05$). Vrednosti leukocita u perifernoj krvi, CRP-a, uree i albumina pokazali su statistički značajno poboljšanje 5. dana hospitalizacije.

Najnoviji stavovi u terapijskom pristupu infekcijama CD podrazumevaju primenu peroralnog metronidazola kod bolesnika sa lakšom kliničkom slikom. U slučaju nepovoljnog terapijskog odgovora kao i u težim formama bolesti indikovana je primena peroralnog vankomicina [3,5,13,16−18]. Kombinovana terapija (probiotik uz antibiotik) u našem istraživanju imala je 100% efikasnost. U Musherovoj studiji, smrtni ishod je registrovan u 27% slučajeva infekcije CD, a autori ga povezuju sa pratećim komorbiditetom [20]. Poredeći efikasnost suplementacije probiotika uz antibiotik, nekoliko studija je ukazalo na različito povoljne terapijske efekte probiotskih bakterija (*Lactobacillus, Bifidobacterium, Saccharomyces*) u mnogim crevnim oboljenjima [21−24]. Incidencija javljanja infekcije CD je bila manja i dozno zavisna od upotrebe probiotika [25].

Relaps bolesti se prema navodima Aberra može očekivati u više od 27% slučajeva (bez probiotika) i to u roku od 3 dana do 3 nedelje nakon završene terapije. Surawicz je randomiziranom kontrolisanom studijom uočio značajno smanjenje stope relapsa davanjem visokih doza vankomicina uz probiotik u poređenju sa antibiotikom bez probiotika. Takođe je utvrdio da je davanje probiotika uz niske doze metronidazola ili vankomicina bilo bez statističkog značaja kod pojave relapsa [2,25]. Niska stopa relapsa kod naših bolesnika (9,5%) verovatno je posledica lakše forme infekcije CD. Prema McFarlandu, upotreba antibiotika u kombinaciji sa probioticima pokazala se obećavajućom kada je u pitanju smanjenje pojave relapsa, naročito u slučajevima sojeva *Lactobacillus spp.* i *Saccharomyces boulardii* [26].

Prema protokolu Evropskog društva za kliničku mikrobiologiju i infektivne bolesti (ESCMID) nema dovoljno dokaza na osnovu kojih bi se preporučio dodatak probiotika antibiotskoj terapiji. Kao prilog tome, novode se studije koje su uočile invazivni tok bolesti nakon upotrebe *Saccharomyces boulardii* kod imunokompromitovanih bolesnika [18,20,22,27]. Međutim, naše istraživanje pokazuje da je upotreba probiotika uz antibiotik kod infekcija CD, imala povoljne kliničke efekte, uz manju pojavu relapsa.

Zaključak

Enetrokolitis čiji je uzročnik *Clostridium difficile* češće se javljao kod starijih bolesnika sa komorbiditetom, prolongiranom hospitalizacijom i upotrebom antibiotika. Bolest se manifestovala srednje teškom kliničkom slikom. Primena antibiotika (vankomicin, metronidazol) u uobičajenim dozama uz probiotik koji je sadržao kombinaciju sojeva (*Lactobacillus acidophilus* Rosell-52*, Lactobacillus rhamnosus* Rosell-11 *i Bifidobacterium longum* Rosell-175) imao je povoljan učinak na težinu kliničke slike i normalizaciju laboratorijskih parametara. Rekuretni enterokolitis koji prouzrokuje *Clostridium difficile* nakon uspešno spovedene terapije javila se kod manjeg broja bolesnika. Neželjena dejstva tokom primenjene terapije nisu zabeležena.

Literatura

1. Pothoulakis C, LaMont JT. Clostridium difficile colitis. N Engl J Med 1994;330:257-62.

2. Aberra FN. Clostridium difficile colitis. [Medscape]. 2012 May [updated 2012 May 18; cited 2012 May 29]. Available from: http://emedicine.medscape.com/article/186458-overview.

3. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for clostridium difficile infection in adults. Infect Control Hosp Epidemiol 2010;31(5):431-55.

4. Goldin BR, Gorbach SL. Clinical indications for probiotics: an overview. CID 2008;46(Suppl 2):96-100.

5. Plummer S, Weaver MA, Harris JC, Dee P, Hunter J. Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. Int Microbiol. 2004;7:59-62.

6. Yan F, Polk DB. Probiotics: Progress toward novel therapies for intestinal diseases. Curr Opin Gastroenterol 2010; 26(2):95-101.

7. Davidson LE, Hibberd PL. Clostridium difficile and probiotics [UpToDate]. Last updated 2011 March 24 [cited 2012 June 18]. Available from: http://www.uptodate.com/contents/clostridium-difficile-and-probiotics.

8. Pollak L. Dodaci prehrani i hrana za posebne prehrambene potrebe. Medicus 2008;17(1):47-55.

9. Hulisz D. Probiotics for antibiotic-associated diarrhea [Medscape]. 2011 July [cited 2012 June 03]. Available from: http://www.medscape.com/viewarticle/746534.

10. Allen SJ, Wareham K, Bradley C, Harris W, Dhar A, Brown H, et al. A multicentre randomised controlled trial evaluating lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea in older people admitted to hospital: the PLACIDE study protocol. BMC Infect Dis 2012; 12:108.

11. Hickson M. Probiotics in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection. Ther Adv Gastroenterol 2011;4(3):185-97.

12. Stefan-Mikić S, Sević S, Doder R, Cvjetković D, Jovanović N, Ružić M. Implementation infulence of antibiotik prescribing guidelines on their usage and costs of therapy. Healthmed J 2011;5(6):1710-8.

13. Leffler DA, Lamont JT. Treatment of clostridium difficile-associated disease. Gastroenterology 2009;136:1899-912.

14. Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy 2010;30(2):119-26.

15. Keller DM. Some clostridium difficile infections associated with previous antibiotic use. 2010 Oct [cited 2012 June 03]. Medscape Medical News: Infectious Diseases Soci-

ety of America (IDSA) 48th Annual Meeting: Abstract 450. Available from: http://www.medscape.com/viewarticle/731213.

16. Al-Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RLP, Donskey CJ. Comparison of clinical and microbiological response to treatment of clostridium difficile-associated disease with Metronidazole and Vancomycin. Clin Infect Dis 2008;47(1):56-62.

17. Dumyati G, Stevens V, Hannett GE, Thompson AD, Long C, MacCannell D, et al. Community-associated clostridium difficile Infections, Monroe County, New York, USA CME [Medscape]. 2012 Feb [cited 2012 June 03]. Emerg Infect Dis. 2012 March;18(3):392-400. Available from: http://wwwnc.cdc.gov/eid/article/18/3/pdfs/10-2023.pdf.

18. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JNV, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea. JAMA 2012;307(18):1959-69.

19. Bošković K, Tomašević-Todorović S, Svorcan J, et al. General health related quality of life in patients with osteoporosis. Osteoporosis Int 2012;23(Suppl 2):S189.

20. Musher DM, Aslam S, Logan N, Nallacheru S, Bhaila I, Borchert F, et al. Relatively poor outcome after treatment of clostridium difficile colitis with metronidazole. Clin Infect Dis 2005;40(11):1586-90.

21. Lang FC. Use of a multi-species probiotic for the prevention of antibiotic associated diarrhea. Naturafoods 2010; 9(2):27-31.

Rad je primljen 7. XII 2012.
Recenziran 30. XII 2012.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:209-213.

22. Gao XW, Mubasher M, Fang CY, Reifer C, Miller LE. Dose – response efficacy of a proprietary probiotic formula of lactobacillus acidophilus CL1285 and lactobacillus casei lbc80r for antibiotic-associated diarrhea and clostridium diffi cile-associated diarrhea prophylaxis in adult patients. Am J Gastroenterol 2010;105:1636-41.

23. Fedorak RN, Madsen KL. Probiotics and Prebiotics in Gastrointestinal Disorders. Curr Opin Gastroentero. 2004; 20(2):146-55.

24. Vuković M. Flonivin BS skraćuje period kliconoštva kod bolesnika sa akutnim netifoidnim salmoneloznim enteritisom. Med Pregl 2001;54(1-2):62-8.

25. Bouza E, Burillo A, Muñoz P. Antimicrobial therapy of clostridium difficile-associated diarrhea. Med Clin North Am 2006;90(6):1141-63.

26. McFarland LV. Evidence-based review of probiotics for antibiotic-associated diarrhea and clostridium difficile infections. 2009 Oct [cited 2012 June 18]. Anaerobe 15. 2009: 274-280. Available from: http://www.chifountain.com/wp-content/uploads/2010/05/evidence-based-review-of-probiotics-for-antibiotic-associated-diarrhea-and-clostridium-difficile-infections.pdf.

27. Bauer MP, Kuijper EJ, van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for clostridium difficile infection (CDI). Clin Microbiol Infect 2009;15:1067-79.

Medical faculty Novi Sad, University Novi Sad
Institute for Child and Youth Health Care of Vojvodina
Department of Pediatrics[1]
Ward of Pediatric Radiology[2]

Originalni naučni rad
Original study
UDK 616.2-003.6-06-053.2
DOI: 10.2298/MPNS1306214T

CLINICAL AND RADIOLOGICAL CHARACTERISTICS OF UNRECOGNISED FOREIGN BODY ASPIRATION INTO RESPIRATORY TRACT IN CHILDREN

KLINIČKE I RADIOLOŠKE KARAKTERISTIKE NEPREPOZNATE ASPIRACIJE STRANOG TELA U RESPIRATORNOM TRAKTU KOD DECE

Đurđevka TENJOVIĆ[1], Slobodanka PETROVIĆ[1], Gordana VILOTIJEVIĆ DAUTOVIĆ[1], Jovan LOVRENSKI[2] and Branislavka BJELICA RODIĆ[1]

Summary

Introduction. Diagnosing of foreign body aspiration in children is often postponed. The aim of this study was to evaluate complications, clinical signs and radiological presentation of respiratory illness arising from unrecognized foreign body aspiration in pediatric population. **Material and Methods**. The study sample consisted of 33 patients aged from one to 18 years who had undergone bronchoscopy for foreign body removal over the 10 years' period (from 2000 to 2010). Neither their parents nor the pediatricians who had treated these patients before admission to hospital recognized the acute aspiration event. All the children were treated unsuccessfully for a period exceeding 10 days. The retrospective analysis included the history of foreign body aspiration, patients' age, kind of aspirated foreign body, clinical manifestations that led to hospitalization, radiographic findings and the time lapse from the first symptoms to diagnosis proven by endoscopic intervention. **Results.** The majority of the foreign bodies were organic (93.93%). Broncho-obstructive syndrome, which was the most frequent clinical presentation, was found in 18 (54.55%) patients; pneumonia was diagnosed in 10 (30.30%) patients, four children were referred to hospital due to infiltrative changes with acute broncho-obstructive syndrome and only one child (3.03%) had persistent productive cough. Radiological findings (chest X-rays) were pathological in all patients. Rigid bronchoscopy was performed in 16 (48.49%) patients 10 days after presenting the first symptoms of respiratory illness, in 6 (18.18%) patients within 10-21 days' period and in 11 (33.33%) patients 3 weeks after the first respiratory symptom. **Conclusion.** Unrecognized foreign body aspiration results in various clinical manifestations and non-responsiveness to the standard therapy applied.

Key words: Foreign Bodies; Respiratory Aspiration; Radiology; Signs and Symptoms

Sažetak

Uvod. Dijagnoza aspiracije stranog tela u dečjem uzrastu je često neprepoznata. Cilj rada je da se utvrde vrsta i učestalost komplikacija, odnosno klinički znaci i radiološke karakteristike respiratorne bolesti koja je posledica neprepozne aspiracije. **Materijal i metode.** Rad predstavlja retrospektivnu analizu istorija bolesti kod 33 deteta (1–18 god.) kojima je izvađeno strano telo iz disajnog puta, u desetogodišnjem periodu (2000–2010 god.). Svi pacijenti su bili lečeni, bez uspeha, u primarnoj zdravstvenoj zaštiti, u periodu do 10 i više dana. Akutnu aspiraciju nisu prepoznali ni roditelji kao i ni lekari koji su lečili dete pre dolaska u bolnicu. Analizirani su sledeći podaci: distribucija pacijenata po uzrastu, vrsti aspiriranog materijala, kliničkim simptomima do hospitalizacije, radiološkom nalazu i vremenu koje je proteklo od početka ispoljavanja kliničkih simptoma do ekstrakcije stranog tela. **Rezultati.** Bronhoopstruktivni sindrom je bio najčešća klinička manifestacija kod 18 dece (54,55%), upala pluća kod 10 dece (30,30%), četvoro dece (12,12%) primljeno je na lečenje zbog infiltrativnih promena sa izraženom bronhoopstrukcijom, a samo jedno (3,03%) dete je imalo prolongirani produktivni kašalj sa jutarnjim iskašljavanjem. Radiološki nalaz je bio pozitivan kod sve dece. Definitivna dijagnoza postavljena je bronhoskopski. Kod 16 dece (48,49%) strano telo je ekstrahovano iz disajnih puteva u periodu od 10 dana od trenutka pojave prvih simptoma, kod 6 (18,18%) u periodu 10–21 dana, a kod 11 dece (33,33%) nakon tri nedelje od pojave prvih simptoma. **Zaključak.** Previđena aspiracija stranog tela uzrok je nastanka brojnih kliničkih ispoljavanja i lošeg odgovora na primenjenu terapiju.

Ključne reči: Strana tela; Respiratorna aspiracija; Radiologija; Znaci i simptomi

Introduction

Aspiration of foreign body (FB) into the respiratory tract represents one of the leading causes of death in childhood, especially in preschool children. The highest incidence is recorded in children aged from one to 3 years. The leading symptoms in conditions after acute aspiration are sudden cough, shortness of breath, suffocation and stridor [1-16]. The signs of acute respiratory distress with

Corresponding Author: Dr Đurđevka Tenjović, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, 21000 Novi Sad, Hajduk Veljkova 10, E-mail:djudjat@gmail.com

Abbreviations
FB – foreign body

cyanosis can occur in certain, more severe cases, in cases with a disproportion of diameter between the respiratory pathway and the size of the foreign body, or with the obstruction at the level of the upper portions of respiratory pathway and trachea. Clinical manifestations and development of symptoms depend also on other factors such as the localization, size, nature of foreign body, time elapsed from the moment of aspiration until the diagnosis is set, or its extraction [2,6,9]. Most aspirations of foreign body are clearly recognized on the basis of the typical symptoms such as sudden cough with asphyxiation in the child while eating, laughing or playing. In a great number of cases aspirations happen in the presence of a witness (other children or adults), and then the foreign body is removed from the respiratory tract on that same day, or during the first days after aspiration. Problems arise when aspirations of a foreign body are not recognized because there are no witnesses to the event and when acute symptoms subside and/or remain unrecognized by other persons in the child's surroundings. Symptoms of a respiratory illness result from the complete or partial obstruction of respiratory pathway, development of infection and subsequent complications in the period ranging from a few days to a few weeks. Clinical manifestations of unrecognized aspiration can be very similar to clinical manifestations of other conditions (asthma, virally induced wheezing, bronchiolitis, gastroesophageal reflux etc.). As a result, children are very often treated unsuccessfully, numerous medications are used (antibiotics, bronchodilators, systemic steroids etc.), multidisciplinary approach is needed, the final outcome is hospitalization due to complications and mortality of pediatric population. Morbidity and mortality rate, as well as complications, can be reduced by timely diagnosis and removal of the foreign body in pediatric population [1,8,9].

The aim of this study was to evaluate the type and frequency of complications, clinical signs and radiological presentation of respiratory disease arising from unrecognized FB aspiration in the study sample over the period of ten years.

Material and Methods

This retrospective study included the analysis of disease history and results of 33 children hospitalized at the Ward of Pulmonary Diseases, Institute for Child and Youth Health Care of Vojvodina, Novi Sad during the period from 2000 to 2010. The characteristics of the study sample were as follows:

– Children aged from 6 months to 18 years, regardless of gender

– Symptoms of respiratory disease lasting for at least 10 days prior to hospitalization

– Pediatric patients treated in primary care in duration of 5 to 7 days.

– Children with clinical manifestations of broncho obstructive syndrome treated with ß2 agonists and/or systemic steroids (non-responsive), and children with clinical and radiological signs of pneumonia treated with oral antibiotics (amoxicyllin, amoxicyllin with clavulonic acid or cephalosporins), not responding to the treatment.

– Children admitted with no data of possible aspiration or with sudden appearance of respiratory symptoms, which would suggest possible aspiration.

– Children admitted with diagnosis of recurrent obstructive bronchitis, pneumonia, asthma in observation, prolonged whooping cough

Time elapsed from the first symptoms of respiratory disease to the moment of extraction of foreign body was used as a criterion of the unrecognized aspiration of a foreign body and it was 10 or more days in the study sample.

The statistical analysis included the distribution by age groups (<12 months, 1-3 years, 3-7 years and >7 years), gender, nature of aspirated material (organic or inorganic) and the time when the foreign body was extracted (on admission, 10-21 days, > 21 days).

Characteristic clinical manifestations were determined according to the dominant symptoms as well as the characteristics of radiological presentation of unrecognized aspiration.

The radiological diagnostic procedures included pulmonary chest X-ray (postero-anterior-positioning and lateral view) done for every child and fluoroscopy done for some children.

Fluoroscopy was done in four children with hyperinflation of either right or left lung/lobe in order to obtain more precise localization of FB in the respiratory pathways (left or right bronchi). Radiological findings obtained from the patients' records for each patient were used for interpreting chest X-rays.

The final diagnosis was made based on endoscopic examination. Extraction of FB was done by rigid "Karl Storz" bronchoscope under general anesthesia.

The Ethical committee of the Institute for Child and Youth Health Care of Vojvodina approved this research, and all patients' parents gave their written consent to the data from their children's patient records being used in this study.

Results

Thirty-three patients with unrecognized aspiration of FB were hospitalized during the study period.

According to **Table 1**, the problem of unrecognized aspiration of FB is most frequent in children aged from one to 3 years, i.e. in 26 (78.78%) patients of both genders alike in the study sample. Regarding the age, the incidence of aspiration of FB greatly decreases in pre-school and schoolchil-

Table 1. Age and gender distribution
Tabela 1. *Distribucija pacijenata po uzrastu i polu*

Age groups/*Dobne grupe*	Male/*Dečaci*	Female/*Devojčice*	Total/*Ukupno %*
< 12 months/< *12 meseci*	1	1	6.07%
1-3 years/*1-3 godina*	13	13	78.78%
3-7 years/*3-7 godina*	4		12.12%
>7 years/>*7 godina*		1	3.03%
Total/*Ukupno*	18 (54.55%)	15 (45.45%)	33 (100%)

dren. Boys (54.55%) are hospitalized more often than girls (45.45%).

Foreign bodies of organic origin (walnuts, seeds, peanuts, popcorns etc) were removed in 31 cases (93.93%), thus being the most frequently extracted FB **(Figure 1a)**. A foreign body of inorganic origin (a bead, plastic toy part) was found in only two (6.07%) children of older age **(Figure 1b)**.

Characteristics of clinical presentations of unrecognized FB aspiration in our patients are shown in **Table 2**.

The following clinical manifestations of unrecognized aspiration of FB were observed:

1. Persistent wheezing (cough, dyspnoea, lung squeaks) in 18 (54.55%) patients;
2. Bronchial obstruction accompanied by pulmonary infection symptoms- fever, cough, tachypnea and dyspnoea in 4 (12.12%) patients;
3. Slowly resolving pneumonias in 10 (30.30%) patients;
4. Isolated persistent cough with periodical morning expectoration of purulent mucous in one (3.03%) patient

All patients had cough as one of the symptoms along with other clinical entities.

All patients had positive pulmonary X-ray findings. Typical radiological changes in children with unrecognized aspiration of FB in our research included:

1. Hyperventilation (of either right or left lung/lobe), in 4 (12.12%) children, patients with persistent broncho obstructive symptoms **(Figure 2a)**
2. Infiltrative shadows in 10 (30.3%) patients with pulmonary infection **(Figure 2b)**
3. Atelectases in 19 (57.58%) patients, with symptoms of pneumonia and/or broncho obstruction **(figure 2c and d)**.

The time lapse from the onset of first respiratory symptoms to bronchoscopic extraction of aspirated FB is variable. In 16 (48.49%) patients with performed bronchoscopic extraction, the FB was extracted from the respiratory pathways straight upon hospital admission, i.e. after at least 10 days since the beginning of illness and/or inadequate response to the applied treatment in primary care.

Six (18.18%) patients underwent bronchoscopy within the first 10 days of hospital admission, and 11 (33.33%) patients after 3 weeks **(Table 3)**.

Almost one half of patients (48.49%) were diagnosed straight upon admission to hospital, while the other half had the endoscopic intervention performed after having been subjected to additional non-invasive diagnostic procedures and/or alternative treatments.

Endoscopic examination revealed the presence of FB, which was extracted in 32 (96.97%) patients, and in one (3.03%) patient only extensive granulations were found - presumably at the location of previously decomposed FB. Granulation tissue was found in 17 (51.51%) patients, who had had a foreign body for some time in the respiratory pathways.

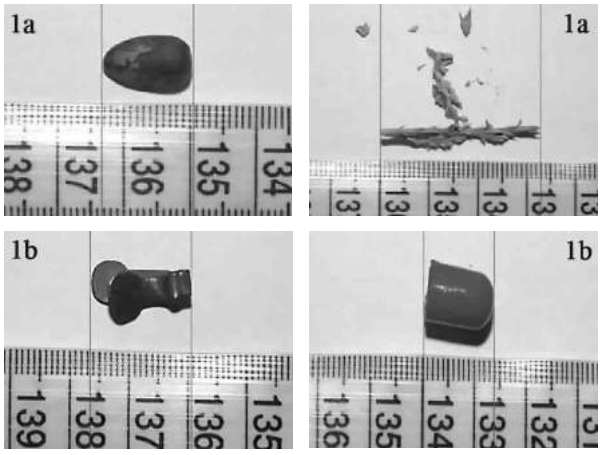


Fig. 1. Samples of organic (a) and inorganic (b) foreign bodies extracted from airways endoscopically
Slika 1. *Uzorci endoskopskim putem ekstrahovanih organskih (a) i neorganskih (b) stranih tela iz disajnih puteva*

Discussion

Little children have a specific way of swallowing, which in combination with specific anatomy of respiratory pathways as well as other factors lead to the fact that this event can be life threatening [1,2]. Acute conditions are treated by endoscopic extraction, mostly at ear-nose and throat hospital wards. Children who had aspirated a foreign body but did not require emergency treatment in the acute phase gradually develop symptoms of a respiratory disease that are non-specific and are common for most respiratory conditions. Complications are common and may result in sequelae causing damage to the respiratory pathways and lungs.

Table 2. Clinical presentations of unrecognized foreign body aspiration
Tabela 2. *Karakteristike kliničke prezentacije neprepoznate aspiracije*

Clinical manifestations/symptoms/*Klinička slika/simptomi*	Number/*Broj*	%
Persistent wheezing/*Perzistirajući vizing*	18	54.55%
Broncho obstruction + pneumonia symptoms *Bronhoopstrukcija + simptomi plućne infekcije*	4	12.12%
Persistent pneumonia/*Perzistirajuća pneumonija*	10	30.30%
Persistent cough/*Perzistirajući kašalj*	1	3.03%
Total/*Ukupno*	33	100%

The size of FB, its nature and localization influence the clinical appearance of symptoms at onset, their order in which they arise, and the clinical severity [1-16]. Timely diagnosis of aspiration is invaluable, bearing in mind that the length in which a FB stays in the trachebronchial branches is proportional to the severity of complications. According to the relevant literature data, 2-23% of respiratory symptoms of unknown etiology are to be assigned to unrecognized FB residing in the respiratory pathway longer than a month [17,18]. Bearing in mind all stated, timely diagnosis is of vital importance to all practitioners dealing with pediatric patients.

The patients from this study sample were hospitalized due to unclear anamnesis. In addition, there was no suspicion of the possibility of aspiration so it was diagnosed with delay, with the resulting development of bronchiectasis in one (3.03%) patient. The expression ”unrecognized aspiration” has a variety of definitions, such as time of a foreign body staying in the respiratory pathway for 24 hours following the aspiration [6,7], or for more than 48 hours [8] or over 72 hours [9,10], which is a relatively short period in comparison to the time we have considered.

Recognition of clinical characteristics of FB aspiration, especially in children presents a problem even in the countries with highly developed medical care; according to different authors, 17-69% of patients are diagnosed after the first week following the event [3,4].

Similar results were published by other authors. A group of authors from Turkey had 28 patients over a period of 9 years (21.8% of all FB aspirations). Their patients had the diagnosis made and the extraction of FB done more than one month after the aspiration [5]. Shlizerman et al. observed a study sample consisting of 136 patients with FB in the respiratory pathways in the period from 1994 to 2004 and they diagnosed aspiration in 19 patients (14%) with symptoms present for more than 7 days [1]. As seen in literature, the percentage of children in whom the moment of aspiration goes unnoticed, or the cause of symptoms is unrecognized is relatively high.

In our study sample, the highest number of aspirations was recorded in the age group from one to 3 years, i.e. in 26 (78.78%) children. This result corresponds to the results of other authors [1-16]. The reasons are anatomical and functional characteristics of the age (children have neither molars nor premolars so they have difficulties in chewing, and the acts of swallowing and breathing are coordinated to a lesser extent). In addition, children in this phase of development get familiarized with the shapes and tastes of the objects around them by putting them into the mouth [2,6,11].

Regarding the distribution of aspiration events by gender, it is similar for both girls and boys especially in children aged 1-3. When the whole group of subjects is observed, the boys are found to have experienced the higher number of FB aspirations than the girls 18 (54.55%) vs. 15 (45.45%), which is also in accordance with the findings of other authors [1,2,4,6-16]. Aspiration of organic vs. inorganic matter is more common in children, which also corresponds to our findings 31 (93.93%)

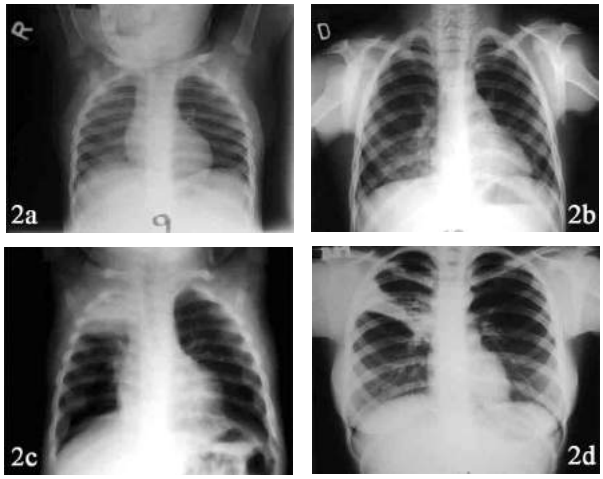


Fig. 2. Chest X-ray findings in children with unrecognized foreign body aspiration: hyperinflation of the left lung (a), right-sided pneumonia paracardially and basally (b), atelectasis of the right upper lobe (c - complete, d - segmental)
Slika 2. *Radiografski nalazi na plućima dece sa neprepoznatom aspiracijom stranog tela: hiperinflacija levog pluća (a), desnostrana pneumonija parakardijalno i bazalno (b), atelektaza u desnom gornjem plućnom lobusu (c – kompletna, d – segmentna)*

Table 3. Time of FB extraction
Tabela 3. *Vreme ekstrakcije stranog tela*

Time of bronchoscopy extraction/*Vreme bronhoskoske ekstrakcije*	Total number/*Ukupno dece (%)*
First day of hospitalization (symptoms lasting up to 10days) *Prvi dan hospitalizacije (simptomi do 10 dana)*	16 (48,49%)
First 10 days of hospitalization (symptoms lasting 10 to 20 days) *U prvih 10 dana hospitalizacije (simptomi 10 - 20 dana)*	6 (18,18%)
After 20 days of hospitalization (symptoms > 4 weeks) *Nakon 20 dana ispitivanja (simptomi > 4 nedelje)*	11 (33,33%)
Total/*Ukupno*	33 (100%)

vs. two (6.07%). Organic foreign bodies cause local inflammatory response with a relatively fast development of complications and appearance of clinical symptoms common also to other respiratory conditions. Inorganic foreign bodies can be clinically silent through a longer period. Besides, in case of aspiration of an inorganic FB, clinical course of illness prior to diagnose can be very variable with interchanging periods of good physiological, clinical and radiological findings and the ones corresponding to various respiratory conditions [19].

Prolonged presence of FB in the respiratory pathways caused a significant reaction of the surrounding tissues – 51.51% of the patients developed granulations with significant production of mucous and purulent secretion. Tokar et al. obtained similar results (66.7%) in their study [9].

Cough was a predominant symptom accompanying broncho obstruction in all subjects, except for one patient who had only this symptom. In literature, cough is present in 30.9% to 92.6% of patients [1,5,6,9,10,13,14]. In most cases cough was accompanied by symptoms of broncho obstruction, which was treated by long-term application of bronchodilators in primary care. Children presenting persistent wheezing were the candidates for further diagnostics in order to prove the presence of asthma. Other authors also reported a high incidence of broncho obstructive symptoms in children with unrecognized aspiration, which were often described as one-sided wheezing [1,11].

Accompanying persistent broncho obstructive symptoms, or persistent cough, pathological auscultatory findings (late inspiratory crepitations and/or shortness of breath, with the symptoms of infection of the lower respiratory pathways not responding to the therapy), were often a reason to perform a bronchoscopic examination in case studies dealing with unrecognized aspiration. The number of children with clinical signs of pneumonia or radiological changes corresponding to infiltrative shadows went from 37-59.3% [3,9,12].

Even though numerous imaging methods are recommended in diagnosing foreign bodies (ultrasound, lung computed tomography, xeroradiography), these are still not routine procedures. When diagnosing aspiration, the most useful method is lung X-rays (postero-anterior, lateral and antero-posterior X-rays chest in left or right lateral decubitus with patient positioned onto the affected side). None of the patients in our series had physiological radiological findings, probably because the unrecognized prolonged presence of the FB in the respiratory pathway was used as a criterion for unrecognized aspiration. The characteristics of radiological finding depend not only on the prolonged stay of a foreign body in the respiratory pathway but also on its properties. Unnoticed foreign bodies are usually located in either of the main bronchi, and fewer are localized in segmental bronchi. As seen in our results, the majority of patients (57.58%) had vast radiological changes such as pneumonic and atelectatic shadows resulting not only from the placement of a foreign body in the respiratory pathway but also from inflammatory changes that led to worsening of ventilatory capacity of the specific lung portion, infection and complications. Lung hyperinflation (unilateral, localized) was noticed in only 4 patients (12,12%). Tokar et al published similar results [9]. Lung hyperinflation was more often reported by other authors in the group of children who had FB residing in respiratory pathway for a period exceeding one month; Mallik in 39.2% and Karakoc in 37.5% of patients [3,12]. Radiological finding in the unrecognized aspiration of FB can also be physiological [7].

Considering literature and clinical experience gained in treating patients of this pathology over many years, and bearing in mind serious complications that can arise out of unrecognized aspiration, it is necessary to educate all levels of community in an understandable and accessible way. Newspaper articles, audiovisual media, educative courses in pediatric care, education of parents and guardians, education in schools in order to recognize the symptoms of FB aspiration in bronchi and necessity of prompt reaction and its extraction would lead to fewer complications and better prospects [15,16,20]. Consequently, there would be a decrease in a foreign body aspiration as a contributing factor to the morbidity and mortality rate in children in Vojvodina and other parts of Serbia [21,22]. Morbidity and mortality could also be reduced by emphasizing the necessity to postpone the introduction of nuts (walnuts, hazelnuts, almonds) into nutrition of infants and small children until their much older age. The same significance can be attributed to the removal of inappropriate toys and other small objects out of reach of children as well as to printing toy declarations and

warnings on products intended for children use, stating the hazard of aspiration, which should be done by manufacturers. Such a campaign in educating parents, guardians, family and public was conducted in Israel from 2000 to 2004. The results of this campaign contributed to a significant decrease in morbidity and mortality caused by aspiration of FB [16].

We did not state the overall number of hospitalized cases admitted under diagnosis of aspiration of FB (suspected or confirmed). These patients had the extraction performed very soon after the aspiration event mostly at the Ear Nose and Throat Department and to a lesser extent at the pulmonary ward of pediatric department. This intervention was delayed in some cases because it had taken time to get the written consent for bronchoscopy.

Conclusion

Unrecognized aspiration of foreign body is still a significant cause of morbidity and mortality in the youngest age group of up to 3 years. Even though there is extensive literature and seminars regarding the subject, the pathology often remains unrecognized, and undiagnosed in pediatric care. Anamnesis proved to be vital to making correct diagnostic decisions. Inadequate response to the therapy applied, deteriorating condition of the patient and persistence of pathological findings should raise suspicion of the presence of foreign body in the respiratory pathway. Clinical manifestations are atypical, and radiological findings do not have to be pathological or can vary in time. Prevention of foreign body aspiration is an imperative to health care system, which can be achieved by raising awareness and conducting educative programs and workshops through all levels of society.

References

1. Shlizerman L, Mazzawi S, Rakover Y, Ashkenazi D. Foreign body aspiration in children: the effects of delayed diagnosis. Am J Otolaryngol. 2010;31(5):320-4.

2. Petrović S, Ljuština R, Bjelica-Rodić B, Značaj aspiracije stranog tela u nastanku bronhoopstruktivnog sindroma u dece. Acta Med Median 1994;33(4):89-96.

3. Karakoc F, Cakir E, Ersu R, Uyan ZS, Colak B, Karadak B, et al. Late diagnosis of foreign body aspiration in children with chronic respiratory symptoms. Int J Pediatr Otorhinolaryngol 2007;71(2):241-6.

4. Lima JAB, Fischer GB. Foreign body aspiration in children. Paediatr Resp Rev 2002;3(4):303-7.

5. Karakoc F, Karadag B, Akbenlioglu C, et al. Foreign body aspiration: what is the outcome? Pediatr Pulmonol 2002; 34(1):30-6.

6. Saki N, Nikakhlagh S, Rahim F, Abshirini H. Foreign body aspirations in infancy: a 20-year experience. Int J Med Sci 2009;6(6):322-8.

7. Mu L, Sun D, He P. Radiological diagnosis of aspirated foreign bodies in children: Review of 343 cases. J Laryngol Otol 1990;104(4):778-82.

8. Metrangolo S, Monetti C, Meneghini L, et al. Eight years experience with foreign body aspiration in children: what is really important for a timely diagnosis? J Pediatr Surg 1999;34:1229-31.

9. Tokar B, Ozkan R, Ilhan H. Tracheobronchial foreign bodies in children: importance of accurate history and plain chest radiography in delayed presentation. Clin Radiol 2004;59(7):609-15.

10. Zerella JT, Dimler M, McGill LC, Pippus KJ. Foreign body aspiration in children: value of radiography and complications of bronchoscopy. J Pediatr Surg 1988;33:1651-4.

11. Evans JNG. Foreign bodies in the larynx and trachea. Chapter 29. In: Scott-Browns WG. Otolaryngology. 6th ed. Boca Raton: CRC Press; 1996. p. 1-10.

12. Mallick MS, Khan AR, Al- Bassam A. Late presentation of tracheal foreign body aspiration in children. J Trop Pediatr 2005;51(3):145-8.

13. Oguzkaya F, Akçalı Y, Kahraman C, Bilgin M, Şahin A. Tracheobronchial foreign body aspirations in childhood: 10-year experience. Eur J Cardiothorac Surg 1998; 14(4): 388-92

14. Rahbarimanesh A, Noroozi E, Molaian M, Salamati P. Foreign body aspiration: a five-year report in a children's hospital Iran J Pediatr [Letter to Editor, Internet]; 2008 Jun [cited 2012 Apryl 28]. Vol 18(No 2), Pp:191-2. Available from: http://journals.tums.ac.ir/upload_files/pdf/_/8021.pdf

15. Singh A, Ghosh D, Samuel C, Bhatti W, Pediatric foreign body aspiration: how much does our community know? J Indian Assoc Pediatr Surg. 2010;15(4):129-32.

16. Sadan N, Raz A, Wolach B. Impact of community educational programmes on foreign body aspiration in Israel. Eur J Pediatr 1995;154(10):859-62.

17. Barrios JE, Gutierrez C, Llana J, et al. Bronchial foreign body: schould bronchoscopy be performed in all patients with a choking crisis. Pediatr Surg Int 1997;12:118-20.

18. Wiseman NE, Schwartz I. The diagnosis of foreign body aspiration in childhood. J Pediatr Surg 1984;19:531-5.

19. Petrovic S, Cegar S, Lovrenski J, Barisic N, Till V. Foreign body aspiration in children: a diagnostic challenge. Balcan Med J 2012;29(1):096-8.

20. Martinov-Cvejin M, Grujić V, Jakovljević Đ. Uloga primarne zdravstvene zaštite u promociji zdravlja. Med Pregl 2000;53(5-6):262-5.

21. Kocić S, Radovanović S, Popović P, Mihailović N, Radević S. Vanbolnički morbiditet stanovništva Šumadijskog okruga. Med Pregl 2010;63(1-2):21-6.

22. Martinov-Cvejin M, Grujić V, Šušnjević S, Kvrgić S, Arsić M, Ač-Nikolić E. Zdravlje stanovništva Vojvodine. Med Pregl 2007;60(11-12:559-63.

Rad je primljen 3. VIII 2012.
Recenziran 20. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:214-219.

POZIV SARADNICIMA

Pozivamo Vas da se pretplatite na časopis „Medicinski pregled". Podsećamo Vas da je pretplata **OBAVEZNA** za sve saradnike časopisa, odnosno za sve one koji žele objavljivati svoje radove.
Molimo Vas da, ukoliko ste zainteresovani, a niste to do sada učinili, uplatite pretplatu za 2013. godinu u iznosu od **3.000,00 dinara (sa uračunatim PDV-om)** za članove sa teritorije Srbije, odnosno **4.000,00 dinara (sa uračunatim PDV-om)** za članove van teritorije Srbije uplatite na račun: **340-1861-70 ili 115-13858-06** s naznakom „Pretplata na časopis Medicinski pregled za 2013" Ujedno Vas molimo da popunite donji formular i dostavite ga lično ili na adresu:

Društvo lekara Vojvodine Srpskog lekarskog društva
Za ČASOPIS „MEDICINSKI PREGLED"
21000 NOVI SAD
Vase Stajića 9

PRETPLATN1K ČASOPISA „MEDICINSKI PREGLED"

Ime, prezime i titula	
Adresa na poslu	
Adresa kod kuće	
Kontakt telefon	
Mobilni, E-mail adresa:	

Popuniti štampanim slovima

PREGLEDNI ČLANCI
REVIEW ARTICLES

Medicinski fakultet Novi Sad
Klinički centar Vojvodine, Klinika za medicinsku rehabilitaciju[1]
Fakultet sporta i fizičkog obrazovanja Novi Sad[2]
Klinički centar Srbije, Klinika za fizikalnu medicinu i rehabilitaciju, Beograd[3]

Pregledni članci
Review article
UDK 616.71-007.233-08:796
DOI: 10.2298/MPNS1306221B

ADAPTIRANA FIZIČKA AKTIVNOST U PREVENCIJI I LEČENJU OSTEOPOROZE

ADAPTED PHYSICAL ACTIVITY IN THE PREVENTION AND THERAPY OF OSTEOPOROSIS

Ksenija BOŠKOVIĆ[1], Branka PROTIĆ GAVA[2], Mirko GRAJIĆ[3], Dejan MADIĆ[2], Borislav OBRADOVIĆ[2] i Snežana TOMAŠEVIĆ TODOROVIĆ[1]

Sažetak

Uvod. Osteoporoza je sistemska bolest skeleta koju karakteriše progresivni gubitak koštane gustine, koja je sa godinama starosti praćena mnogobrojnim komplikacijama. **Epidemiologija.** Izračunato je da je 2010. godine u svetu bilo 25% žena i 4% muškaraca starijih od 50 godina sa osteoporozom. Pretpostavlja se da će se na svakih deset godina u 21. veku broj obolelih uvećavati za 30%. Mnogo je razloga za to − svetska populacija postaje sve starija, ishrana sve siromašnija vitaminima i mineralima a fizička aktivnost je sve manja. **Kvalitet i kvantitet koštanog tkiva.** Kosti u razvoju mnogo bolje odgovaraju na mehaničko opterećenje i fizičku aktivnost nego zrele kosti. To ukazuje da vežbanje u ranom detinjstvu može biti važan faktor u prevenciji osteoporoze u kasnijem životu. Važno je napomenuti i da kvalitet kosti koji se postigao vežbanjem ne može trajno da se održava ukoliko se to ne podržava fizičkom aktivnosti kasnije u životu. **Adaptirana fizička aktivnost** predstavlja individualno prilagođenu fizičku aktivnost prema psihosomatskim mogućnostima osobe kao i prema cilju koji treba da se postigne. Primenjiva je u svakom životnom dobu sa ciljem održavanja čvrste kosti i smanjenja rizika za prelom kosti. Adaptirana fizička aktivnost različita je za muškarce i žene, za različito životno doba, kao i za pojedine osobe. Aerobne vežbe, koje dovode do ubrzanja disanja, ubrzanog rada srca i lakog znojenja, vežbe sa opterećenjem i vežbe protiv otpora – sa istezanjem elastičnih traka, za ruke, noge i trup dokazano povećavaju koštanu gustinu i popravljaju čvrstinu kosti. Vežbe koordinacije i balansa važne su u individualnom programu vežbanja. Objašnjenje dejstva adaptirane fizičke aktivnosti je osnova za teoriju kontrole i modulacije gubitka koštane gustine, mišićne snage, koordinacije i balansa. Fizička aktivnost veoma efikasno smanjuje nivo sklerostina za koji znamo da je inhibitor koštane izgradnje. Isto tako, fizički trening podiže nivo faktora rasta sličnog insulinu, što ima veoma dobar pozitivni efekat na formiranje kosti. **Zaključak.** Adaptirana fizička aktivnost ima za cilj što bolju izgradnju kosti u mladosti, u odraslom dobu očuvanje koštane mase, a u starosti sprečavanje gubitka kosti, smanjenje rizika od pada kao i rizika za nastanak preloma, odnosno da prouzrokovanu onesposobljenost svede na minimum i poboljša kvalitet života.

Ključne reči: Fizička aktivnost; Osteoporoza + terapija; Osteoporoza + prevencija i kontrola; Gustina kosti; Insulinu sličan faktor rasta I; Adolescent; Dete; Postura; Sedeći način života

Summary

Introduction. Osteoporosis, a disease characterized by the progressive loss of bone tissue, is one of the most common complications of aging. **Epidemiology.** According to some calculations, there were 25% of women and 4% of men older than 50 years with osteoporosis in the world in 2010. It is assumed that the number of patients with osteoporosis will increase by 30% in every 10 years in the 21st century. There are many reasons for that: the world's population is growing older, diet is getting poorer in vitamins and minerals and physical activity is decreasing. **The Quality and Quantity of Bone Tissue.** Developing bones are much more responsive to mechanical loading and physical activity than mature bones. This suggests that training in early childhood may be an important factor in the prevention of osteoporosis in later life. It is important to note that the quality of bone achieved by training at younger age cannot be maintained permanently if it is not supported by physical activity later in life. **Adapted physical activity** represents physical activity individually tailored according to the psychosomatic capabilities of a person and the goal to be achieved. It can be applied at any age in order to maintain strong bones and reduce the risk of fracture. Adapted physical activity is different for men and women, for different age, as well as for the individuals. Aerobic exercises, which lead to an acceleration of breathing, increased heart rate and mild perspiration, as well as resistance exercises and exercises against resistance done by stretching elastic bands, for hands, legs and torso have been proven to increase bone density and improve bone strength. Coordination and balance exercises are important in an individual workout program. An explanation of the action of adapted physical activity is the basis for the theory of control and modulation of bone loss, muscle strength, coordination and balance. Physical activity is very effective in reducing sclerostin, which is known to inhibit bone formation. In addition, physical training enhances the levels of insulin-like growth factor, which has a very positive effect on bone formation**. Conclusion**. The aim of adapted physical activity is to improve bone formation in youngsters, to preserve the bone mass in adults and to prevent the bone loss in the elderly thus reducing the risk of falls and resulting fractures; in other words, to minimize the disability caused by fractures and improve the quality of life.

Key words: Exercise; Osteoporosis + therapy; Osteoporosis + prevention&control; Bone Density; Insulin-Like Growth Factor I; Adolescent; Child; Postural Balance; Sedentary Lifestyle

Adresa autora: Prof. dr Ksenija Bošković, Klinika za medicinsku reahbilitaciju, 21000 Novi Sad, Hajduk Veljkova 1-7

Uvod

Osteoporoza kao progresivno sistemsko metaboličko oboljenje skeletnog sistema, nastaje kada pod uticajem različitih faktora dođe do poremećaja skeletne homeostaze [1]. Tokom detinjstva i ranog adultnog perioda, formiranje prevazilazi razgradnju kosti, tako da se koštana gustina povećava i dostiže svoj maksimum između 25−30 godina života, što se održava do menopauze odnosno klimaksa [2]. Fizička aktivnost dokazano igra značajnu ulogu u povećanju koštane mase tokom detinjstva i rane adolescencije [3,4]. Nakon 35−40. godine života resorpcija se ubrzava i prevazilazi koštano formiranje, tako da se gustina kosti smanjuje i može dovesti do razvoja osteoporoze. Adaptirana fizička aktivnost doprinosi održavanju koštane mase tokom ovog perioda, a kod starijih osoba usporava gubitak kosti i utiče na smanjenje rizika od preloma [5].

Ovo oboljenje se često javlja u svom asimptomatskom obliku kao „klinički nema bolest" ili „tihi kradljivac kostiju", ali se u drugom obliku ispoljava sa prelomima kostiju i intenzivnim bolom. Upravo taj drugi oblik ispoljavanja osteoporoze doprineo je rasvetljavanju socioekonomskog značaja oboljenja i fokusirao nacionalnu zdravstvenu politiku kako u pravcu primarne prevencije nastanka osteoporoze, tako i u pravcu sekundarne i tercijarne prevencije pada i nastanka osteoporotičnih preloma [6].

Kada se dijagnostikuje osteoporoza, treba sprovesti edukaciju pravilnih pokreta tela radi sprečavanja pada i povređivanja [7]:

– kako podizati predmete sa poda bez savijanja leđa;
– kako se kretati bez uvrtanja kičme;
– primeniti mere za preveniranje padanja kod kuće, na poslu, kao i pri kretanju;
– koje se vežbe mogu bezbedno raditi i
– tražiti pomoć za podizanje teških predmeta ili za penjanje.

Epidemiologija

Osteoporoza je toliko raširenо oboljenje da predstavlja zdravstveni problem globalnih razmera [1,2]. Najčešće se javlja:

– kod žena nakon menopauze (postmenopauzalna osteoporoza),
– osoba oba pola starijih od 65 godina (senilna osteoporoza) i
– osoba koje imaju pridružene bolesti ili uzimaju lekove koji utiču na metabolizam koštanog tkiva (sekundarna osteoporoza).

Izračunato je da je 2010. godine u svetu bilo 25% žena i 4% muškaraca starijih od 50 godina sa osteoporozom [5]. Pretpostavlja se da će se na svakih deset godina u 21. veku broj obolelih uvećavati za 30%. Mnogo je razloga za to − svetska populacija postaje sve starija, ishrana sve siromašnija vitaminima i mineralima a fizička aktivnost je sve manja.

Najčešći prelomi osteoporotične geneze do 70. godine života su prelomi kičmenih pršljenova a verovatnoća njihovog nastanka kod žena posle 50. godine života je 40%, prevalencija je oko 24%. Vertebralni prelomi često nastaju i bez pada tokom uobičajenih dnevnih aktivnosti. Mogu se predvideti ukoliko postoji značajno smanjenje telesne visine za 4-5 cm, kifoza praćena naglo nastalim akutnim bolom, ali su najčešće asimptomatski [5]. Vertebralni prelom predstavlja prediktor povećanja rizika od nastanka novog vertebralnog preloma za 4-5 puta, od preloma vrata butne kosti 2-3 puta, od preloma podlaktice i drugih preloma za 1-2 puta. Posle 70. godine života javljaju se nevertebralni prelomi, a posebno prelomi kuka [8]. Za razliku od vertebralnih preloma, oni su posledica pada i praćeni su bolom, poremećajem pokretljivosti i deformacijama. Najteže posledice ima prelom kuka, jer 24% ovih osoba umire u prvoj godini posle preloma zbog komplikacija, najveći broj ostaju invalidi, a manje od 20% bolesnika se potpuno oporavi [9]. Najvažniji prediktor vertebralnih fraktura je smanjenje koštane gustine, za razliku od nevertebralnih fraktura, kod kojih je sklonost padovima podjednako važan prediktor. I na koštanu gustinu i na sklonost padovima možemo preventivno delovati adaptiranom fizičkom aktivnošću.

Kvalitet i kvantitet koštanog tkiva

Kosti u razvoju mnogo bolje odgovaraju na mehaničko opterećenje i fizičku aktivnost nego zrele kosti. To ukazuje da vežbanje u ranom djetinjstvu može biti važan faktor u prevenciji osteoporoze u kasnijem životu [3]. Smatra se da su vežbe koje utiču na sagorevanje masti (antigravitacione, uspravan položaj tela, npr. hodanje) i vežbe snage (kao što su vežbe sa tegovima, gimnastika, fudbal i odbojka) najefikasnije u unapređenju prirasta koštane mase ukoliko se započne sa vežbanjem u periodu puberteta [4,10]. Važno je napomenuti i da kvalitet kosti koji se postigao vežbanjem ne može trajno da se održava ukoliko se to ne podržava fizičkom aktivnosti kasnije u životu [11].

Nakon 40. godine života koštana masa se smanjuje oko 0,5% godišnje, bez obzira na pol ili rasu. Na ovo utiču faktori kao što su genetika, ishrana, hormonski status, uobičajene fizičke aktvnosti. To otežava procenu u kojoj meri je gubitak kosti neizbežna posledica procesa starenja [4].

Gubitak koštane mase se javlja brže ukoliko nema nikakvog opterećenja na kost. Problem starijih osoba je taj što teško mogu nastaviti sa aktivnostima koje bi pružile adekvatno opterećenje kako bi se održala koštana masa [12]. Adaptirana fizička aktivnost, umerenog do srednjeg intenziteta, kod žena starosti između 65 i 75 godina može dovesti do poboljšanja mišićne snage, što će uticati i na poboljšanje kvaliteta kosti. Kohrt i saradnici [13] pokazali su da je kod starijih osoba zdravlje kosti u vezi sa intenzitetom i sa količinom fizičke

aktivnosti. Kod muškaraca zdravlje kosti je blisko vezano sa dnevnim trajanjem fizičke aktivnosti umerenog intenziteta. Kod žena je u vezi sa brojem koraka u toku dana (preporuka za starije osobe je više od 7 000 koraka u toku dana). Za starije ljude, čak i spora šetnja u trajanju od 1 sat, koja inače predstavlja nizak nivo fizičke aktivnosti, može pozitivno delovati na kvalitet kostiju.

Adaptirana fizička aktivnost

Adaptirana fizička aktivnost predstavlja individualno prilagođenu fizičku aktivnost kako prema psihosomatskim mogućnostima osobe tako i prema cilju koji treba da se postigne [14]. Primenjiva je u svakom životnom dobu sa ciljem kako održavanja čvrste kosti tako i smanjenja mogućnosti preloma. Adaptirana fizička aktivnost je različita za muškarce i žene, za različito životno doba, kao i za pojedine osobe [15].

Pre početka primene fizičke aktivnosti važno je obaviti temeljan lekarski pregled da se utvrdi koje se vežbe mogu bezbedno primeniti. Ne postoji režim vežbanja koji je najbolji za sve osobe sa osteoporozom. Režim vežbi treba da bude individualno prilagođen na osnovu medicinske procene: rizika za prelom, mišićne snage, obima pokreta, nivoa fizičke aktivnosti, sposobnosti, hoda i balansa [16].

Fizička aktivnost veoma efikasno smanjuje nivo sklerostina za koji znamo da je inhibitor koštane izgradnje. Isto tako, podiže nivo faktora rasta sličnog insulinu (IGF-1), što ima veoma dobar pozitivni efekat na formiranje kosti.

Aerobne vežbe, koje dovode do ubrzanja disanja, ubrzanog rada srca i lakog znojenja, vežbe sa opterećenjem i vežbe protiv otpora – sa istezanjem elastičnih traka, za ruke, noge i trup dokazano povećavaju koštanu gustinu i popravljaju čvrstinu kosti.

Vežbe koordinacije i balansa su važne u individualnom programu vežbanja. Značajno poboljšanje dobija se posle 15 nedelja vežbanja taj čija, sa serijom sporih, umerenih i kontinuiranih pokreta. Pogodne su za starije osobe i pomažu im da ojačaju mišiće, poboljšaju balans i koncentraciju [17].

Glavni cilj vežbanja kod žena u postmenopauzi je da se poveća mišićna masa, poboljšaju parametri mišićne funkcije − snaga i balans, koji su važni faktori rizika za pad i nezavisno od koštane gustine, faktori rizika za prelom [18]. Vežbe jačanja mišića obavljaju se elastičnim trakama, mašinama, tegovima i drugim izometrijskim vežbama.

U poslednje vreme adaptirane fizičke vežbe se posebno fokusiraju na korekciju posturalnog disbalansa, naročito na korekciju hiperkifoze, zbog sedenternog načina življenja i slabljenja mišića ekstenzora trupa [15]. Sprovode se individualno, dozirano uz postepeno povećanje opterećenja, uz izbegavanje dinamičkih vežbi za trbušne mišiće, naglo ustajanje iz sedećeg položaja i preterano savijanje trupa, pokreti uvrtanja, kao i vežbe sa naglim povlačenjem ili opterećenjem velikom silom koje mogu dovesti do preloma pršljena [19].

Na kraju potrebno je istaći da je veoma važno podizanje svesti osoba u odnosu na potrebu primene svakodnevne kontinuirane adaptirane fizičke aktivnosti, kako bi se održalo postignuto povećanje koštane mase, mišićne snage, balansa i koordinacije pokreta, sve sa ciljem postizanja adekvatnog kvaliteta života [20].

Zaključak

Ukazujući na ozbiljnost zdravstveno-ekonomskog aspekta osteoporoze, razumljiva je borba za jače, gušće, čvršće i kvalitetnije kosti, koja traje tokom celog života. Adaptirana fizička aktivnost ima za cilj što bolju izgradnju kosti u mladosti, u odraslom dobu očuvanje koštane mase, a u starosti sprečavanje gubitka kosti, smanjenje rizika od pada kao i rizika za nastanak preloma, odnosno da prouzrokovanu onesposobljenost svede na minimum i poboljša kvalitet života.

Literatura

1. The North American Menopause Society: NAMS Continuing medical education activity: management of osteoporosis in postmenopausal women. Menopause 2010;17(1):23-56.

2. Bošković K. Osteoporoza. U: Pjević M, Kojadinović Ž, Simić S, Patarica-Huber E, Jovanović L, Bošković K. Interaktivni priručnik: lečenje hroničnog bola kod odraslih. Novi Sad: Medicinski fakultet Novi Sad; 2011.

3. Obradović B, Madić D, Milošević Z, Maksimović N, Mikalački M, Kovačev-Zavišić B. Body composition and bone mineral density of prepubertal boys involved in different kinesiologic treatments. Med Pregl 2009;62(1-2):23-6.

4. Madić D, Obradović B, Marić D, Smajić M, Obradović J, Bošković K. Bone density and body composition of prepubertal boys angaged in intensive physical activity. Vojnosanit Pregl 2010;67(5):386-90.

5. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 2009;62(2):105-8.

6. Compston J. Monitoring osteoporosis treatment. Best Pract Res Clin Rheumatol 2009;23:781-8.

7. Beaudreuil J. Nonpharmacological treatments for osteoporosis. Ann Readapt Med Phys 2006;49(8):581-8.

8. Zvekić-Svorcan J, Janković T, Lazarević M, Bošković K, Subin-Teodosijević S, Filipov P. Učestalost vertebralnih fraktura kod pacijenata sa smanjenom koštanom gustinom: analiza rezultata iz bonlink. Acta Rheumatol Belgrad 2011;41(1):121.

9. Boskovic K. Impact of emotional disorders on functional recovery after osteoporotic hip fracture. Ann Rheum Dis 2012;71(Suppl 3):616.

10. Protić-Gava B, Krneta Ž, Bošković K, Romanov R. Efekti programiranog vežbanja na status kičmenog stuba osmogodišnje dece Novog Sada. J Anthropol Soc Serb 2010;45:365-7.

11. Rautava E, Lehtonen-Veromaa M, Kautiainen H, Kajander S, Heinonen OJ, Viikari J, et al. The reduction of physi-

cal activity reflects on the bone mass among young females: a follow-up study of 142 adolescent girls. Osteoporos Int 2007;18:915-22.

12. Ashe MC, Liu-Ambrose TY, Cooper DM, Khan KM, McKay HA. Muscle power is related to tibial bone strength in older women. Osteoporos Int 2008;19:1725-32.

13. Kohrt WM, Bloomfield AS, Little KD, Nelson ME, Yngling VR. ACSM Position Stand: physical activity and bone health. Medicine and Science adults: cross-sectional data from the Nakanojo Study. Osteoporos Int 2004;18:285-93.

14. Boskovic K, Tomasevic-Todorovic S, Zvekic-Svorcan J. General health related quality of life in patients with osteoporosis. Osteoporos Int 2012;23(Suppl 2):189.

15. Boškovic K, Naumovic N, Tomaševic S, Lazarević M, Devečerski G, Knežević A. Osteoporoza i reumatske bolesti. Balneoclimatologia 2009;35(Suppl 3):7-13.

16. Cangussu LM, Nahas-Neto J, Petri Nahas EA, Rodrigues Barral AB, Buttros Dde A, Uemura G. Evaluation of postural balance in postmenopausal women and its relationship with bone mineral density: a cross sectional study. BMC Musculoskelet Disord 2012;13(1):1.

17. Cvjetkovic-Bosnjak M, Knezevic A, Soldatovic-Stajic B. Depression in older persons. Med Pregl 2000;53(3-4):184-6.

18. Smulders E, van Lankveld W, Laan R, Duysens J, Weerdesteyn V. Does osteoporosis predispose falls? A study on obstacle avoidance and balance confidence. BMC Musculoskelet Disord 2011;12:1.

19. Young M, Weeks K, Beck R. Simple, novel physical activity maintains proximal femur bone mineral density, and improves muscle strength and balance in sedentary, postmenopausal caucasian women. Osteoporos Int 2007;18:1379-87.

20. Bošković K, Erdeljan B, Janković T, Lazarević M, Stojković S. Procena kvaliteta života kod bolesnika sa smanjenom koštanom gustinom. Balneoclimatologia 2007;31(Suppl 2):19.

Rad je primljen 8. III 2013.
Recenziran 11. III 2013.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:221-224.

Medicinski fakultet Univerziteta u Beogradu
Institut za medicinsku fiziologiju[1]
Kliničko-bolnički centar Zemun, Beograd, Interistička služba[2]
Vojnomedicinska akademija, Beograd, Klinika za kardiologiju[3]

Pregledni članci
Review article
UDK 616.12-079.97:796
DOI: 10.2298/MPNS1306225M

ELEKTROKARDIOGRAFSKE SPECIFIČNOSTI KOD SPORTISTA

ELECTROCARDIOGRAPHIC SPECIFICITIES IN ATHLETES

Sanja MAZIĆ[1], Biljana LAZOVIĆ[2], Marina ĐELIĆ[1], Zoran STAJIĆ[3] i Zdravko MIJAILOVIĆ[3]

Sažetak

Uvod. Primena elektrokardiograma kod sportista kao rutinske skrining metode za dijagnostikovanje potencijalno opasnih kardiovaskularnih oboljenja još uvek je predmet debate. Prema preporukama Evropskog udruženja kardiologa primena ove metode kod sportista je obavezno, dok prema preporukama Američke asocijacije za srce nije, već se insistira na detaljnoj ličnoj i porodičnoj anamnezi i fizikalnom pregledu. **Klasifikacija promena elektrokardiograma kod sportista.** Prema klasifikaciji Evropskog udruženja kardiologa, podeljene su u dve grupe: a) uobičajene (fiziološke) koje su povezane sa fizičkim treningom, b) neuobičajene (potencijalno klinički značajne) koje nisu u vezi sa njim. **Iznenadna srčana smrt kod sportista.** Najčešći uzroci su hipertrofijska kardiomiopatija i kongenitalne anomalije koronarnih arterija; ostali uzroci se samo sporadično nalaze na obdukciji. **Fiziološke promene elektrokardiograma kod sportista.** Kod sportista bez simptoma su česte i ne zahtevaju dalje ispitivanje. Obuhvataju sledeće nalaze: sinusnu bradikardiju, atrioventrikularne blokove I stepena i II stepena – *Wenkebach*, izolovano uvećanje QRS voltaže, inkompletni blok desne grane Hisovog snopa, ranu repolarizaciju. **Potencijalno patološke promene elektrokardiograma kod sportista.** Nisu uobičajene ali predstavljaju alarm da se pristupi daljem ispitivanju sa ciljem dijagnostikovanja kardiovaskularnog oboljenja i sprečavanja iznenadne srčane smrti. Obuhvataju: inverziju T-talasa, depresiju ST segmenta, kompletni blok desne ili leve grane Hisovog snopa, sindrom preekscitacije pretkomora − WPW, prolongirani QT interval, skraćeni QT interval, nalaz sličan Brugadinom sindromu. **Zaključak.** Uključivanje snimanja elektrokardiograma u skrining program kod sportista povećava senzitivnost pregleda i može pomoći u otkrivanju kardiovaskularnih oboljenja bez simptoma koja mogu biti uzrok iznenadne srčane smrti. Nalaz opisanih potencijalno patoloških promena kod sportista zahteva poseban oprez i dalju evaluaciju.

Ključne reči: Sportsko srce; Elektrokardiografija; Sportisti; Dijagnoza; Skrining; Iznenadna srčana smrt

Summary

Introduction. The use of electrocardiogram in athletes as a routine screening method for diagnosing potentially dangerous cardiovascular diseases is still an issue of debate. According to the guidelines of the European Society of Cardiology, the recording of electrocardiogram is necessary in all athletes as a screening method, whereas the guidelines of the American Heart Association do not necessitate an electrocardiogram as a screening method and they insist on detailed personal and family history and clinical examination. **Classification of** e**lectrocardiogram changes in athletes.** According to the classification of the European Society of Cardiology, electrocardiogram changes in athletes are divided into two groups: a) usual (physiological) that are connected with training; b) unusual (potentially clinically relevant) that are not connected with training. **Sudden cardiac death in athletes.** The most frequent causes include hypertrophic cardiomyopathy and congenital coronary artery anomalies, while others may be found only sporadically at autopsy. **Physiological electrocardiogram changes** are frequent in asymptomatic athletes and they do not require further assessment. They include sinus bradycardia, atrioventricular blocks of I and II degree – Wenkebach, isolated increased QRS voltage, incomplete right bundle branch block and early repolarization. **Potentially pathological electrocardiogram changes in athletes** are not frequent but they are alarming and they urge further assessment to diagnose the underlying cardiovascular disease as well as the prevention of sudden cardiac death. They include: T wave inversion, ST segment depression, complete right or left bundle branch block, atrial pre-excitation syndrome-WPW, long QT interval, short QT interval, Brugada like electrocardiogram finding. **Conclusion.** Introduction of electrocardiogram recording into the screening protocol in athletes increases the sensitivity of evaluation and may help to discover asymptomatic cardiovascular diseases that may cause sudden cardiac death. Special attention and further assessment are required when the above potentially pathological electrocardiogram changes are found in athletes.

Keywords: Cardiomegaly, Exercise Induced; Electrocardiography; Athletes; Diagnosis; Mass Screening; Death, Sudden, Cardiac

Uvod

O upotrebi elektrokardiograma (EKG) kao skrining metode pre aktivnog bavljenja sportom postoje i dalje brojne kontroverze. Do sada nije postignut konsenzus o identifikovanju i stratifikovanju sportista koji su u riziku od iznenadne srčane smrti [1]. Međutim, trenutno postoje dva aktuelna međuna-

Adresa autora: Asist. dr Zoran Stajić, Vojnomedicinska akademija, Klinika za kardiologiju, 11040 Beograd, Crnotravska 17, E-mail: zoran0312@yahoo.com

Skraćenice

LK – leva komora
EKG – elektrokardiogram
HCM – hipertrofijska kardiomiopatija
AV – atrioventrikularni
PLH – prednji levi hemiblok

rodna skrining protokola (preporuke) koji se bave prevencijom iznenadne srčane smrti kod sportista. Prema preporukama Američkog udruženja kardiologa EKG nije obavezan deo pregleda sportista, već se insistira na detaljnoj ličnoj i porodičnoj anamnezi, uz fizikalni pregled [2]. Nasuprot tome, preporuke Evropskog udruženja kardiologa savetuju sveobuhvatan fizikalni pregled sa posebnim osvrtom na kardiološku anamnezu pre takmičenja svake dve godine, kao i dinamičke testove za procenu srčane funkcije uključujući i EKG [3].

Rezultati velike opservacione italijanske studije incidencije iznenadne srčane smrti kod sportista tokom dvadesetpetogodišnjeg perioda praćenja (1979–2004) pokazali su značajan pad stope mortaliteta nakon uvođenja obaveznog EKG-a u okviru skrining programa (1982. godine). Godišnja incidencija iznenadne srčane smrti kod sportista umanjena je za čak 89%, sa 3,6/100 000 u periodu pre obaveznog EKG-a skrininga (1979–1981) na 0,4/100 000 u periodu posle obaveznog EKG skrininga (1994–2003), sugerišući veliki značaj EKG za sprečavanje iznenadne srčane smrti sportista [4].

Ovaj rad predstavlja sistematski pregled literature i naših iskustava u ovoj oblasti. S obzirom da se na našim medicinskim fakultetima još uvek značajnije ne izučava sportska medicina, smatramo da naši lekari nisu dovoljno upoznati sa ovom izuzetno važnom problematikom, posebno imajući u vidu veliki broj osoba koje se bave sportom (profesionalni i rekreativni sportisti, sportisti veterani, učenici i studenti na nastavi fiskulture). Stoga je ovaj rad namenjen svim lekarima koji se u svom radu susreću sa problemom interpretacije EKG-a kod sportista.

Klasifikacija EKG promena kod sportista

Prema preporukama Evropskog udruženja kardiologa, EKG promene kod sportista podeljene su u dve grupe: 1. uobičajene (česte, klinički neznačajne) koje su povezane sa treningom (fizičkom aktivnošću) i 2. neuobičajene (manje česte, potencijalno klinički značajne − patološke) koje nisu povezane sa treningom **(Tabela 1)**. Utrenirani sportisti, čak i do 80% njih, usled fizioloških adaptacije srca na dejstvo autonomnog nervnog sistema pokazuju EKG promene kao što su sinusna bradikardija, atrioventrikularni (AV) blok prvog stepena i rana repolarizacija [1,5]. Takođe, EKG kod sportista može pokazati jasne voltažne kriterijume za hipertrofiju leve komore (LK) koja reflektuje fiziološko remodelovanje LK sa zadebljanjem zida i uvećanjem dimenzija komore [5]. Za razliku od navedenih, EKG promene kao što su ST-T abnormalnosti repolarizacije, patološki Q-zubac, odstupanje od leve osovine, interventrikularni poremećaji sprovođenja, komorska preekscitacija, prolongiran ili kratak QT interval i repolarizacija slična Brugadinom sindromu mogu biti odraz kardiovaskularnog oboljenja, naročito nasledne kardiomiopatije ili bolesti jonskih kanala, koje pak mogu dovesti do iznenadne srčane smrti [6,7]. Sportisti koji imaju EKG promene koje su posledica adaptacije na fizički napor (klinički irelevantne EKG promene) mogu nastaviti sa bavljenjem takmičarskim sportovima bez dodatne kliničke evaluacije a u odsustvu pozitivne lične ili porodične anamneze, simptoma ili patološkog fizikalnog nalaza [8]. Za razliku od njih, druga grupa sportista sa potencijalno patološkim EKG promenama iziskuje dalju kardiološku obradu. Stoga se može reći da ova klasifikacija ima potencijalno povoljne efekte na dalje kardiološko praćenje sportista, stratifikaciju rizika ali i uštedu u vremenu i novcu [5].

Obim morfoloških i električnih promena srca kod sportista zavisi od pola, rase, stepena utreniranosti i vrste sporta [8,9]. Dokazano je da su genetska i etnička pripadnost predisponirajući faktori za kardiovaskularno remodelovanje, pa su fiziološke EKG promene češće kod muškaraca sportista afričkog i karipskog porekla. Kod žena sportista EKG nalaz je u većini slučajeva normalan usled blagih morfoloških promena LK koje ne dovode do promena u EKG-u, ali i zbog manje zastupljenosti žena u napornijim sportskim disciplinama. Međutim, to nije slučaj kad su u pitanju sportistkinje crne rase. Smatra se da rasna pripadnost utiče na vagalnu osetljivost i izraženije uvećanje LK, što se elektrokardiografski manifestuje kroz voltažne kriterijume za hipertrofiju LK i ranu repolarizaciju [9]. Svakako treba istaći da intenzitet i trajanje treninga i/ili takmičenja, kao i aerobni kapacitet i vrsta sporta utiču na EKG promene. Sportovi koji iziskuju veću izdržljivost, kao što su npr. biciklizam, nordijsko skijanje i veslanje, imaju veću učestalost fizioloških promena na EKG-u [5].

Iznenadna srčana smrt sportista

Iako su sportisti generalno pod niskim rizikom od iznenadne srčane smrti, veliki broj kongenitalnih, a klinički neispoljenih, oboljenja povezan je sa iznenadnom srčanom smrti kod mladih sportista naročito nakon napornog fizičkog treninga [3]. Na osnovu obdukcijskih studija, hipertrofijska kardiomiopatija (HCM) je najčešći uzrok iznenadne srčane smrti kod mladih sportista, dok su na drugom mestu po učestalosti kongenitalne anomalije koronarnih arterija (anomalni ostijumi kao i polazište leve koronarne arterije iz desnog Valsavinog sinusa). Ostale strukturne abnormalnosti (valvularna oboljenja srca, ateroskleroza, dilatativna kardiomiopatija, Marfanov sindrom, aritmogena displazija desne komore) nalaze se samo sporadično pri obdukciji [10].

Tabela 1. Klasifikacija EKG promena kod sportista
Table 1. *Classification of ECG changes in athletes*

Grupa 1. Učestale EKG promene u skladu sa fizičkom aktivnošću (klinički neznačajne) ***Group 1.*** *Common training-related ECG changes (clinically irrelevant)*	**Grupa 2.** Neuobičajene EKG promene koje nisu u skladu sa fizičkom aktivnošću (potencijalno klinički značajne) ***Group 2.*** *Uncommon training-unrelated ECG changes (potentially clinically relevant)*
Sinusna bradikardija/*Sinus bradycardia*	Inverzija T-talasa/*T-wave inversion*
AV blok I stepena/*First-degree AV block*	Depresija ST segmenta/*ST-segment depression*
Inkompletni blok desne grane *Incomplete right bundle branch block*	Patološki Q-zubac *Pathological Q-wave*
Rana repolarizacija/*Early repolarization*	Uvećanje leve pretkomore/*Left atrial enlargement*
QRS voltažni kriterijum za hipertrofiju leve komore *Isolated QRS voltage criteria for left ventricular hypertrophy*	Odstupanje od leve osovine/prednji levi hemiblok *Left-axis deviation/left anterior hemiblock*
	Odstupanje od desne osovine/zadnji levi hemiblok *Right-axis deviation/left posterior hemiblock*
	Hipertrofija desne komore/*Right ventricular hypertrophy*
	Preekscitacija komora/*Ventricular pre-excitation*
	Kompletni levi ili desni blok grane *Complete left or right bundle branch block*
	Prolongirani ili skraćeni QT interval *Long or short QT interval*
	Rana repolarizacija slična Brugadinom sindromu *Brugada-like early repolarization*

ECG – *electrocardiogram*

Oko 2% naprasno umrlih mladih sportista ima normalan morfološki nalaz na srcu i velikim krvnim sudovima na obdukciji [9]. Uzrok smrti kod ovih sportista nije u velikim i jasno vidljivim strukturnim abnormalnostima, već manjim strukturno-funkcionalnim poremećajima pri čemu su najčešće u pitanju aritmije kao što su bolest jonskih kanala (Brugadin sindrom, dugi QT sindrom), Volf–Parkinson–Vajtov sindrom, strukturne abnormalnosti sprovodnog sistema, mikrovaskularne promene, kateholaminergične polimorfne tahikardije, koronarni vazospazam ili suptilne morfološke forme HCM [10].

Fiziološke EKG promene kod sportista

Sinusna bradikardija

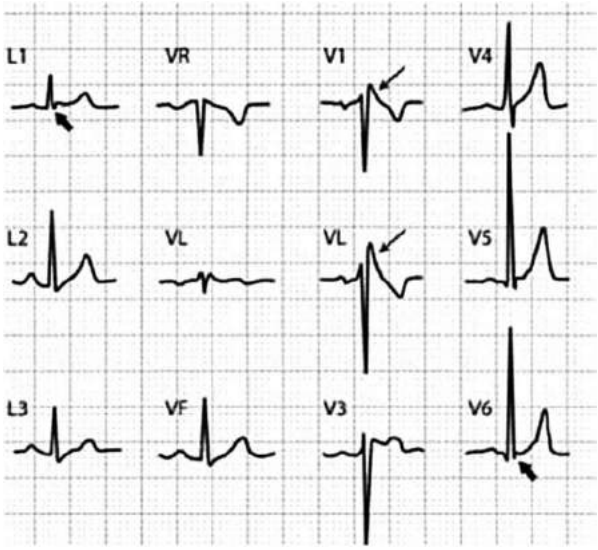
Kod sportista bradikardija nastaje kao fiziološki adaptivni odgovor autonomnog nervnog sistema na intezivnu fizičku aktivnost. Definiše se srčanom frekvencijom manjom od 60/min, a zavisi od vrste sporta i stepena utreniranosti [5]. Frekvencija je znatno niža kod sportova izdržljivosti kao što je npr. maraton i u obrnutoj je korelaciji sa stepenom utreniranosti. Nalaz srčane frekvencije manje od 30/min na 24 h-EKG-holteru kao i asimptomatskih pauza od 2-3 sekunde vrlo je učestao nalaz, naročito tokom spavanja [6]. Sinusna bradikardija se lako prevazilazi vežbanjem, što implicira da visoki vagalni tonus dovodi do sporijeg stvaranja impulsa u sinoatrijalnom čvoru. Sinusna aritmija različite frekvencije sreće se kod 13−69% sportista [11]. Smatra se da nastaje kao individualni odgovor na pojačan vagalni tonus, ali i na stepen utreniranosti. Razlikovanje sinusne bradikardije kod sportista i bolesti sinusnog čvora postiže se ukoliko: a) ne postoje simptomi kao što su sinkopa ili vrtoglavica, b) srčana frekvencija se normalizuje tokom vežbanja ili lekovima uz očuvanje maksimalne frekvencije, c) povlačenjem bradikardije nakon smanjenja ili proređivanja inteziteta treninga [1].

Atrioventrikularni blokovi

Atrioventrikularni blok I i AV blok II stepena oblika *Mobitz I−Wenkebach*, kod sportista se sreću u oko 35% slučajeva [1]. Nastaju kao posledica povećane parasimpatičke i/ili smanjene simpatičke aktivnosti i smatraju se adaptivnim odgovorom na fizičku aktivnost. Povlačenje AV bloka nakon vežbanja isključuje patološki nalaz [5]. AV blok II stepena oblika *Mobitz* II, kao i AV blok III stepena su retki nalazi kod sportista, a kada se nađu zahtevaju obaveznu dalju kardiološku evaluaciju.

Izolovano uvećanje QRS voltaže

Intenzivna fizička aktivnost dovodi do morfoloških promena samog srca, kao što su uvećanje srčanih šupljina, debljine zidova i mase leve komore [6]. Fiziološka hipertrofija LK kod sportista se vizualizuje elektrokardiografski kao izolovano uvećanje QRS amplitude (*Sokolow-Lyon index*), uz normalnu osovinu, aktivaciju pretkomora i ko-

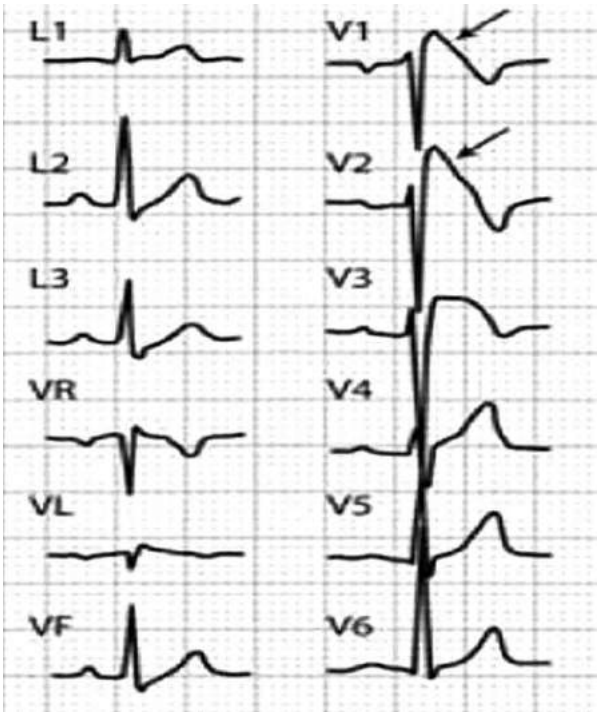


Slika 1. Granični EKG kod pacijenta sa Brugadinim sindromom koji imitira blok desne grane. Zapaziti odsustvo recipročnih S-talasa u D1 i V6 kao u bloku desne grane (prikazano strelicama)
Fig. 1. *Borderline Brugada ECG imitating right bundle branch block. Note the absence of reciprocal S waves in D1 and V6 as well as in the right bundle branch block (marked with arrows)*

mora, kao i ST i T- repolarizaciju [12]. Ove EKG promene sreću se kod oko 60% sportista i ne predstavljaju patološki nalaz ukoliko su bez simptoma, a sreću se naročito kod onih koji se bave sportovima velike izdržljivosti. Dokazano je da ovi sportisti nemaju strukturna oštećenja srca, uključujući HCM [1]. S druge strane, izolovani nalaz uvećane QRS voltaže redak je nalaz kod HCM [13].

Inkompletni blok desne grane Hisovog snopa

Ovaj elektrokardiografski nalaz sreće se kod 35−50% sportista i ukoliko je bez simptoma ne predstavlja patološki nalaz [1]. U populaciji zdravih mladih osoba njegova incidencija je 10% [5]. Smatra se da uvećana desna komora (uvećanje mišićne mase) dovodi do produženog vremena sprovođenja i da EKG nalaz (QRS < 120 ms) nije odraz specijalizovanog sprovodnog sistema. U nekim slučajevima inkompletni blok desne grane Hisovog snopa teško se razlikuje od Brugadinog sindroma, pa se dijagnoza postavlja tek nakon testa sa blokatorima natrijumovih kanala koji smanjuju visinu J-talasa i normalizuju ST segment [14]. Za razliku od R´ talasa u bloku desne grane Hisovoh snopa, J-talas u Brugadinom sindromu ne implicira kasnu aktivaciju desne komore, već odražava ranu repolarizaciju sa uzdignutom J-tačkom i visokim polazištem ST segmenta. Spuštanje ST segmenta praćeno je negativnim (kao uvala) ili pozitivnim (kao sedlo) T-talasom. U tipičnom bloku desne



Slika 2. Tipičan EKG nalaz Brugadinog sindroma
Fig. 2. *Typical ECG pattern of Brugada syndrome*

grane Hisovog snopa, R´ registrovan u V1 i V2 u recipročnom odnosu je sa S-talasom u D1 i V6, i nema ST elevacije u desnim prekordijalnim odvodima **(slike 1 i 2)** [15].

Rana repolarizacija

EKG nalaz rane repolarizacije predstavlja normalan nalaz u populaciji zdravih mladih ljudi, a kod sportista je više pravilo nego izuzetak i sreće se kod 50−80% sportista usled hipervagotonije nastale treniranjem [5]. Potpuno je reverzibilan fenomen koji nestaje nakon smanjenja ili prekida sportske aktivnosti [1]. Karakteriše ga elevacija QRS-ST spojnice (J- tačka) najmanje 0,1 mV iznad izoelektične linije, predominantno u levim prekordijalnim odvodima V4−V6 sa širokim i uspravnim T-talasom [15]. Elevacija ST segmenta može biti u lateralnim (D1, aVL, V5, V6), inferiornim (D2, D3, aVF), ili anteriornim odvodima (V2, V3). Osnovni mehanizam ST elevacije sličan je kao i u Brugadinom sindromu [16]. Eksperimentalno je dokazano da elevacija ST segmenta nastaje usled smanjenog epikardnog akcionog potencijala koji se prvi repolarizuje, a koji sam po sebi nije dovoljan da dovede do repolarizacione heterogenosti za nastanak tahikardija sa kružnim kretanjem [16]. Međutim, spoljašnji podražaji koji prevazilaze akcioni potencijal mogu dovesti do faze 2 akcionog potencijala i prouzrokovati ventrikularnu tahikardiju ili ventrikularnu fibrilaciju [17]. Smatra se da do ove pojave dovodi smanjenje tonusa simpatikusa koji razotkriva inherentnu asimetriju u repolarizaciji. Ovakvi slučajevi se retko susreću u kliničkoj prak-

si. Ponekad je diferencijalno-dijagnostički teško razlučiti da li su ST-T promene u desnim prekordijalnim odvodima odraz rane repolarizacije, aritmogene displazije desne komore ili Brugadinog sindroma [18]. U ovakvim slučajevima neophodno je dopunsko elektrofiziološko ispitivanje.

Potencijalno patološke EKG promene kod sportista

Inverzija T-talasa

Ovakav elektrokardiografski nalaz ubraja se u spektar kardiovaskularne adaptacije na intezivnu fizičku aktivnost. Njegova incidencija slična je kao kod kontrolne zdrave grupe mladih i iznosi oko 4,4% u odnosu na 4% [19]. Inverzija T-talasa > 2 mm u dva ili više odvoda je nespecifičan nalaz, za razliku od inverzije u inferiornim ili lateralnim odvodima koji mogu uputiti na ishemijsku bolest, kardiomiopatiju, bolest aortnih zalistaka ili sistemsku hipertenziju [20]. U velikom broju slučajeva, u vreme postavljanja dijagnoze HCM i aritmogene displazije desne komore, inverzija T-talasa bila je jedini patognomoničan nalaz [21]. Ukoliko kod sportista posle puberteta postoji inverzija T-talasa izvan V1 odvoda, postavlja se sumnja na kongenitalnu srčanu bolest ili ređe naslednu bolest jonskih kanala, koja iziskuje detaljno kardiološko ispitivanje. Inverzija T-talasa < 2 mm ili aplatirani T-talas u dva ili više odvoda (uglavnom inferiorni i/ili lateralni) smatra se odrazom povećanog vagalnog tonusa. Njegova incidencija je manja od 0,5% kod sportista, ali je čest nalaz kod kardiomiopatija. Iz tog razloga, neophodno je detaljno ispitivanje i praćenje kako bi se ove promene definitivno pripisale fiziološkom remodelovanju [22].

Depresija ST segmenta

Ovakav redak nalaz obično se opisuje sa inverzijom T-talasa, tako da je incidencija izolovanog nalaza nepoznata. Ukoliko ovaj nalaz postoji na EKG-u u mirovanju, bilo da je povezan sa T-talasom ili izolovan, iziskuje brzo ispitivanje [23].

Poremećaji intraventrikularnog sprovođenja

Kompletni blok leve i desne grane Hisovog snopa redak je nalaz i sreće se kod oko 0,4% sportista, dok je prevalencija u opštoj populaciji mlađih od 40 godina 0,6% kod muškaraca i 0,3% kod žena [1]. U slučaju prednjeg levog hemibloka (PLH), njegova prevalencija je ista kod sportista i u opštoj populaciji zdravih mlađih od 40 godina i iznosi 0,5−1% [5]. PLH je najčešće slučajan EKG nalaz kod sportista bez dokazanog strukturnog oboljenja srca, a opisani su slučajevi udruženosti PLH sa različitim kardiovaskularnim poremećajima [24]. Zadnji levi hemiblok kao jedini patološki zapis izuzetno je redak nalaz, a obično je udružen sa blokom desne grane [23]. Ovakav nalaz upućuje na značajan poremećaj specijalizovanog sprovodnog sistema koji nosi povećan rizik za nastanak AV bloka višeg stepena. U slučaju bloka grane, kao i hemibloka, neophodno je dalje kardiološko ispitivanje. Bifascikularni blok kod sportista obično je odraz genetski determinisanog oboljenja sprovođenja − Lenegreove bolesti [25].

Preekscitacija pretkomora – WPW sindrom

Prevalencija ovog nalaza je 0,1−0,3% i jednaka je kod sportista i u opštoj populaciji mladih [5]. Elektrokardiografski se registruje skraćen PR interval (< 0,12 s), sa nazubljenim početnim delom QRS kompleksa (delta talas) i proširenim QRS kompleksom, što je posledica fuzione aktivacije komora preko aberantnog puta, s jedne, i AV čvora i His-Purkinjeovog sistema, s druge strane. U većini slučajeva je bez simptoma [26]. Međutim, WPW sindrom je potencijalno vrlo opasan poremećaj koji može dovesti do aritmija kao što je atrijalna fibrilacija sa brzim komorskim sprovođenjem i potencijalnom malignom ventrikularnom fibrilacijom kao uzrokom iznenadne srčane smrti, kao rezultat brzog sprovođenja kroz akcesorni put sa kratkim anterogradnim refrakternim periodom. Rizik od iznenadne srčane smrti kod sportista bez simptoma je 0,15%, odnosno 0,25% kod sportista sa simptomima [26]. Smatra se da fizička aktivnost povećava rizik za nastanak ventrikularne fibrilacije. Manje poznata varijanta preekscitacije sa nodoventrikularnim ili fascikulo-ventrikularnim Manhajmovim vlaknima sa kratkim PR intervalom (< 0,12 s) i bez delta talasa iziskuje pažljivu evaluaciju jer može reflektovati Loun–Genong–Levineov sindrom ili strukturno oboljenje srca (HCM, Fabrijeva bolest). Sportisti sa elektrokardiografskim nalazom sindorma preekscitacije neodložno moraju biti hospitalizovani i detaljno kardiološki ispitani. Veliki uspeh u lečenju sindroma preekscitacije postiže se primenom radiofrekventne ablacije akcesornog puta, što je doprinelo da ova metoda postane terapija prvog izbora čak i kod sportista bez simptoma [26].

Prolongirani QT interval

QT interval je interval od početka Q-zupca do završetka T-talasa i ekvivalent je akcionog potencijala komora, tj. njihove depolarizacije i repolarizacije. Na njegovu dužinu utiču frekvencija srčanog rada, godine života i pol [24]. Kao preciznija mera srčanog ciklusa komora uzima se korigovana vrednost QT intervala (QTc) koja se izračunava po Bazetovoj formuli tako što se vrednost QT intervala podeli kvadratnim korenom rastojanja između dva R-zupca [24]. Najpreciznije merenje QT intervala je u odvodima D2, V3 ili V5 jer je tu i najveća vrednost [27]. Normalne vrednosti QTc intervala su do 440 ms, a vrednosti 440−460 ms kod muškaraca i 440−470 ms kod žena smatraju se graničnim [28]. Merenje vrednosti QT intervala kod sportista ima izvesna ograničenja zbog sinusne aritmije, blago proširenog QRS i T-U kompleksa. Korekcija za srčanu frekvenciju < 40/min i > 120/

min može biti neprecizna. QT interval je produžen kod sportista zbog niže srčane frekvencije u mirovanju usled intenzivne fizičke aktivnosti. Međutim, registrovanje QTc intervala iznad normalnih vrednosti postavlja sumnju na stečeni ili kongenitalni kardiovaskularni poremećaj [27]. Najčešći uzroci prolongiranog QT intervala su korišćenje lekova (antihistaminici, antibiotici, antimikotici, antipsihotici), bradikardija, metaboličke promene, elektrolitski disbalans kao i druge promene koje su u vezi sa intezivnom fizičkom aktivnošću [28]. S druge strane, sindrom prolongiranog QT intervala je genetski determinisano oboljenje jonskih kanala koje je potencijalno maligni poremećaj i može proizvesti maligne ventrikularne aritmije kao što su ventrikularna tahikardija oblika *torsades-de-pointes* i ventrikularna fibrilacija [29]. Različiti molekularni mehanizmi mogu objasniti različita klinička ispoljavanja i okolnosti pod kojima se poremećaji ritma događaju: jedna grupa ima sinkope ili srčani zastoj koji nastane tokom fizičke aktivnosti, najčešće tokom plivanja; druga grupa je osetljiva na emocionalni stres i akustične nadražaje; treća grupa ima bradikardiju zavisnu od QT produženja i obično kod njih srčani zastoj nastane u mirovanju, najčeše tokom spavanja [30]. Elektrokardiografski nalaz produženog QTc intervala nameće potrebu detaljnog kliničkog ispitivanja, uključujući i detaljnu porodičnu anamnezu i serijsko EKG merenje QTc intervala kod svih članova porodice, 24-časovni holter EKG-a, test opterećenja, a ponekad i genetsko mapiranje. Normalizovanje QTc intervala nakon prestanka fizičke aktivnosti predstavlja adaptivni mehanizam na intezivni trening [31].

Skraćeni QT interval

Ovaj entitet predstavlja naslednu bolest kalijumskih kanala i karakteriše ga kratak QT interval (vrednost QT 330 ms, QTc 360-380 ms) i povećani rizik za nastanak pretkomorskih i komorskih aritmija usled skraćenog vremena repolarizacije. Za precizno određivanje QT intervala neophodno je da srčana frekvencija bude < 80/min [1]. Uz kratak QT interval vrlo česta pojava je i skraćeni/odsutni ST segment i morfološki abnormalan visoki, uski T-talas u prekordijalnim odvodima. Nalaz kratkog QTc intervala (< 380 ms) kod sportista nameće potrebu da se najpre isključe potencijalni prolazni uzroci skraćenja kao što su hiperkalijemija, hipertermija, acidoza i neki lekovi (npr. digitalis). Međutim, ovakav nalaz može biti znak zloupotrebe anaboličkih androgenih steroida [32]. Nakon isključenja stečenih uzroka skraćenja QT intervala, neophodan je porodični EKG skrining kao i genetska analiza [33].

Slika 3. Različite EKG manifestacije Brugadinog sindroma A: ST elevacija kao „uvala" > 2 mm sa negativnim T; B: ST elevacija kao „sedlo" sa visokim polazištem > 2 mm i bifaznim T-talasom (B); C: ST elevacija kao „sedlo" sa visokim polazištem > 2 mm i pozitivnim T-talasom; D: J-elevacija > 2 mm sa terminalnim ST < 1 mm

Fig. 3. *Different ECG manifestations of Brugada syndrome A: ST elevation "cove"-like > 2 mm with negative T; B: ST elevation "saddle"-like with high take-off >2 mm and biphasic T wave (B); C: ST elevation "saddle"-like with high take-off > 2 mm and positive T wave; D: J elevation >2 mm with terminal ST < 1 mm*

EKG nalaz sličan Brugadinom sindromu

Brugadin sindrom je aritmogeni poremećaj koji je povezan sa visokim rizikom od iznenadne srčane smrti [34]. Elektrokardiografski ga karakteriše prolazni blok desne grane Hisovog snopa (naglašen J-talas), ST elevacija u desnim prekordijalnim (V1-V3) ili inferiornim (D2, D3, aVF) odvodima i negativan (kao uvala) ili pozitivan (sedlasti) T-talas **(Slika 3)**. Tokom vremena dinamičke promene u EKG-u su uobičajeni nalaz i mogu dovesti do prolazne, kompletne normalizacije nalaza. Međutim, stanja kao što su povišena telesna temperatura, elektrolitski disbalans, manevri ili okolnosti povezane sa povišenom vagalnom aktivnošću dovode do pojačavanja elevacije ST segmenta/J-talasa i mogu biti okidač brze polimorfne ventrikularne tahikardije ili srčanog zastoja usled ventrikularne fibrilacije. Iako iznenadna srčana smrt u Brugadinom sindromu nije povezana sa fizičkim naporom, povišeni tonus vagusa, koji se razvija kao posledica kontinuirane fizičke aktivnosti, može povećati mogućnost iznenadne smrti kao rezultat povećanog vagalnog oporavka. Neretko se iznenadna srčana smrt u ovom sindromu dešava u mirovanju, tokom spavanja ili neposredno nakon vežbanja [35]. Bez obzira što nije utvrđena povezanost vežbanja sa nastankom aritmija, sportistima sa potvrđenim Brugadinim sindromom zabranjeno je takmičarsko bavljenje sportom [36]. Međutim, još nije utvrđeno da li zdravim genetskim nosiocima bez fenotipske ekspresije treba ograničiti bavljenje sportom. Sportisti kod kojih se elektrokardiografski postavi sumnja na postojanje Brugadinog sindroma odmah se upućuju na dalje kardiološko, elektrofiziološko i farmakološko testiranje sa blokatorima natrijumskih kanala [37].

Zaključak

Prevencija iznenadne srčane smrti kod sportista je primarni cilj sportske medicine. Fizikalni pregled pre aktivnog bavljenja sportom predstavlja prvi i svakako najvažniji korak u dijagnostikovanju kardiovaskularnih oboljenja bez simptoma i potencijalno opasnih kardiovaskularnih oboljenja kod sportista. Uključivanje elektrokardiograma u skrining program povećava senzitivnost i značajno doprinosi ovom cilju, što je potvrđeno i rezultatima velike italijanske studije. Elektrokardiografskim

pregledom se pored učestalih, klinički irelevantnih promena kod izvesnog, malog broja sportista mogu otkriti i elektrokardiografske promene koje potencijalno mogu biti patološke i imati klinički značaj, te zahtevaju poseban oprez i dalju evaluaciju.

Literatura

1. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. Eur Heart J 2010;31:243-59.

2. Maron BJ, Thompson PD, Ackerman MJ, Balady G, Berger S, Cohen D, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update. Circulation 2007;115:1643-55.

3. Corrado D, Drezner J, Basso C, Pelliccia A, Thiene G. Strategies for the prevention of sudden cardiac death during sports. Eur J Cardiovasc Prev Rehabil 2011;18:197-208.

4. Pelliccia A, Maron BJ. Preparticipation cardiovascular evaluation of the competitive athlete: perspectives from the 30-year Italian experience. Am J Cardiol 1995;75:827-9.

5. Pelliccia A, Maron BJ, Culasso F, Di Paolo FM, Spataro A, Biffi A, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. Circulation 2000; 102:278-84.

6. Mazic S, Ilic V, Djelic M, Arandjelovic A. Sudden cardiac death in young athletes. Srp Arh Celok Lek 2011;139:394-401.

7. Mijailovic ZM, Stajic Z, Tavciovski D, Matunovic R. Sudden cardiac death in young athletes. Med Pregl 2009;62:37-41.

8. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. J Am Coll Cardiol 2008;51:2256-62.

9. Magalski A, Maron BJ, Main ML, McCoy M, Florez A, Reid KJ, et al. Relation of race to electrocardiographic patterns in elite American football players. J Am Coll Cardiol 2008;51:2250-5.

10. Popovic D, Mazic S, Nesic D, Velkovski S, Stojiljkovic S, Scepanovic L, et al. Athlete's heart syndrome. Srp Arh Celok Lek 2007;135:222-9.

11. Serra-Grima R, Puig T, Donate M, Gich I, Ramon J. Long-term follow-up of bradycardia in elite athletes. Int J Sports Med 2008;29:934-7.

12. Corrado D, Michieli P, Basso C, Schiavon M, Thiene G. How to screen athletes for cardiovascular diseases. Cardiol Clin 2007;25:391-7.

13. Pelliccia A, Culasso F, Di Paolo FM, Accettura D, Cantore R, Castagna W, et al. Prevalence of abnormal electrocardiograms in a large, unselected population undergoing preparticipation cardiovascular screening. Eur Heart J 2007;28:2006-10.

14. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510-5.

15. Brugada P, Brugada R, Brugada J. Sudden death in patients and relatives with the syndrome of right bundle branch block, ST segment elevation in the precordial leads V(1) to V(3) and sudden death. Eur Heart J 2000;21:321-6.

16. Yan GX, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: Cellular basis and clinical significance. J Am Coll Cardiol 2003;42:401-9.

17. Hlaing T, DiMino T, Kowey PR, Yan GX. ECG repolarization waves: their genesis and clinical implications. Ann Noninvasive Electrocardiol 2005;10:211-23.

18. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008; 52:1231-8.

19. Nasir K, Bomma C, Tandri H, Roguin A, Dalal D, Prakasa K, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation 2004;110:1527-34.

20. Uberoi A, Stein R, Perez MV, Freeman J, Wheeler M, Dewey F, et al. Interpretation of the electrocardiogram of young athletes. Circulation 2011;124:746-57.

21. Corrado D, Pelliccia A, Bjornstad HH, Vanhees L, Biffi A, Borjesson M, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Eur Heart J 2005;26:516-24.

22. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308-20.

23. Popovic D, Brkic P, Nesic D, Stojiljkovic S, Scepanović Lj, Ostojic M. Elektrofiziološke karakteristike sportskog srca. Med Pregl 2007;60:156-9.

24. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007;153:891-9.

25. Elizari MV, Acunzo RS, Ferreiro M. Hemiblocks revisited. Circulation 2007;115:1154-63.

26. Pappone C, Santinelli V, Rosanio S, Vicedomini G, Nardi S, Pappone A, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff- Parkinson-White pattern: results from a large prospective long-term follow-up study. J Am Coll Cardiol 2003;41:239-44.

27. Platisa MM, Mazic S, Nestorovic Z, Gal V. Complexity of heart beat interval series in young healthy trained and untrained men. Physiol Meas 2008;29:439-50.

28. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-22.

29. Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 2005;294:2975-80.

30. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000;102:2849-55.

31. Kapetanopoulos A, Kluger J, Maron BJ, Thompson PD. The congenital long QT syndrome and implications for young athletes. Med Sci Sports Exerc 2006;38:816-25.

32. Schimpf R, Borggrefe M, Wolpert C. Clinical and molecular genetics of the short QT syndrome. Curr Opin Cardiol 2008;23:192-8.

33. Maury P, Extramiana F, Sbragia P, Giustetto C, Schimpf R, Duparc A, et al. Short QT syndrome: update on a recent entity. Arch Cardiovasc Dis 2008;101:779-86.

34. Antzelevitch C, Brugada P, Brugada J, Brugada R, Towbin JA, Nademanee K. Brugada syndrome: 1992–2002: a historical perspective. J Am Coll Cardiol 2003;41:1665-71.

35. Arandjelovic A, Pavlovic S, Mazic S, Aleksandric B. Sudden cardiac death in athletes. Srp Arh Celok Lek 2004; 132:194-7.

36. Pelliccia A, Fagard R, Bjornstad HH, Anastassakis A, Arbustini E, Assanelli D, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease. Eur Heart J 2005;26:1422-45.

37. Steinvil A, Chundadze T, Zeltser D, Rogowski O, Halkin A, Galily Y, et al. Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death proven fact or wishful thinking? J Am Coll Cardiol 2011;57:1291-6.

Rad je primljen 14. VI 2012.
Recenziran 10. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:225-232.

STRUČNI ČLANCI
PROFESSIONAL ARTICLES

Primary and Secondary School Centre ”Milan Petrovic” with Dormitory, Novi Sad[1]
Department of Rehabilitation and Special Education, Novi Sad[2]

Stručni članak
Professional article
UDK 376.3/.4 i UDK 616.89-008.48-053.2
DOI: 10.2298/MPNS1306233T

SYSTEMIC MULTIMODAL APPROACH TO SPEECH THERAPY TREATMENT IN AUTISTIC CHILDREN

SISTEMSKI MULTIMODALNI PRISTUP U LOGOPEDSKOM TRETMANU DECE SA AUTIZMOM

Daniela TAMAŠ[1], Slavica MARKOVIĆ[1] and Vesela MILANKOV[2]

Summary

Introduction. Conditions in which speech therapy treatment is applied in autistic children are often not in accordance with characteristics of opinions and learning of people with autism. A systemic multimodal approach means motivating autistic people to develop their language speech skill through the procedure which allows reliving of their personal experience according to the contents that are presented in the their natural social environment. This research was aimed at evaluating the efficiency of speech treatment based on the systemic multimodal approach to the work with autistic children. **Material and Methods.** The study sample consisted of 34 children, aged from 8 to 16 years, diagnosed to have different autistic disorders, whose results showed a moderate and severe clinical picture of autism on the *Childhood Autism Rating Scale*. The applied instruments for the evaluation of ability were the Childhood Autism Rating Scale and Ganzberg II test. The study subjects were divided into two groups according to the type of treatment: children who were covered by the continuing treatment and systemic multimodal approach in the treatment, and children who were covered by classical speech treatment. **Results.** It is shown that the systemic multimodal approach in teaching autistic children affects the stimulation of communication, socialization, self-service and work as well as that the progress achieved in these areas of functioning was retainable after long time, too. **Conclusion.** By applying the systemic multimodal approach when dealing with autistic children and by comparing their achievements on tests applied before, during and after the application of this mode, it has been concluded that certain improvement has been achieved in the functionality within the diagnosed category. The results point to a possible direction in the creation of new methods, plans and programs in dealing with autistic children based on empirical and interactive learning.

Key words: Speech Therapy; Child; Autistic Disorder; Combined Modality Therapy; Communication

Sažetak

Uvod. Uslovi u kojima se primenjuje logopedski tretman za decu sa autizmom često nisu usklađeni sa karakteristikama mišljenja i učenja osoba sa autizmom. Sistemski multimodalni pristup podrazumeva podsticanje govorno-jezičkog razvoja putem postupka koji omogućava proživljavanje ličnog iskustva u skladu sa sadržajima koji se prezentuju detetu u prirodnom socijalnom okruženju. Osnovni cilj istraživanja je bila procena efikasnosti logopedskog tretmana zasnovanog na sistemskom multimodalnom pristupu u radu sa decom sa autizmom. **Materijal i metode**. Ispitivani uzorak činilo je trideset četvoro dece sa dijagnozom iz spektra autističnih poremećaja, uzrasta od 8 do16 godina, čiji su rezultati na *Childhood Autism Rating Scale* skali pokazali umerenu i tešku kliničku sliku autizma. Uz ovu skalu za procenu sposobnosti primenjen je i Ganzberg II test. U odnosu na vrstu tretmana ispitanici su podeljeni u dve grupe − deca koja su bila obuhvaćena kontinuiranim tretmanom i sistemskim multimodalnim pristupom u tretmanu i deca koja su bila obuhvaćena klasičnim logopedskim tretmanom. **Rezultati**. Pokazano je da se sistemskim multimodalnim pristupom u radu sa decom sa autizmom utiče na stimulaciju razvoja komunikacije, socijalizacije, samoposluživanja i rada kao i da je postignuti napredak u ovim oblastima funkcionisanja održiv i nakon dužeg vremena. **Zaključak.** Primenom sistemskog multimodalnog načina rada sa decom sa autizmom i poređenjem njihovih postignuća na testovima primenjenim pre, za vreme i posle primene ovog načina rada, zaključujemo da se pokazao napredak u funkcionalnosti u okviru dijagnostikovane kategorije. Rezultati ukazuju na mogući smer u kreiranju novih metoda, planova i programa u radu sa decom sa autizmom baziranih na iskustvenom i interaktivnom učenju.

Ključne reči: Logopedski tretman; Dete; Autizam; Multimodalna terapija; Komunikacija

Corresponding Author: Mr Daniela Tamaš, psiholog, Škola za osnovno i srednje obrazovanje ”Milan Petrović”, 21000 Novi Sad, Braće Ribnikara 32, E-mail: autizam.mp@gmail.com

Abbreviations
CARS – Childhood Autism Rating Scale

Introduction

Speech and language therapy for autistic children, which is used in many of our institutions, is usually based on the promotion of language skills according to the age, often in conditions that are not conformed to the characteristics of thinking and learning of autistic people. The traditional methods of speech therapy in treatment of autistic children often rely on the exercise of speech, sign language and methods of showing images that require good previous knowledge of specific skills. The focus of treatment is usually on an isolated segment of speech and language structure that must be corrected in a child, without abridging the already trained and adapted contents with other functional structures of the child. An autistic child who has difficulty in understanding and generalization of concepts in such conditions has not been given an opportunity to learn empirically. Classical speech therapy treatment lacks the empirical moment and the possibility of spreading experience into different social and communicational situations that will enable the child to develop speaking linguistic structures in appropriate circumstances, while using communication and modification of these conditions.

The systemic multimodal approach involves encouraging of the development of speech and language structures through a channeled and planned process that enables these children to live out their own personal experience in accordance with the contents that are presented to them in their natural social environment.

The content presented to a child in order to encourage the development of speech and language specific structure permeates all areas of life and learning, and all systems of social interaction (school, family, wider social system). This method means working in large and small groups of children with similar abilities of communication, individual encouragement, compulsory cooperation with other members of the professional team and partnership with the parents of the child. The systemic multimodal approach to speech therapy treatment of autistic children requires all the contents presented to the child to permeate as many life and educational training areas (modules) and social situations (the system) as possible, thus enabling the development of certain speech and language structures encouraged by the development of awareness through stimuli coming through all sensory and social systems. By including these children in the social environment, they are given the opportunity to develop speech and language structures through personal experience [1]. Frustration resulting from unknown situations can be reduced by the targeted and gradual introduction of the child into more complex social systems. This is the way to encourage the child's independence and desire for spontaneous interaction. Having become more aware of the social environment, the child develops the interest and desire to interact with the environment and to become a part of the environment itself [2,3]. To gain the trust of an autistic child our reactions must be appropriate, purposeful and supported by various and concrete examples from life. By dividing the content presented to our child into as many sections as possible, we will enable their proper, more precise and clearer understanding. Thus, we shatter the stereotypical environmental schemes that happen according to the established order [4]. One of the basic rules of success in working with children with autism is to familiarize with them, recognize their desires, needs, preferences, and introduce a tailor-made speech therapy. The generalization of learning is often a problem with autistic children and communication skills must be encouraged in a way that will enable the child to connect and group the terms. If stimulus of speaking language skills is limited to only one location, due to difficulties in the generalization of concepts, children may think that certain rules are applied only in situations related to that place.

The development of speech and language skills should be stimulated gradually through the more complex structure of the child's functioning. The area being encouraged is extended through various activities during the day and in different situations, so this way of working is called multimodal. This encouraging should be done gradually and systematically from the cabinet circles outwards into wider circles, such as family, in the contact with the closest family members. If we take into consideration that the treatment is tailor-made according to the wishes, needs and interests of the child and that a certain kind of stimulation is thus repeated several times but through situations that get more complicated by introducing new activities, a new person in the interaction, or by applying it in a new situation, then we take a child through a convoluted path of incentives in the field of speech language where each new circle of activities will be on a higher level of request complexity. Such a stimulation treatment of speech language functions that enables the participation and interaction in various life surroundings, where appropriate models, stimulants and natural point are available, encourages the social skills learning at the same time [5].

Development of the ability to use the language for more and more purposes (greetings, questions, statements, information, etc), understanding of others in the communication and adequate reactions, development of the ability to take part in the communication (how to start the communication, how to respond during the interaction, how to maintain the interaction, and so on) depend on the exposure

to different social models of communication that affect the child during the development.

The complexity of the situation and requirements is being changed as the environment together with the people around child and the ways of communication are changing, all of which encourage the children to use skills acquired and modified according to the situation in which they find themselves. Targeted and focused guidance of a child in the situations that gradually become more complex and go out of the learned patterns enables the child to learn and improve the ability to communicate and establish social interactions based on their own experience. Such an approach will enable the child to raise the abilities in the communication skills to a higher level, and if such a development is presented as a spiral, we can see that a higher level of competence, which is represented by a spiral coil, is constantly expanding by adding a new link to the chain that have just been formed under the influence of factors of various social situations in which the child has been.

The treatments in the natural, social surrounding are also targeted, pre-selected and channeled by the therapist, but the natural social surrounding provides something that is impossible in the cabinet conditions and that is the impact of external factors, which often put and set the pace and course of a situation, such as various limiting, distracting, confusing factors which we can not predict and plan and which require a certain amount of tolerance and accommodation.

In everyday speech therapy work within the treatment of autistic children, both multimodal systemic and classical approach to speech therapy are applied.

The main aim of this study was to evaluate the effectiveness of speech therapy system based on multimodal approach to teaching autistic children compared to the classical speech therapy approach.

Material and Methods

Thirty-four children, aged between 8 and 16, diagnosed to have different types of autism disorders were included in the prospective, controlled study whose results show moderate to severe clinical picture of autism on the Childhood Autism Rating Scale (CARS). The study sample was divided into two groups. The study group was divided into two sub-groups with 17 subjects each by the random choice method.

The first group consisted of children continually treated by systemic multimodal approach. The subjects in the first group were treated in the organizational unit for treatment of autistic people at Primary and Secondary School Centre ”Milan Petrović” in Novi Sad.

The other group consisted of 11 children, who were the members of the Organization to help autistic people in Krusevac and 6 children treated by classical speech therapy at Primary and Secondary School Centre ”Vuk Karadžić” in Sombor. The groups were matched according to their performance which ranged from moderate to severe autism.

The following instruments were used to assess the abilities of the autistic children: Ganzberg II – the test to assess children's psychomotor skills and the CARS (Schopler, Reichler 1988), the scale to determine the degree of autistic disorder. Ganzberg II test contains items designed so that responses to the questions give information about the quantity of successful performance of certain tasks. CARS is a qualitative test containing open questions which provides data about the extent of the present difficulties, i.e. the quality of performance of certain tasks. Both tests assess the same areas of functioning since it is possible to group the scales at CARS test in accordance with the Ganzberg II areas such as: socialization, communication, work and general condition. Higher scores on Ganzberg II scale and lower scores on CARS scales show better results and a better clinical picture.

Since the main objective is focused on checking the effectiveness of the treatment, the draft including three repeated measurements was chosen. The measurements were done before the beginning, in the middle and after the end of the treatment with the same intervals of 5 months.

The first phase of research lasted a year, with a comparative analysis of the monitored parameters. Throughout the school year, i.e. the period during which the research was conducted, the first group was included in the speech therapy based on the systemic multimodal approach. The topics discussed during the speech therapy treatment correlated with other pedagogical and educational areas included in the special curriculum for children with autism. The emphasis in this study was given to the acquisition of communicative and social skills while gaining personal experience of the subjects. The second group was included in the classical speech therapy administered in the speech classroom, individually, without the correlation with other pedagogical and educational areas or opportunities to acquire communicative and social skills through personal experience.

In order to assess the possibility to retain the acquired skills after 5 years, the repeated measurement using CARS and Ganzberg II test was done. The assessment was made for the first group of subjects treated within the systemic multimodal approach. The group consisted of the same subjects as previously.

The results were analyzed using the appropriate statistic tests, depending on the group size, characteristics or distribution type. The data were processed by using standard descriptive statistic methods. The t-test was used for dependent samples to check the significance of differences.

Table 1. Average scores of the variable Communication in three measurements
Tabela 1. *Prosečni skorovi varijable Komunikacija na tri merenja*

Sort of test *Vrsta testa*	Treatment *Tretman*	1st measurement *1. merenje*	2nd measurement *2. merenje*	3rd measurement *3. merenje*
Ganzberg II	Systemic multimodal/*Sistemski multimodalni*	10.29	19.82	26.00
Ganzberg II	Classical speech therapy/*Klasičan logopedski*	7.59	9.94	10.24
CARS	Systemic multimodal/*Sistemski multimodalni*	4.71	4.59	4.24
CARS	Classical speech therapy/*Klasičan logopedski*	7.41	7.29	7.06

Results

In order to determine whether the systemic multimodal treatment showed better effects than the classical speech therapy in the development of communication skills, socialization, and general condition of autistic children, the following two factors were studied: the treatment (multimodal system and classical speech therapy) and time (first, second and third measurement) as well as their interaction shown by the values obtained in the tests Ganzberg II and CARS.

The results of the tests done after both kinds of treatment (the systemic multimodal and classical speech therapy) suggest the progress in communication skills in each of conducted measurements **(Table 1)**.

The autistic children, who were included in the systemic multimodal approach, progressed in communication skills. The progress implied a more frequent use of various forms of communication and more intensive use of the existing communication abilities.

In comparison to the observed aspect of socialization, the results obtained by the tests showed that the difference was present when they were observed through the quantitative values obtained by Ganzberg II test, while qualitative changes showed no statistically significant difference **(Table 2)**.

The group of children who were included in the multimodal treatment showed improvements in quantitative terms, i.e. better motivation for work and success in performing the work assignments, self-serving and independence. The results of the achievement in the Ganzberg II test show a statistically significant difference **(Table 3)**.

Further analysis was to discover if the severity of symptoms of disorders within the autistic spectrum and overall functioning of autistic children changed with the acquisition of communication skills influenced by the systemic multimodal treatment **(Table 4)**.

The results of both tests indicate that there was some improvement in the general functioning of children. After a year, the systemic multimodal approach to autistic children enabled them to become more receptive and open to new contents offered to them from their closest environment, and to apply the acquired knowledge and skills in different social situations. By encouraging children to take part in the spontaneous, natural, everyday communication gradually enhanced and consolidated by various systems of social interactions, we enabled them to learn from their personal experience. By expanding their experience, their consciousness was awakened not only in the sphere of communication, but also in being aware of themselves and their own existence in the environment and of opportunities to interact with it. This type of work increases the interest in the environment and the opportunities offered in it.

The CARS test results, which did not confirm the hypothesis in certain areas, indicate that although the symptoms of autism are still present, the general condition of autistic children can be improved by giving them the access to the environment.

The results of measurements repeated after five years show the possibility to retain the acquired abilities and skills in the children included in the systemic multimodal approach to treatment. No deteriorations of certain functions have been observed. The difference was evident only with the results of the Ganzberg II test, while the CARS results showed no difference **(Table 5)**.

Table 2. Average scores of the variable Socialization in three measurements
Tabela 2. *Prosečni skorovi varijable Socijalizacija na tri merenja*

Sort of test *Vrsta testa*	Treatment *Tretman*	1st measurement *1. merenje*	2nd measurement *2. merenje*	3rd measurement *3. merenje*
Ganzberg II	Systemic multimodal/*Sistemski multimodalni*	9.71	14.06	16.94
Ganzberg II	Classical speech therapy/*Klasičan logopedski*	4.18	5.65	6.41
CARS	Systemic multimodal/*Sistemski multimodalni*	9.21	8.47	7.82
CARS	Classical speech therapy/*Klasičan logopedski*	12.26	11.62	11.26

Table 3. Average scores of the variable Work in three measurements
Tabela 3. *Prosečni skorovi varijable Rad na tri merenja*

Sort of test *Vrsta testa*	Treatment *Tretman*	1st measurement *1. merenje*	2nd measurement *2. merenje*	3rd measurement *3. merenje*
Ganzberg II	Systemic multimodal/*Sistemski multimodalni*	17.12	24.00	30.06
Ganzberg II	Classical speech therapy/*Klasičan logopedski*	6.47	8.47	10.71
CARS	Systemic multimodal/*Sistemski multimodalni*	11.29	11.00	9.79
CARS	Classical speech therapy/*Klasičan logopedski*	13.82	13.26	12.56

It can be concluded that not only there was no deterioration of certain functions but there was an obvious improvement in all areas assessed by Ganzberg II test: communication, socialization, and self-service and work, all proved by statistically significant differences in the results from the previous period and after five years.

Discussion

Many different forms of treatment have been promoted as the ones that make significant improvements in the function of autistic children. There have often been doubts about the choice and intensity of treatment to be applied as well as the age when to apply it. According to the previous research, not a single approach has proved to be either superior to the other or equally effective for all individuals. Given the complexity of the condition of autism, interference levels and skills displayed by these children, the expectations that a single treatment will have the same effect on all are unrealistic [6]. The results of our study suggest that the development of speech and language skills are encouraged more efficiently in the natural social environment and the acquired communication skills are used more intensively. The treatment designed on the basis of an interactive approach to support autistic children enables them to relive their personal experience at all levels of communication, which in addition to our support makes them more functional, gives them directions and motivates them to achieve social inclusion. The results of our research show that the children who were included in the systemic multimodal approach have advanced in the area of socialization in terms of quantity and that social interactions have been established much more frequently.

The starting points when designing programs for the treatment of autistic people should be a combination of different sources: theoretical knowledge, the results obtained by the scales for evaluation and tests for the assessment of the child, the empirical data obtained on the basis of well-formed small groups and on the basis of individual studies [7]. The components of treatment must be tailored to each individual and their family. The program should be individualized according to the cognitive level of the individuals, their age, needs and manifested symptoms and temperament [8,9]. The clear structure of the educational and daily life provides an autistic person with a predictable and easily understandable surrounding, thus decreasing confusion and minimizing frustration [10,11].

It is necessary to ensure that communication is in accordance with the individual abilities of the user, and that verbal messages should often be accompanied by visual signs. According to Rogers, programs focusing on the weaknesses of social communication can have significant effects [12]. Our experience also confirms this fact, which can be seen by the progress in the frame of quantitative assessment, which shows that the multimodal system method allowing children to gain knowledge and skills in the natural and social environment encourages children to participate in activities. When these children are gradually introduced into more complex social situations, they get to know their environment and gain confidence in people around them and start to feel safe and accepted. Since the systemic multimodal approach stimulates the development of all segments of functioning and encourages these children to make choices and decisions, to express their needs, thoughts and desires and to show anyhow that they have made contact with others, they get

Table 4. Average scores of the variable General Condition in three measurements
Tabela 4. *Prosečni skorovi varijable: opšte stanje, na tri merenja*

Sort of test *Vrsta testa*	Treatment *Tretman*	1st measurement *1. merenje*	2nd measurement *2. merenje*	3rd measurement *3. merenje*
Ganzberg II	Systemic multimodal/*Sistemski multimodalni*	63.00	90.53	111.24
Ganzberg II	Classical speech therapy/*Klasičan logopedski*	35.18	43.82	49.53
CARS	Systemic multimodal/*Sistemski multimodalni*	2.74	2.59	2.32
CARS	Classical speech therapy/*Klasičan logopedski*	3.24	3.18	3.18

Table 5. Socialization, Communication, Work, General Condition
Tabela 5. *Socijalizacija, komunikacija, rad, opšte stanje*

Scale *Skala*	Measurement *Merenje*	Arithmetic mean *Aritmetička sredina*	T-test	DF	P
Socialization (Ganzberg II) *Socijalizacija*	3rd measurement/*3. merenje*	16.94	-3.00	16	0.01 *
	Control measurement/*Kontrolno merenje*	18.53			
Socialization (CARS) *Socijalizacija*	3rd measurement/*3. merenje*	7.82	-0.91	16	0.38
	Control measurement/*Kontrolno merenje*	8.09			
Communication (Ganzberg II) *Komunikacija*	3rd measurement/*3. merenje*	26.00	-2.47	16	0.03 *
	Control measurement/*Kontrolno merenje*	28.94			
Communication (CARS) *Komunikacija*	3rd measurement/*3. merenje*	4.24	1.07	16	0.30
	Control measurement/*Kontrolno merenje*	4.12			
Work (Ganzberg II) *Rad*	3rd measurement/*3. merenje*	30.06	-1.82	16	0.09 *
	Control measurement/*Kontrolno merenje*	30.06			
Work (CARS) *Rad*	3rd measurement/*3. merenje*	9.79	1.65	16	0.12
	Control measurement/*Kontrolno merenje*	9.32			
General state Ganzberg II total *Opšte stanje Ganzberg II ukupno*	3rd measurement/*3. merenje*	111.24	-3.09	16	0.01 *
	Control measurement/*Kontrolno merenje*	122.53			
General state CARS total *Opšte stanje CARS ukupno*	3rd measurement/*3. merenje*	29.41	0.87	16	0.40
	Control measurement/*Kontrolno merenje*	28.82			

to know their environment and develop the feeling of satisfaction through inter-personal relations. Children become aware of their environment and they are encouraged to get interested in the world around them and to perform various activities offered to them. When children are given the possibility to gain knowledge about the environment around them by gradual and planned introduction into it by experiencing various situations in accordance with the individual plan of support, they are stimulated to feel the need to become a part of that environment. By performing various assignments, the children are taught the causal relationships in the work procedures, as a reaction caused by the results of their activities. It has been noticed that when the children are introduced to their surrounding gradually and purposefully, they perform certain work assignments and self-service activities more frequently and more independently, which indicates an improvement in the general condition of children.

Many undesirable ways of behavior are a reflection of the limited behavioral repertoire or poor communication skills. The treatment based on encouraging the development of communication skills often contributes to the reduction of destructive and aggressive behavior [13]. Treatment approaches centered in the family result in greater generalization and consolidation of acquired skills. Designing a program that can be implemented at any time, but in a way that does not require additional sacrifices in terms of time, money, or other aspects of family life is the most beneficial for all involved [14]. Practical support from experts can be crucial for the family, especially at an early age of the child.

When children with disabilities characteristic of autism acquire communication skills in isolated social situations, they can hardly be expected to generalize and apply these skills in different contexts and modify them accordingly. Such children should be enabled to acquire communication and socialization skills in natural situations. Systemic multimodal approach is based on this idea and its structure makes it possible for the child to learn empirically and link situations at that particular level. It is tailor-made to fit the individual characteristics of the situation, interests, needs, child's age and the conditions in which s/he lives.

Gradual expansion of the social situation and the environment, where the treatment is carried out, is meant to avoid rote learning and stereotypical behaviors, and the involvement of family and wider environment is essential for achieving the best possible results.

Conclusion

By applying the system of multimodal approach to children with moderate and severe clinical manifestations of autism and by comparing their achievements with the relevant tests applied before, during and after the application of this method, we can conclude that it was not possible to influence the change in terms of categories, but it has shown some progress in the functionality of diagnostic category. This shows the lack of statistically significant differences in the Childhood Autism Rating Scale, as well as the level of symptoms, and statistically significant differences in Ganzberg II test that tells us about the level of skills in quantitative terms, i.e. the frequency of performing ac-

tivities covered by the test and independence in the domains of functioning.

The results of both tests indicate that there has been some significant progress in the general state of children functioning. Having been treated by systemic multimodal approach for a year, the autistic children became more receptive and open to accept new contents offered to them from their immediate surrounding and to apply the acquired knowledge and skills in different social situations. Encouraged to enter spontaneous, natural, everyday communication, which was getting more complicated and consolidated by the variety of systems of social interactions, children were enabled to learn from their personal experience. By expanding the experiential circle, we encouraged the children not only to acquire the communication skills but also to gain knowledge about themselves and their environment as well as the opportunities to interact with it. Such a way is good for encouraging the development of interest in the environment and the opportunities offered by this environment.

The results of this study indicate the likely direction in designing new methods, plans and programs to work with children with autism. Systemic multimodal approach to autistic children as a form of targeted experiential and interactive learning is a form of treatment that, with the appropriate adjustments and adaptations, can be used as the primary or adjuvant treatment in all segments of the educational work and during all phases of life, regardless of age and the clinical picture. Detailed research towards the implementation of treatment and possibility to retain its effects as well as the impact of factors of maturation and the treatment itself on the development of certain functions would contribute to the promotion of the systemic multimodal approach and its correction in order to achieve better results.

References

1. Nizamie, Sengupta, Mishra BR, Praharaj SK, Nizamie SH. parts were sung by of ran multimodal interventions in a case with autistic regression. Acta Neurol Taiwan 2010;19(1):51-6.

2. T. Tykkyläinen Task-setting at home and in speech and language therapy. Child Lang Teach Ther 2009;25(3):319-40.

3. Terziev (D, N. Polnareva Autism spectrum disorders, Gen Med. 2011;13(2):24-31.

4. Qureshi, Al-Ghamdy ys, Al-Habeeb THE, pervasive developmental disorders: etiological, diagnostic and treatment conundrum, Neurosciences, 2003;8(3):143-55.

5. Dwyer KK. The multidimensional model: teaching students the Jurisic Sturm-manage the high communication apprehension by Jurisic Sturm-selecting treatments. Communic Educ 2000;49(1):72-81.

6. Howlin P. The effectiveness of interventions for children with autism. J Neural Transm 2005;(Suppl 69):101-19.

7. Prizant were reported by international, Rubin E. Contemporary issues in interventions for autism spectrumdisorders: a commentary. J Assoc Persons Severe Handicaps. 1999;24:199-208.

8. Koegel RL, Koegel LK, McNerney EC. Pivotal areas in intervention for autism. J Clin Child Psychol. 2001;30:19-32.

9. Golubovic Š, Tubic T, Markovic S. Reedukacija psihomotorike: pokret kao terapijska metoda. Med Pregl 2011;64(1-2):61-3.

10. Schopler E. Interpret of TEACCH philosophy. In: Cohen DJ, Volkmar FR, eds. Handbook of autism and pervasive developmental disorders. 2nd ed. New York: JohnWiley; 1997. p. 767-98.

11. Maksimovic J, Golubovic Š. Značaj individualnih obrazovnih planova u inkluzivnom obrazovanju učenika sa posebnim potrebama. Naučni skup "Nasuka i politika"; 2010 maj 22-23; zbornik radova. Tom 2. Knj. 5. Pale, RS. Pale: Filozofski fakultet; 2010. str. 501-12.

12. Meanwhile Mr. Rogers wanted SJ. interventions that facilitate socialization in children with autism. J Autism Dev Disord. 2000;30:399-410.

13. Durand VM, Merges E. Functional communication training: a contemporary behavior analytic intervention for problem behavior. Focus Autism Dev Disord. 2001;16:110-9.

14. Marcus LM, Kunce Lj, Schopler E. Working with families. In: Cohen D, Volkmar F, eds. Handbook of autism and pervasive developmental disorders. 2nd ed. New York: Wiley; 1997 p. 631-49.

Rad je primljen 21. IX 2012.
Recenziran 12. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:233-239.

Institut za javno zdravlje Vojvodine, Medicinski fakultet Novi Sad
Centar za promociju zdravlja[1]
Centar za analizu, planiranje i organizaciju zdravstvene zaštite[2]
Centar za informatiku i biostatistiku u zdravstvu[3]

Stručni članak
Professional article
UDK 613.96:616.89-008.441.44
DOI: 10.2298/MPNS1306240C

STAVOVI ADOLESCENATA O SAMOUBISTVU

ATTITUDES TOWARDS SUICIDE AMONG ADOLESCENTS

Dušan ČANKOVIĆ[1], Sonja ČANKOVIĆ[2], Snežana UKROPINA[1], Olja NIĆIFOROVIĆ ŠURKOVIĆ[1], Sanja HARHAJI[3] i Ivana RADIĆ[3]

Sažetak

Uvod. Republika Srbija sa relativno visokom stopom samoubistva od 19,5 na 100 000 stanovnika svrstava se u gornju polovinu liste evropskih zemalja po broju samoubistava. Međutim, naročito zabrinjavajuće stanje je u Vojvodini, koja u okviru Srbije, ali i bivše Jugoslavije, dugoročno predstavlja područje visoke smrtnosti stanovništva usled samoubistva. U Vojvodini je u periodu od pet i po decenija broj samoubistava povećan za oko 50%, a svaki osmi smrtni slučaj usled samoubistva bio je slučaj mlade osobe. Cilj ovog rada je da se ispitaju stavovi adolescenata o samoubistvu kao i da li razlika u starosnom dobu utiče na promenu stava prema samoubistvu. **Materijal i metode.** U ovom istraživanju korišćen je upitnik o samoubistvu, tzv. *Suicide Opinion Questionnaire* autora Džordža Dominoa. Upitnik o samoubistvu ispunile su ukupno 254 mlade osobe podeljene u dve starosne grupe. Od ukupnog broja, 124 pripadaju starosnom dobu od 13 do 15 godina, a 130 starosnom dobu od 18 do 19 godina. **Rezultati.** Rezultati ove studije ukazuju na to da se stavovi o samoubistvu mlađe i starije grupe adolescenata uglavnom poklapaju i ne postoji statistički značajna razlika u odgovorima prema posmatranim faktorskim skalama. **Zaključak.** Ovo istraživanje ukazuje da su stavovi ispitanika obe starosne grupe pokazatelj nedostatka svesti o samoubistvu, njegovim uzrocima i dinamici razvoja ovog javnozdravstvenog problema. Ovo ostavlja prostor za intenzivniji edukativni rad u oblasti mentalnog zdravlja stanovništva, posebno mladih kao i za dalja istraživanja problema samoubistva kao osnove za razradu strategije i prevencije ovog javnozdravstvenog problema.

Ključne reči: Adolescent; Samoubistvo; Stav prema smrti; Stav; Epidemiologija; Faktori starosti; Upitnici; Mentalno zdravlje; Javno zdravlje

Summary

Introduction. Having a relatively high suicide rate of 19.5 per 100.000 inhabitants, the Republic of Serbia is in the first half on the list of the European countries concerning the number of suicides. However, the situation is particularly alarming in Vojvodina, which has been one of the areas with a very high population mortality rate caused by suicide for a long period of time not only in Serbia of nowadays, but also in former Yugoslavia. The number of suicides has increased by almost 50% over the last five and a half decades, and every eighth suicide was committed by a young person. The aim of this paper was to explore adolescents' attitudes towards suicide and to find out whether the difference in age affects changes in attitudes regarding suicide. **Material and Methods.** The George Domino's Suicide Opinion Questionnaire was completed by 254 adolescents divided into two age groups – 124 respondents were in the age group 13 to 15 and 130 of them in the age group 18 to 19. **Results.** The results of this study suggest that the attitudes of younger and older group of adolescents towards suicide mostly coincide and there is no statistically significant difference in the answers according to the analyzed clusters. **Conclusion.** This research shows that the attitudes of respondents of both age groups indicate a lack of awareness about suicide, its causes and dynamics of development of this public health problem. This leaves space for more intensive educational work in the mental health of the population, especially young people and for further research of the suicide problem as a basis for developing strategies.

Key words: Adolescent; Suicide; Attitude to Death; Attitude; Epidemiology; Age Factors; Questionnaires; Mental Health; Public Health

Uvod

Proučavanje, tretman i prevencija samoubistva, dešavaju se u okviru konteksta kulture ali, kao što su mnogi primetili [1], taj kontekst je u velikoj meri zapostavljen. Postoji obimna literatura o skoro svim aspektima samoubistva, ali malo radova govori o stavovima jedne društvene grupe koja okružuje samoubicu. Stav je ujednačen i postojan način odnosa prema nečemu ili klasi nečega [2]. Mada se ispoljava u odnosu prema konkretnim stvarima, stav je opšte prirode i uslovljen je strukturom i sadržajem celokupne ličnosti, njenim obrazovanjem i pod uticajem je socijalne sredine. Važna osobina stavova je trajnost. Stavovi su u dužem vremenu nepromenljivi, i ako ne konačni, odlikuju se postojanjem individualne varijabilnosti i razlikom između pojedinih kultura. Stav je bliže određen svojim psihološkim funkcijama: utilitarna funkcija, funkcija ekonomije, funkcija ekspresije i funkcija ego-odbrane. Ličnost

Adresa autora: Asist. dr Dušan Čanković, Institut za javno zdravlje Vojvodine,
21000 Novi Sad, Futoška 121, E-mail: dusan.cankovic@izjzv.org.rs

Skraćenice
SOQ – Suicide Opinion Questionnaire

sa negativnim stavovima prema nečemu, neće dozvoliti upoznavanje sa informacijama koje govore protiv njenog stava ili će ih ubrzo zaboraviti. Ako neki stav objedinjuje u sebi nekoliko funkcija, među kojima i ego-odbranu, odbrana stava je i odbrana od raspada ličnosti i konzervacije stavova (ideološki stavovi, dogme). Značajna je i utilitarna funkcija koja obezbeđuje jedinstvo sa grupom [3].

U današnje vreme samoubistvo predstavlja jedan od najznačajnijih mentalno-zdravstvenih problema savremenog društva. Svakih 40 sekundi ubije se jedna osoba u svetu, a naročito zabrinjava činjenica da značajno raste stopa samoubistava među mladima [4]. Među mladima, suicidna ponašanja nisu neuobičajena [5]. Pretpostavlja se da genetski i biološki, socijalni i demografski faktori, nepovoljna rana iskustva i osobine ličnosti čine grupu povezanih egzogenih faktora koji utiču na individualnu podložnost za mentalne poremećaje i osetljivost na probleme i stresove, koji, zatim, deluju kao neposredni uticaji na suicidno ponašanje. Takođe, egzogeni faktori mogu doprinositi suicidnom ponašanju i nezavisno od posredničkih faktora mentalnog zdravlja i stresnih životnih događaja [6]. Skoro četvrtinu samoubistava u svetu izvrše tinejdžeri i mladi ispod 25 godina (250 000 samoubistava godišnje), tako da samoubistvo predstavlja drugi vodeći uzrok prerane smrti kod mladih starosnog doba od 10 do 24 godine, čineći više od 20 miliona izgubljenih zdravih godina života [4]. Međutim, procenjuje se da su kod mladih pokušaji 200 puta učestaliji od samih samoubistava [7].

Republika Srbija sa relativno visokom stopom samoubistva od 19,5 na 100 000 stanovnika svrstava se u gornju polovinu liste evropskih zemalja po broju samoubistava. Međutim, naročito zabrinjavajuće stanje je u Vojvodini, koja u okviru Srbije, ali i bivše Jugoslavije, dugoročno predstavlja područje visoke smrtnosti stanovništva usled samoubistva. U Vojvodini je u periodu od pet i po decenija broj samoubistava povećan za oko 50%, sa 292 samoubistva 1953. godine na 484 samoubistva 2009. godine, a svaki osmi smrtni slučaj usled samoubistva bio je slučaj samoubistva mlade osobe [8,9]. Ovo praktično znači da se skoro 2 osobe dnevno ubiju.

S obzirom na veličinu i značaj problema samoubistva u Vojvodini i raširenosti među mladima, cilj ovog rada je da se sagledaju stavovi adolescenata prema samoubistvu kao i da li razlika u starosnom dobu utiče na promenu stava u odnosu na samoubistvo.

Materijal i metode

U ovom istraživanju korišćen je upitnik o samoubistvu, tzv. *Suicide Opinion Questionnaire* (SOQ, 1980) autora Džordža Dominoa (Georg Domino). Ovaj upitnik sadrži stavove prema samoubistvu, izvedene u formatu petostepene Likertove skale i ima psihometrijska svojstva. Upitnik sadrži ravno stotinu iskaza raspoređenih u petnaest tematskih celina verifikovanih faktorskom analizom, a o kojima se ispitanik izjašnjava na osnovu skale od pet nivoa: Potpuno se slažem, Slažem se, Neodlučan sam, Ne slažem se, Potpuno se ne slažem. Ove tematske celine se mogu grupisati u osam faktorskih skala:

1. Skala odnosa prema samoubistvu kao izrazu mentalne bolesti;
2. Skala razmatranja samoubistva u funkciji apela;
3. Skala odnosa prema samoubistvu kao izraza slobode izbora;
4. Skala religiozne obojenosti stavova o samoubistvu;
5. Skala odnosa prema samoubistvu kao aspektu impulsivnog ponašanja,
6. Skala vrednovanja prihvatljivosti i normalnosti samoubilačkog čina;
7. Skala razmatranja samoubistva kao manifestacije agresivnosti;
8. Skala razmatranja samoubistva kroz prizmu moralnosti.

Upitnik je preveden i prilagođen uslovima našeg podneblja. Naša iskustva sa SOQ su vrlo oskudna. Primenjen je u samo jednom istraživanju, kada su analizirani stavovi prema samoubistvu studenata Medicinskog fakulteta u Novom Sadu [10].

U ovom radu, primenjena je forma ovog upitnika sa 100 iskaza. Upitnik o samoubistvu ispunile su ukupno 254 mlade osobe. Od ukupnog broja, 124 pripadaju starosnom dobu od 13 do 15 godina, a 130 starosnom dobu od 18 do 19 godina. Mlađu grupu sačinjavaju učenici sedmog (n = 28) i osmog (n = 30) razreda osnovne škole, kao i učenici prvog razreda srednje škole (n = 66). Starijoj grupi pripadaju učenici završnih godina gimnazije (n = 60), ekonomske škole (n = 34) i srednje stručne škole − smer frizeri (n = 36). U ovom istraživanju petostepena skala je transformisana u trostepenu skalu, tako što su odgovori *Potpuno se slažem* i *Slažem se* prikazani zajedno kao i *Potpuno se ne slažem* i *Ne slažem se*. Takođe, faktorske skale 5 i 7 prikazane su kao jedna faktorska skala.

U odnosu na postojećih osam faktora skala, odgovori naših ispitanika su obrađivani samo u odnosu na sledećih pet:

1. Skala odnosa prema samoubistvu kao izrazu mentalne bolesti;
2. Skala razmatranja samoubistva u funkciji apela;
4. Skala religiozne obojenosti stavova o samoubistvu;
5. Skala odnosa prema samoubistvu kao aspektu impulsivnog ponašanja;
7. Skala razmatranja samoubistva kao manifestacije agresivnosti.

Statistička analiza

Podaci su statistički obrađeni korišćenjem programa *Microsoft Office Excel 2003*. Rezultati su dati kao frekvencija. Razlike u učestalosti su testirane primenom χ^2 testa.

Rezultati

Najveći broj anketiranih adolescenata (50,3%) smatra da je samoubistvo izraz mentalne bolesti, više mlađi učenici (52,4%) nego stariji (48,5%). Svaki četvrti učenik uzrasta 18–19 godina se ne slaže sa ovim stavom, iako razlike nisu statistički značajne ($p > 0,05$) **(Tabela 1)**.

Stavom da je samoubistvo u funkciji apela složilo se 38,1% anketiranih adolescenata, više stariji uzrast (40%) nego mlađi (36,3%), koji su prisutniji u grupi neodlučnih (33,9% : 27,6%). Međutim, svaka treća osoba smatra da samoubistvo nije u funkciji apela ($p > 0,05$).

Po pitanju religiozne obojenosti stavova o samoubistvu ne postoje statistički značajne razlike između posmatranih starosnih kategorija ($p > 0,05$).

Sa stavom da je samoubistvo aspekt impulsivnog ponašanja i manifestacije agresivnosti slaže se 43,7% adolescenata. Neodlučnih je više kod adolescenata uzrasta 13−15 godina dok se stariji uzrast u većem procentu ne slaže sa ovim stavom. Razlike nisu statistički značajne ($p > 0,05$).

Diskusija

Rezultati ovog istraživanja ukazuju da se stavovi o samoubistvu mlađe i starije grupe učenika većinom podudaraju. Najveći broj ispitanika izrazio je slaganje s tim da je samoubistvo izraz mentalne bolesti. Rezultati istraživanja Kimberly A. prikazuju da i grupa američkih adolescenata navodi mentalna oboljenja kao značajan doprinos u izvršenju samoubistva, iako prednost daju nedostatku podrške i stresu kao faktorima za pojavu suicidnih misli [11]. Apsolventi medicinskog fakulteta u Novom Sadu, lekari opšte medicine i studenti tehničkih nauka u Novom Sadu, takođe se slažu u najvećem procentu sa stavom da je samoubistvo izraz mentalne bolesti, dok faktor životnog i profesionalnog iskustva nije od presudnog značaja [3]. Prema procenama Svetske zdravstvene organizacije i sprovedenih istraživanja, mentalne bolesti, pre svega afektivni poremećaji, predstavljaju najznačajnji faktor rizika za ozbiljne pokušaje i za samoubistva, te se smatra da bi njihovo eliminisanje za oko 80% smanjilo rizik od ozbiljnih pokušaja samoubistva [12,13]. Zna se da trećina pacijenata lekara opšte medicine ima psihičke probleme, pri čemu većinom iskazuju odlike sindroma depresije [14]. Podaci jasno ukazuju da je većina starijih osoba koje su počinile samoubistvo imala neki oblik psihičkog problema, a da je depresija kao specifičan oblik psihopatologije najviše povezana sa samoubistvom kod starijih osoba [15]. Nesporno je da psihijatrijski poremećaji, prvenstveno depresija, alkoholizam, shizofrenija, imaju značajnu ulogu, ali su bitni faktori i životne krize, telesne bolesti, problemi adolescencije − nedostatak podrške i razumevanja, problemi staračkog života, kao i faktori socijalne sredine (ekonomska depresija, nezapo-

Tabela 1. Odgovori učenika mlađe i starije grupe u odnosu na pet faktorskih skala
Table 1. *Answers of younger and older group of pupils regarding five factor scales*

Broj skale *Scale number*	Faktorske skale/ *Factor scales*	13−15 godina/*age*		18−19 godina/*age*		p
		n	%	n	%	
Skala 1 *Scale 1*	Skala odnosa prema samoubistvu kao izrazu mentalne bolesti *Scale of suicide perception as an expression of mental disease*					
	Slažem se/*Agree*	65	52,4	63	48,5	
	Neodlučan/*Undecided*	35	28,2	33	25,5	p > 0,05
	Ne slažem se/*Disagree*	24	19,4	34	25	
Skala 2 *Scale 2*	Skala razmatranja samoubistva u funkciji apela *Scale of suicide perception in the function of appeal*					
	Slažem se/*Agree*	45	36,3	52	40	
	Neodlučan/*Undecided*	42	33,9	36	27,6	p > 0,05
	Ne slažem se/*Disagree*	37	29,8	42	32,4	
Skala 4 *Scale 4*	Skala religiozne obojenosti stavova o samoubistvu *Scale of religious dimension of attitudes toward on suicide*					
	Slažem se/*Agree*	39	31,4	45	34,6	
	Neodlučan/*Undecided*	48	38,7	46	35,4	p > 0,05
	Ne slažem se/*Disagree*	37	29,9	39	30	
Skale 5 i 7 *Scale 5 and 7*	Skala odnosa prema samoubistvu kao aspektu impulsivnog ponašanja i razmatranja samoubistva kao manifestacije agresivnosti/*Scale of suicide perception as the aspect of impulsive behavior and suicide perception as an aggression manifestation*					
	Slažem se/*Agree*	54	43,5	57	43,8	
	Neodlučan/*Undecided*	38	30,6	30	23	p>0,05
	Ne slažem se/*Disagree*	32	25,9	43	33,2	

slenost) [16]. U razmatranju da je samoubistvo u funkciji apela, jedna trećina naših ispitanika je neodlučna, dok jedna trećina ne prihvata mišljenje da samoubistvo može biti poziv u pomoć (apel). Kod lekara i apsolvenata medicine dobijeni su daleko veći skorovi o samoubistvu u funkciji apela u odnosu na studente. To ukazuje da je psihijatrijsko suicidološko obrazovanje bitno za formiranje ovog stava, a životno doba i profesionalna orijentacija nemaju značajnu ulogu [3], što potvrđuju i rezultati sprovedenih istraživanja [17]. Po pitanju religiozne obojenosti stavova o samoubistvu, u našem istraživanju najveći broj ispitanika obe starosne grupe je neodlučan, što ukazuje na nedovoljno razvijenu svest o samoubistvu. Mehmet u svojoj studiji otkriva da kod turskih adolescenata čije se obrazovanje zasniva na religiji, postoje manje šanse da prihvate samoubistvo kao rešenje u odnosu na kontrolnu grupu [18]. Lekari opšte medicine u istraživanju Gajić Z. uglavnom se slažu da su ljudi koji se odlučuju za samoubistvo manje religiozni pošto je samoubilačko ponašanje u suprotnosti sa učenjem većine velikih religija [3] što se poklapa sa stavom starije grupe ispitanika (60−95 godina) u istraživanju Segal D.L. i saradnika [17]. Upotreba religije i duhovnosti kao strategije u suočavanju s problemom imaju tendenciju rasta s godinama i ovakav stav može biti protektivan [19,20]. Međutim, u svetlu istraživanja Domina i Milerove, ukazuje se na prisustvo brojnih kontradiktornosti u razmišljanjima o samoubistvu osoba sa izraženim religioznim uverenjima, što pruža prilično ubedljivu argumentaciju o značaju predrasuda i dogmatski ili afektivno oblikovanim stavovima [21]. U razmatranju skala odnosa prema samoubistvu kao aspektu impulsivnog ponašanja i razmatranja samoubistva kao manifestacije agresivnosti, u našem istraživanju obe dobne grupe skoro u indentičnom postotku složile su se sa ovom postavkom. Neodlučan odgovor je zastupljeniji kod mlađe dobne grupe, dok je neslaganje sa postavkom u ovoj skali izraženije kod starije dobne grupe. U oblikovanju ovakvog stava uticaj životnog i radnog iskustva je neznatan, dok je značajan uticaj opšte životne i profesionalne orijentacije, iako postoji konceptualna nedorečenost literature posvećene mestu impulsivnosti u etiopatogenezi suicidnog ponašanja [3]. Veza između agresivnosti i suicidnosti je dobro poznata. Naročito kod usamljenih i odbeglih adolescenata postoji značajna povezanost između agresivnog ponašanja i pokušaja samoubistva [22]. Mnoge studije podržavaju stav da postoji veza između agresije koja je usmerena spolja i samoubilačkog čina [23−26]. Ljudi sa visokim nivoom ispoljene agresivnosti i odbojnosti su u većem riziku od fatalnog ishoda samoubistva i drugih nasilnih uzroka [27]. Italijanska studija Paole Miotto i saradnika sprovedena na 950 adolescenata oba pola, starosti od 15 do 19 godina, ukazuje na to da veća sklonost dečaka ka agresiji povećava rizik od smrti samoubistvom u odnosu na devojke, uprkos nižoj učestalosti suicidne ideje [28].

Naredni pravac istraživanja bilo bi ispitivanje razlika u stavovima u odnosu na edukativni profil ispitanika, što u ovom radu nije prikazano.

Zaključak

U ovom istraživanju prikazani stavovi ispitanika obe starosne grupe su pokazatelj nedovoljne svesti o samoubistvu, njegovim uzrocima i dinamici razvoja ovog javnozdravstvenog problema. Ovo ostavlja prostor za intenzivniji edukativni rad u oblasti mentalnog zdravlja stanovništva, posebno mladih kao i za dalja istraživanja problema samoubistva kao osnove za razradu strategije i prevencije ovog javnozdravstvenog problema.

Literatura

1. Kalish RA, Reynolds DK, Farberow NL. Community attitudes toward suicide. Community Ment Health J 1974;10: 301-8.

2. Krstić D. Psihološki rečnik. Beograd: Savremena administracija; 1991.

3. Gajić Z. Prevencija samoubistva u praksi lekara opšte medicine, Stavovi prema samoubistvu i njihov značaj u prevenciji (magistarski rad). Novi Sad: Medicinski fakultet, Univerzitet u Novom Sadu; 1996.

4. WHO. Mental health. 2009. Suicide prevention (SUPRE). [cited 2011 July]; Available at: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/

5. Evans E, Hawton K, Rodham K, Deeks J. The prevalence of suicidal phenomena in adolescents: a systematic review of population-based studies. Suicide Life Threat Behav 2005;(35)3:239-50.

6. Beautrais A. Life, course, factors associated with suicidal behaviors in young people. Am Behav Sci 2003;46:1137-56.

7. Hawton K. Harris L. How often does deliberate self-harm occur relative to each suicide? Suicide Life Threat Behav 2008;38(6):650-60.

8. Penev G. Stanković B. O samoubistvima starih i mladih u Vojvodini. Zb Matice Srp Druš Nauke. 2010;131:137-47.

9. Demografska statistika. Beograd: Republički zavod za statistiku; 2001.

10. Selaković-Buršić S, Gajić Z, Đurđev O. Attitudes toward suicide in Serbian medical students. XVIIth Congress of the International Association for Suicide Prevention and Crisis Intervention. Montreal: International Association for Suicide; 1993.

11. Kimberly A, Schwartz Sara A, Pyle M, Dowd D, Sheehan K. Attitudes and beliefs of adolescents and parents regarding adolescent suicide. Pediatrics. 2010;125(2):221-7.

12. van Heringen K, Hawton K, Williams JMG. Pathways to Suicide: an Integrative Approach. In: Hawton K, van Heeringen K, eds. The international handbook of suicide and attempted suicide. Chichester: John Wiley & Sons Ltd; 2002. p. 223-34.

13. WHO. For which strategies of suicide prevention is there evidence of effectiveness? Geneva: WHO Regional Office for Europe's Health Evidence Network - HEN; 2004.

14. Gastpar M. Epidemiology of depression and suicide in Switzerland: depressionet suicide. Paris: Pergamon Press; 1981. p. 121-6.

15. Duberstein PR, Conwell Y. Suicide. In: Whitbourne SK, ed. Psychopathology in later adulthood. New York: Wiley; 2000. p. 245-75.

16. Selaković-Buršić S. Suicide prevention: myth or reality? Med Pregl 2003;56(11-12):499-502.

17. Segal DL, Mincic MS, Coolidge FL, O'Riley A. Attitudes toward suicide and suicidal risk among younger and older persons. Death Studies. 2004;28:671-8.

18. Mehmet E. The effects of religious versus secular education on suicide ideation and suicidal attitudes in adolescents in Turkey. Soc Psychiatry Psychiatr Epidemiol 2004;39:536-42.

19. Koenig H, George L, Siegler I. The use of religion and other emotion regulating coping strategies among older adults. Gerontologist, 1988;28:303-10.

20. Miller JS, Segal DL, Coolidge FL. A comparison of suicidal thinking and reasons for living among younger and older adults. Death Studies, 2001;25:357-65.

21. Domino G, Perrone L. Attitudes toward suicide: Italian and USA physicians. J Death Dying. 1993;27(3):195-206.

22. Booth RE, Zhang Y. Severe aggression and related conduct problems among runaway and homeless adolescents. Psychiatr Services. 1996;47:75-80.

23. Åsberg M, Schalling D, Traskman-Bendz L, Wagner A. Psychobiology of suicide, impulsivity and related phenomena. In: Meltzer HY, ed. Psychopharmacology: the third generation of progress. New York: Raven Press; 1987. p. 655-68.

24. Mann JJ. Violence and aggression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995. p. 1919-28.

25. Virkkunen M, De Jong J, Bartko J, Linnoila M. Psychobiological concomitants of history of suicide attempts among violent offenders and impulsive fire setters. Arch Gen Psychiatry. 1989a;46:604-6.

26. Virkkunen M, Dejong J, Bartko J, Goodwin FK, Linnoila M. Relationship of psychobiological variables to recidivism in violent offenders and impulsive fire setters. Arch Gen Psychiatry. 1989b;46:600-3.

27. Romanov K, Hatakka M, Keskinen E, Laaksonen H, Kaprio J, Rose RJ, et al. Self-reported hostility and suicidal acts, accidents and accidental deaths: a prospective study of 21 443 adults aged 25–59. Psychosom Med. 1994;56:328-36.

28. Miotto P, De Coppi M, Freza M, Petretto D, Masala C, Preti A. Suicidal ideation and aggressiveness in school-aged youths. Psychiatry Res. 2003;120:247-55.

Rad je primljen 22. I 2013.
Recenziran 25. II 2013.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:240-244.

PRIKAZI SLUČAJEVA
CASE REPORTS

Vojnomedicinska akademija, Beograd
Klinika za kardiologiju

Prikaz slučaja
Case report
UDK 616.132.2-073
DOI: 10.2298/MPNS1306245S

KORONAROGRAFIJA IPSILATERALNIM ULNARNIM PRISTUPOM KOD BOLESNIKA SA RADIJALNOM ARTERIJOM MALOG DIJAMETRA

CORONARY ANGIOGRAPHY THROUGH IPSILATERAL ULNAR APPROACH IN A PATIENT WITH SMALL-DIAMETER RADIAL ARTERY

Zoran STAJIĆ i Zdravko MIJAILOVIĆ

Sažetak

Uvod. Koronarne procedure nije moguće izvesti započetim radijalnim pristupom kod oko 5−15% pacijenata zbog čestih anatomskih malformacija radijalne arterije i vazospazma. U ovim slučajevima ulnarni pristup može biti efikasan i bezbedan alternativni pristup iz ruke. **Prikaz slučaja.** Bolesnik star 60 godina, sa stabilnom anginom pektoris, hipertenzijom, dislipidemijom i pozitivnim ergometrijskim testom primljen je u našu kliniku radi koronarografije. Zbog bolova u kičmi i nemogućnosti dužeg ležanja bolesnika na leđima zbog problema sa kičmom, odlučili smo se za pristup iz ruke (standardni radijalni pristup) nakon učinjena oba modifikovana Alenova testa koji su bili pozitivni. Nakon insercije uvodnika u desnu radijalnu arteriju i nemogućnosti napredovanja žice-vodiča i katetera, urađena je angiografija desne ruke koja je pokazala da je desna radijalna arterija malog dijametra sa dominacijom desne ulnarne arterije. Nakon toga, uspešno je punktirana desna ulnarna arterija i koronarografija je urađena ulnarnim pristupom. Oba uvodnika su odmah nakon koronarografije simultano izvađena i hemostaza je uspostavljena kompresijom dvema Terumo trakama iznad obe punktirane arterije, bez komplikacija. Pulsevi obe arterije su tokom narednih 24 h regularno kontrolisani i bili su normalni. Takođe, 24 h nakon procedure urađen je i kontrolni ultrazvučni pregled koji je potvrdio postojanje normalnih protoka u obe punktirane arterije. Tokom perioda praćenja od mesec dana nakon koronarografije, pacijent je bio bez tegoba i nisu registrovane ishemijske komplikacije šake. **Zaključak.** Naš slučaj pokazuje mogućnost izvođenja koronarografije ipsilateralnim ulnarnim pristupom kao bezbednim i efikasnim alternativnim pristupom kod pacijenata sa pozitivnim Alenovim testom a u slučaju neuspeha inicijalnog pokušaja radijalnim pristupom, kada se želi izbeći femoralni pristup i održati pristup iz ruke.

Ključne reči: Koronarna angiografija; Ulnarna arterija; Radijalna arterija + abnormalnosti; Starost 45-64 godina; Muško; Ishod tretmana

Summary

Introduction. Coronary procedures cannot be completed in 5-15% of cases through initially used radial artery approach due to frequent radial artery anomalies and vasospasm. In these cases, the ulnar artery approach could be the safe and effective alternative wrist approach. **Case report.** A 60-year-old patient with stable angina pectoris, hypertension, dyslipidaemia and positive endurance test was admitted to our hospital for coronary angiography. Due to the backbone pains which also made prolonged lying in bed very uncomfortable and painful, we opted for the wrist approach (standard radial approach) after both modified Allen's tests had been performed, which gave the positive result. After sheath insertion into the right radial artery and unsuccessful advancement of the guidewire and the catheter, we performed the right forearm angiography, which revealed that the right radial artery had a small diameter and the right ulnar artery was the dominant one. Afterwards, the right ulnar artery was cannulated successfully and the coronary angiography was performed through this approach. Both sheaths were removed simultaneously immediately after the procedure and hemostasis was secured by the compression with two Terumo-bands over the puncture sites without any complications. The pulses of both arteries were checked regularly over the next 24 hours and they remained normal. A day after the procedure, the control Doppler-ultrasound check-up was performed and it confirmed the normal flow in both cannulated arteries. One-month follow-up was uneventful, and the patient did not experience any ischemic symptoms of the hand. **Conclusion.** This case is the proof that the ipsilateral ulnar approach can be a safe and effective alternative approach in patients with positive Allen's test after the failure of initial radial attempt in cases where femoral approach should be avoided or the wrist approach should be maintained.

Key words: Coronary Angiography; Ulnar Artery; Radial Artery + abnormalities; Middle Aged; Male; Treatment Outcome

Adresa autora: Asist. dr Zoran Stajić, Vojnomedicinska akademija, Klinika za kardiologiju, 11040 Beograd, Crnotravska 17, E-mail: zoran0312@yahoo.com

Skraćenice
TR – Terumo

Uvod

Radijalni pristup za koronarne procedure (koronarografije, i perkutane koronarne intervencije) u poslednjih nekoliko godina postao je veoma popularan kako za interventne kardiologe, tako i pacijente [1]. Radijalni pristup je povezan sa značajno manjom incidencijom lokalnih vaskularnih komplikacija (krvarenje, hematomi, pseudoaneurizme) u odnosu na tradicionalni femoralni pristup, a u važne prednosti spada i veći komfor za pacijenta zbog izbegavanja dužeg ležanja u postelji i kraćeg zadržavanja u bolnici, što je značajno i za zdravstveno osiguranje zbog smanjenja troškova lečenja [2,3]. Međutim, kod oko 5−15% pacijenata nije moguće izvesti koronarne procedure radijalnim pristupom zbog anatomskih varijacija radijalne arterije (tortuoziteti, stenoze, aberantno polazište, mali dijametar, hipoplazija) ili izraženog spazma radijalne arterije [4]. U ovim slučajevima, ukoliko se želi izbeći femoralni pristup, mogao bi se primeniti ulnarni pristup, kao podjednako efikasan i bezbedan alternativni pristup za koronarne procedure iz ruke koji pored toga što zadržava sve prednosti radijalnog pristupa [5], ima i dodatnu prednost zbog prezervacije radijalne arterije kao mogućeg arterijskog grafta za potencijalnu hiruršku revaskularizaciju miokarda.

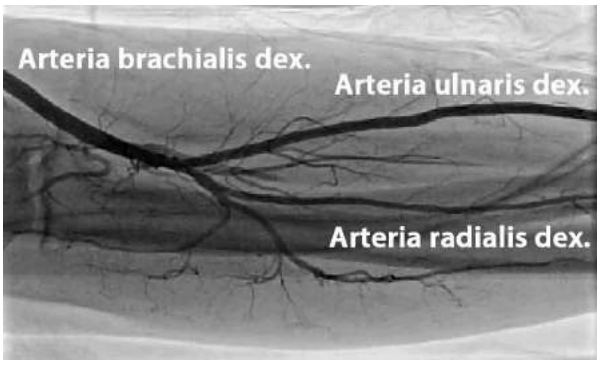
Većina dosadašnjih studija sa ulnarnim pristupom uzimala je kao relativne kontraindikacije za ulnarni pristup negativan inverzan Alenov test, neuspešan pokušaj punkcije ipsilateralne radijalne arterije u istom aktu, kao i u prethodnom aktu urađenu koronarnu proceduru pristupom preko ipsilateralne radijalne arterije, zbog potencijalne ishemije ruke [6]. Međutim, u dosadašnjem iskustvu sa ulnarnim pristupom nije zabeležen nijedan slučaj ishemije ruke zbog prisustva dvojne cirkulacije i dobro razvijene mreže kolaterala u ruci [7].

U ovom prikazu predstavljamo jedno od mogućih rešenja u slučaju neuspešnog pokušaja izvođenja koronarne procedure radijalnim pristupom ukoliko se želi izbeći femoralni pristup – ipsilateralni ulnarni pristup kao bezbedan i efikasan alternativni pristup iz ruke u istom aktu.

Prikaz slučaja

Bolesnik star 60 godina, lečen je poslednjih nekoliko godina od stabilne angine pektoris, hipertenzije i dislipidemije. U regionalnom zdravstvenom centru urađen mu je ergometrijski test na pokretnoj traci koji je pokazao smanjenu koronarnu rezervu i indikovana mu je koronarografija, zbog čega je smešten u našu ustanovu.

U sklopu pripreme za koronarografiju, nakon razgovora sa pacijentom i njegove želje da se koronarografija uradi iz ruke zbog bolova u kičmi i



Slika 1. Angiografija desne radijalne arterije (malog dijametra) i desne ulnarne arterije (dominantna)
Fig. 1. *Angiography of the right radial artery (of small-diameter) and the right ulnar artery (dominant)*

nemogućnosti dužeg ležanja na leđima, urađeni su modifikovani Alenov test i modifikovani inverzni Alenov test. Oba testa bila su pozitivna označavajući očuvanost protoka kroz desnu radijalnu i desnu ulnarnu arteriju, nakon čega je odlučeno da se koronarografija uradi pristupom preko desne radijalne arterije – standardnim pristupom iz ruke.

Nakon davanja lokalne anestezije 2% lidokainom, učinjena je perkutana punkcija desne radijalne arterije a zatim i insercija uvodnika u istu arteriju, uz intraarterijsku aplikaciju heparina 5 000 i.j. i vazodilatatora (nitroglicerin 300 μg, verapamil 2,5 mg). Nekoliko pokušaja napredovanja žice-vodiča i dijagnostičkog katetera *Tiger 4-5 Fr* (Terumo, Tokyo, Japan) u brahijalnu arteriju je bilo neuspešno, čak i nakon dodatne aplikacije vazodilatatora. Zbog nemogućnosti napredovanja katetera urađena je angiografija desne radijalne arterije ubrizgavanjem kontrasta kroz uvodnik koja je pokazala da je desna radijalna arterija malog dijametra sa dominacijom desne ulnarne arterije uz normalan tok i dijametar brahijalne arterije **(Slika 1)**. Nakon dodatnog razgovora sa pacijentom, odlučili smo da nastavimo proceduru iz iste ruke pristu-

Slika 2. Uvodnici plasirani u desnoj radijalnoj arteriji i desnoj ulnarnoj arteriji
Fig. 2. *Sheaths inserted into the right radial artery and the right ulnar artery*

pom preko desne ulnarne arterije. Nakon lokalne anestezije 2% lidokainom, učinjena je perkutana punkcija desne ulnarne arterije 2 cm od pisiformne kosti, insercija uvodnika i intraarterijska aplikacija vazodilatatora (nitroglicerin 300 μg, verapamil 2,5 mg) **(Slika 2)**. Dijagnostički kateter *Tiger 4-5 Fr* (Terumo, Tokyo, Japan) putem žice-vodiča je lako, brzo i bez otpora plasiran duž desne ulnarne arterije, brahijalne arterije, supklavije i brahiocefaličnog stabla do korena aorte. Selektivna koronarografija obe koronarne arterije učinjena je navedenim kateterom. Koronarografijom je nađeno postojanje dvosudovne bolesti sa značajnim stenozama na prednjoj descedentnoj koronarnoj arteriji i desnoj koronarnoj arteriji i indikovana je elektivna angioplastika u drugom aktu jer nije uzimao klopidogrel [8]. Odmah nakon procedure simultano su izvađena oba uvodnika i hemostaza je uspotavljena postavljenjem dve Terumo trake (TR) (Terumo, Tokyo, Japan) iznad oba punkciona mesta **(Slika 3)**. Popuštanje kompresije je vršeno svakih sat vremena tokom narednih šest sati, nakon čega su TR-traka uklonjeni a hemostaza uspostavljena. Tokom koronarografije kao i tokom hemostaze pacijent nije imao tegoba u desnoj ruci. Nakon uklanjanja TR-traka puls je redovno, na svaka tri sata kontrolisan tokom narednih 24 h, i bio je palpabilan i dobro punjen iznad obe punktirane arterije, bez znakova ishemije ruke.

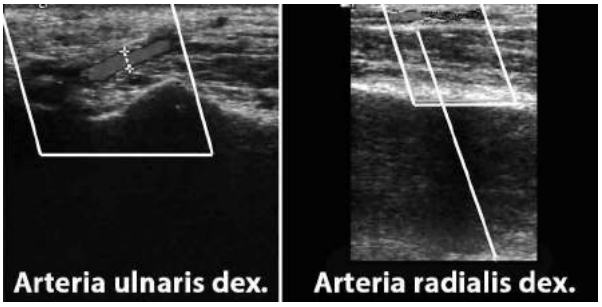
Dan nakon koronarografije urađen je i kontrolni dopler ultrazvučni pregled koji je potvrdio da je desna radijalna arterija značajno manjeg dijametra (2,1 mm) od desne ulnarne arterije (2,9 mm), sa normalnim profilom protoka u obe punktirane arterije **(Slika 4)**. Bolesnik je istog dana otpušten kući. Tokom mesec dana praćenja nisu registrovane ishemijske komplikacije ruke.

Diskusija

Ulnarni pristup za koronarne procedure uveo je u kliničku praksu Terashima 2001. godine [9], i iako se smatra dobrim alternativnim pristupom iz ruke, još uvek se u svetu retko primenjuje [5]. Prema našim saznanjima, ovaj prikaz je prvi publikovani slučaj koronarografije urađene ulnarnim pristupom u našoj zemlji.

Slika 3. Hemostaza uspostavljena kompresijom dvema TR trakama pozicioniranim iznad mesta punkcije desne radijalne arterije i desne ulnarne arterije

Fig. 3. *Hemostasis was secured by the compression with two TR bands placed over the puncture sites of the right radial artery and the right ulnar artery*



Slika 4. Dopler ultrazvuk desne ulnarne arterije i desne radijalne arterije pokazuje normalan protok 24 h nakon koronarografije. Desna radijalna arterija je malog dijametra (2,1 mm) dok je desna ulnarna arterija dominantna (dijametar 2,9 mm)

Fig. 4. *Doppler ultrasound of the right ulnar artery and the right radial artery 24 hours after coronary angiography shows the normal flow. The right radial artery is of a small diameter (2.1 mm) while the right ulnar artery is the dominant one (its diameter being 2.9 mm)*

Ulnarni pristup deli sve prednosti radijalnog pristupa u odnosu na tradicionalni femoralni pristup: značajno manja incidencija lokalnih vaskularnih komplikacija (hematomi, pseudoaneurizme, arterio-venske fistule) i veći komfor bolesnika zbog mogućnosti brze mobilizacije i kraćeg zadržavanja u bolnici [2,3,10]. Poslednje je značajno i sa ekonomske strane zbog smanjenja troškova lečenja. Dodatna prednost ulnarnog pristupa u odnosu na radijalni, ukoliko se ulnarni pristup koristi kao primarni, jeste očuvanje radijalne arterije za primenu prilikom eventualne hirurške revaskularizacije miokarda kao potencijalnog arterijskog grafta [11].

Ulnarna arterija leži neposredno pored vene i nerva tako da potencijalno postoji mogućnost njihove povrede prilikom punkcije, za razliku od radijalne arterije u čijoj blizini se ne nalaze vene i nervi. Povreda ulnarnog nerva prilikom punkcije može dovesti do prolaznih neprijatnih (bolnih) senzacija u predelu ruke i šake, a povreda vene do nastanka supkutane hemoragije. Obe komplikacije su retke i mogu se izbeći pažljivom punkcijom i korišćenjem punkcione igle malog dijametra. Ostale vaskularne komplikacije koje mogu nastati su iste kao i kod radijalnog pristupa i obuhvataju hematome, pseudoaneurizme i arterijsko-venske fistule [9,12].

Prema podacima iz literature, radijalna arterija je češće većeg dijametra (dominantna) od ulnarne arterije. U studiji Vassileva i saradnika [13] pokazano je da je srednji dijametar radijalne arterije (3,11 ± 0,12 mm) bio značajno veći u odnosu na srednji dijametar ulnarne arterije (2,76 ± 0,08 mm). Takođe, u istoj studiji pokazano je da je radijalna arterija dominantna kod oko 75% pacijenata koji su

podvrgnuti koronarografiji pristupom iz ruke. Međutim, uprkos tome što je ulnarna arterija češće manjeg dijametra od radijalne, ulnarna arterija ima manje α-adrenergičkih receptora u odnosu na radijalnu arteriju, što je čini manje sklonom nastanku vazospazma tokom kanulacije (incidencija vazospazma prilikom kanulacije radijalne arterije iznosi oko 10%). Takođe, jedna od važnih karakteristika ulnarne arterije koja je čini pogodnom za kanulaciju je pravilan tok, bez krivina, za razliku od radijalne arterije kod koje postoji sklonost krivinama, a kod 10−15% slučajeva i urođenim anatomskim abnormalnostima kao što su tortuoziteti, stenoze, aberanto polazište, petlje i hipoplazija [14]. Sve ove anomalije, kao i relativno česta pojava vazospazma mogu biti razlog neuspešnog pokušaja izvođenja koronarne procedure radijalnim pristupom.

Tehnički, kanulacija ulnarne arterije je značajno zahtevnija u odnosu na radijalnu, pre svega zbog dublje anatomske lokalizacije, odsustva koštane podloge, blizine vene i nerva. Međutim, uprkos ovome, kod operatora s velikim iskustvom u radijalnom pristupu, kriva učenja nije značajno produžena. U skladu s ovim, smatra se da je uspeh kanulacije ulnarne arterije kod iskusnih operatora približno jednak uspehu kanulacije radijalne arterije [15]. Navedeno potkrepljuje i prospektivna studija Aptecara i saradnika [16], u kojoj je pokazano da nije bilo značajne razlike u uspešnosti kanulacije radijalne arterije (95,5%) u odnosu na ulnarnu arteriju (93,1%).

Od uvođenja ulnarnog pristupa, postojala je i stalna zabrinutost u pogledu mogućih ishemijskih komplikacija u slučaju nastanka okluzije ulnarne arterije, s obzirom na njen značaj u cirkulaciji šake. Međutim, dosadašnje kliničko iskustvo ukazuje na odsustvo ishemijskih komplikacija, kako akutnih tako i hroničnih. Učestalost kasne, klinički aspimtomatske postproceduralne okluzije radijalne ili ulnarne arterije kreće se 3−6% [17]. Štaviše, ne postoji nijedno publikovano saopštenje o nastanku akutne ili hronične ishemije ruke nakon ulnarnog pristupa. Razlog za odsustvo ishemijskih komplikacija, čak i u slučaju nastanka okluzije radijalne/ulnarne arterije leži u postojanju dvojne cirkulacije krvi u ruci koju obezbeđuje radijalna i ulnarna arterija, odnosno njihovi superficijalni i duboki palmarni lukovi, kao i postojanje i razvoj dodatnih kolaterala između ove dve arterije.

Sve je više dokaza u literaturi koji ranije kontraindikacije za primenu ulnarnog pristupa (negativan modifikovani inverzni Alenov test, kanulacija ispilateralne radijalne arterije u prethodnom ili istom aktu, dokazana okluzija radijalne arterije) dovode u pitanje. Slogoff i saradnici [18] još davne 1983. godine saopštili su da u seriji od 22 kardiohirurška pacijenta, nijedan nije imao ishemiju ruke nakon konkomitantne, ipsilateralne kanulacije ulnarne i/ili radijalne arterije rađene sa ciljem invazivnog hemodinamičkog monitoringa. Na ovo ukazuje i činjenica da se u anesteziologiji radi invazivnog monitoringa i/ili određivanja gasnih analiza rutinski primenjuje kanulacija radijalne i/ili ulnarne arterije samo na osnovu palpacije pulsa bez dodatne dijagnostike i potvrde kompetentnosti dvojne cirkulacije u ruci, tj. patentnosti radijalne i ulnarne arterije, odnosno superficijalnog i dubokog palmarnog luka Alenovim testovima. To je podstaklo De Andradea i saradnike [19] da potvrde odsustvo ishemijskih komplikacija nakon konkomitantne kanulacije ulnarne arterije posle neuspešne kanulacije radijalne arterije a bez prethodno urađenog Alenovog testa. Takođe, postoje prikazi bolesnika sa uspešnom koronarografijom ipsilateralnim ulnarnim pristupom kod bolesnika sa angiografski dokazanom hroničnom okluzijom ispilateralne radijalne arterije [20]. Nedavno je publikovan i prvi prikaz bolesnika koji je veoma sličan našem slučaju, kod koga je koronarna procedura urađena ipsilateralnim ulnarnim pristupom nakon neuspešnog radijalnog pokušaja [21] zbog postojanja petlje (eng. *loop*) radijalne arterije.

Moramo da napomenemo da je i nakon deset godina od uvođenja u kliničku praksu, ulnarni pristup uprkos jednakim prednostima u poređenju sa radijalnim pristupom, ostao samo alternativni pristup iz ruke zbog i dalje prisutne bojazni od ishemijskih komplikacija. Zbog toga su svakako potrebni dodatni dokazi u vidu većih serija bolesnika odnosno randomizovane kliničke studije koje bi nedvosmisleno potvrdile bezbednost ulnarnog pristupa ne samo kao alternativnog već i kao primarnog pristupa iz ruke.

Zaključak

Kod pacijenata kod kojih se koronarna procedura ne može uraditi započetim radijalnim pristupom, a ukoliko se želi održati pristup iz ruke zbog svojih prednosti ili zbog nemogućnosti femoralnog pristupa, ipsilateralni ulnarni pristup može biti jednako efikasan i bezbedan alternatnivni pristup iz ruke. Za primenu ulnarnog pristupa koji je tehnički zahtevniji od radijalnog, neophodno je prethodno veliko iskustvo operatora u radijalnom pristupu.

Literatura

1. Caputo RP, Tremmel JA, Rao S, Gilchrist IC, Pyne C, Pancholy S, et al. Transradial arterial access for coronary and peripheral procedures: executive summary by the Transradial Committee of the SCAI. Cathet Cardiovasc Interv 2011;78:823-39.

2. Chase AJ, Fretz EB, Warburton WP, Klinke WP, Carere RG, Pi D, et al. Association of the arterial access site at angioplasty with transfusion and mortality: the MORTAL study (Mortality benefit of reduced transfusion after percutaneous coronary intervention via the arm or leg). Heart 2008;94:1019-25.

3. Rao SV, Ou FS, Wang TY, Roe MT, Brindis R, Rumsfeld JS, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. JACC Cardiovasc Interv 2008;1:379-86.

4. Lo TS, Nolan J, Fountzopulos E, Behan M, Butler R, Hetherington SL, et al. Radial artery anomaly and its influence on transradial coronary procedure outcome. Heart 2009;95:410-5.

5. Roberts EB, Palmer N, Perry RA. Transulnar access for coronary angiography and interventions: an early review to guide research and clinical practice. J Invas Cardiol 2007;19:83-7.

6. Dashkoff N, Dashkoff PB, Zizzi JA, Wadhwani J, Zizzi JA. Ulnar artery cannulation for coronary angiography and percutaneous coronary intervention: case reports and anatomic considerations. Cathet Cardiovasc Interv 2002;55:93-6.

7. Lotan C, Hasin Y, Mosseri M, Rozenman Y, Admon D, Nassar H, et al. Transradial approach for coronary angiography and angioplasty. Am J Cardiol 1995;76:164-7.

8. Mijailović ZM, Stajić Z, Jevtić M, Aleksandrić S, Tavčiovski D, Matunović R. Terapijski pristup kod pacijenata koji se podvrgavaju perkutanim koronarnim intervencijama. Med Pregl 2009;62:331-6.

9. Terashima M, Meguro T, Takeda H, Endoh N, Ito Y, Mitsuoka M, et al. Percutaneous ulnar artery approach for coronary angiography: a preliminary report in nine patients. Cathet Cardiovasc Interven 2001;53:410-4.

10. Li Y, Zhao Y, Zhao Y, Guo Y, Liu Y, Shi D, et al. Safety and efficacy of transulnar approach for coronary angiography and intervention. Chin Med J 2010;123:1774-9.

11. Manasse E, Sperti G, Suma H, Canosa C, Kol A, Martinelli L, et al. Use of the radial artery for myocardial revascularization. Ann Thorc Surg 1996;62:1076-83.

12. Bazemore E, Mann JT. Problems and complications of the transradial approach for coronary interventions. J Invas Cardiol 2005;17:156-9.

13. Vassilev D, Smilkova D, Gil R. Ulnar artery as access site for cardiac catheterization: anatomical considerations. J Inter Cardiol 2008;1:56-60.

14. Yokohama N, Takeshida S, Ochiai M, Koyoma Y, Hoshino S, Isshiki T, et al. Anatomic variations of the radial artery in patients undergoing transradial coronary intervention. Cathet Cardiovasc Interv 2000;49:357-62.

15. Karacalar S, Ture H, Baris S, Karkaya D, Sarihasan B. Ulnar artery versus radial artery approach for arterial cannulation: a prospective, comparative study. J Clin Anesth 2007; 19:209-13.

16. Aptecar E, Pernes JM, Chabane-Chaouch M, Bussy N, Catarino G, Shahmir A, et al. Transulnar versus transradial artery approach for coronary angioplasty: the PCVI-CUBA study. Cathet Cardiovasc Interv 2006;67:711-20.

17. Huzjan R, Brkljacic B, Delic-Brkljacic D, Biocina B, Suftlic Z. B-mode and color Doppler ultrasound of the forearm arteries in the preoperative screening prior to coronary artery bypass grafting. Coll Antropol 2004;28(Suppl 2):235-41.

18. Slogoff S, Keats AS, Arlund C. On the safety of radial artery cannulation. Anesthesiology 1983;59:42-7.

19. De Andrade PB, Tebet M, Andrade M, Mattos L, Labrunie A. Performance of coronary procedures through the transulnar access without assessment of the integrity of the deep palmar arch. J Interv Cardiol 2008;21:562-5.

20. Lanspa T, Reyes AP, Oldemeyer JB, Williams MA. Ulnar artery catheterization with occlusion of corresponding radial artery. Cathet Cardiovasc Interv 2004;61:211-3.

21. Agostoni P, Zuffi A, Biondi-Zoccai G. Pushing wrist access to the limit: homolateral right ulnar artery approach for primary percutaneous coronary intervention after right radial failure due to radial loop. Cathet Cardiovasc Interv 2011;78:894-7.

Rad je primljen 26. VI 2012.
Recenziran 20. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:245-249.

Klinički centar Vojvodine, Novi Sad
Klinika za maksilofacijalnu hirurgiju

Prikaz slučaja
Case report
UDK 616.716-006-089
DOI: 10.2298/MPNS1306250M

ŠVANOM INFRATEMPORALNE REGIJE − PRIKAZ SLUČAJA

INFRATEMPORAL FOSSA SCHWANNOMA

Ivana MIJATOV, Bojan PEJAKOVIĆ, Benjamin NALIĆ, Saša MIJATOV i Aleksandar KIRALJ

Sažetak

Uvod. Infratemporalna regija zbog svog sadržaja i odnosa sa susednim regijama ima veliki klinički značaj. Primarni tumori ove regije, kako benigni tako i maligni, veoma su retki, ali zahtevaju hirurški tretman koji je uslovljen veličinom i lokalizacijom tumora. **Prikaz slučaja**. U radu je prikazan slučaj pacijentkinje stare 72 godine koja se javila na Kliniku zbog parestezija u predelu leve polovine lica, a kojoj je prethodnim imidžing metodama dijagnostikovan tumor leve infratemporalne jame. Nakon preopertaivne pripreme, pacijentkinji je transfacijalnim-transzigomatičnim pristupom u celosti otklonjen tumor. Patohistološkim pregledom utvrđeno je da se radi o švanomu. Postoperativni tok protekao je bez komplikacija. Na kontrolnom pregledu nakon mesec dana pacijentkinja nije imala tegoba. **Zaključak.** Za uspešno hirurško lečenje tumora infratemporalne jame, osim precizne dijagnostike, veoma je važan izbor odgovarajućeg hirurškog pristupa koji treba da obezbedi kompletno uklanjanje tumora uz očuvanje sadržaja infratemporalne jame.

Ključne reči: Švanom; Temporalna kost + anatomija i histologija; Temporalna kost + patologija; Dijagnoza; Znaci i simptomi; Operativne hirurške procedure; Stari; Žensko; Magnetna rezonanca; CT

Summary

Introduction. Due to its contents and relations with neighboring regions, the infratemporal fossa has a great clinical significance. Primary tumors of this region, both benign and malignant, are rare, but they do require surgical treatment, which is determined by the size and localization of the tumor. **Case Report.** The paper presents the case of a 72-year-old female patient who was referred to hospital for paresthesia in the left half of the face after having been found to have a tumor of left infratmeporal fossa by imaging methods. The tumor was completely removed by transfacial-transzygomatic approach and, according to histopathological findings, it was a schwannoma. The postoperative course was without complications and the patient did not have any discomforts at the check-up a month later. **Conclusion.** In addition to the accurate diagnosis, the success rate of the surgical treatment of tumors depends on the appropriate surgical approach to ensure the complete removal of the tumor while preserving the content of the infratemporal region.

Key words: Neurilemmoma; Temporal Bone + anatomy & histology; Temporal Bone + pathology; Diagnosis; Signs and Symptoms; Surgical Procedures, Operative; Aged; Female; Magnetic Resonance Imaging; Tomography, X-Ray Computed

Uvod

Infratemporalna jama je anatomski prostor ograničen spolja ramusom mandibule, unutra pterigoidnim nastavkom sfenoidalne kosti kao i bočnim zidom nosnog i usnog dela ždrela od koga ga odvaja laterofaringealni prostor; napred je organičen telom maksile i parotidnim predelom, gornja granica je slepoočni predeo i velika krila sfenoidne kosti koja ga odvajaju od srednje lobanjske jame. Infratemporalna jama komunicira sa srednjom lobanjskom jamom preko neurovaskularnih otvora (*foramen spinosum, foramen ovale* i *foramen lacerum*). Medijalno infratemporalna jama komunicira sa pterigopalatinskom jamom preko pterigomaksilarne fisure a preko donje orbitalne fisure sa orbitom.

Zbog svog sadržaja (*a. maxillaris* i *plexus pterygoideus*, *n. mandibularis*, *n. maxillaris* i pterigoidni mišići), kao i odnosa sa retrostiloidnim delom laterofaringealnog prostora i njegovim sadržajem koji čini *a. carotis interna, v. jugularis interna*, kranijalni nervi (IX, X, XI, XII), ovaj prostor ima veliki klinički značaj. Prisustvo neurovaskularnih struktura ograničava hirurški pristup ovoj regiji jer je prilikom odabira hirurškog pristupa potrebno identifikovati i sačuvati ove strukture [1].

U infratemporalnoj jami najčešće se javljaju tumori iz okolnih zona kao što su paranazalni sinusi, srednja lobanjska jama, nazofarinks, parotidna žlezda i spoljašnji ušni kanal [2]. Manji broj tumora potiče iz tkiva infratemporalnog prostora i oni se terminološki označavaju kao primarni tumori. Metastaze drugih tumora se takođe mogu naći u infratemporalnoj jami. Benigni tumori uglavnom poštuju granice širenja u okviru anatomskog prostora i ravni mekih

Adresa autora: Dr Ivana Mijatov, Klinika za maksilofacijalnu hirurgiju,
21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: ivanamijatov@orion.rs

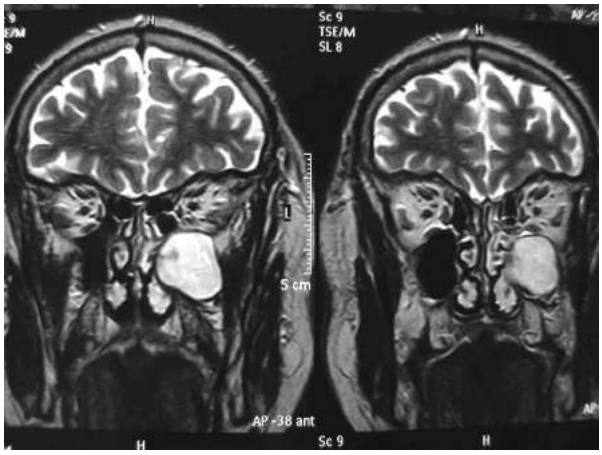
Skraćenice
CT – kompjuterizovana tomografija
NMR – nuklearna magnetna rezonancija

tkiva a ređe se šire kroz postojeće otvore (na primer kroz *foramen ovale* ili pterigomaksilarnu fisuru) [3].

Maligni tumori međutim mogu da infiltriraju i unište sve strukture koje ograničavaju prostor infratemporalne jame.

Prikaz slučaja

Na Kliniku za maksilofacijalnu hirurgiju Kliničkog centra Vojvodine u Novom Sadu oktobra 2010. godine primljena je pacijentkinja stara 72 godine. Maksilofacijalom hirurgu se javlja zbog trnjenja u predelu leve polovine lica. Tegobe su počele šest meseci pre javljanja lekaru u vidu trnjenja u predelu gornje usne koje se širilo ka levom oku da bi se vremenom proširilo na celu levu polovinu lica. Nakon sprovedene kompjuterizovane tomografije (CT) i nuklearne magnetne rezonancije (NMR) dijagnostikovana je tumorska masa u levom infratemporalnom prostoru **(Slika 1).**



Slika 1. Prikaz tumorske mase u levoj infratemporalnoj regiji - NMR snimak
Fig. 1. *Showing of the tumor in the left infratemporalnoj fossa- MRI*

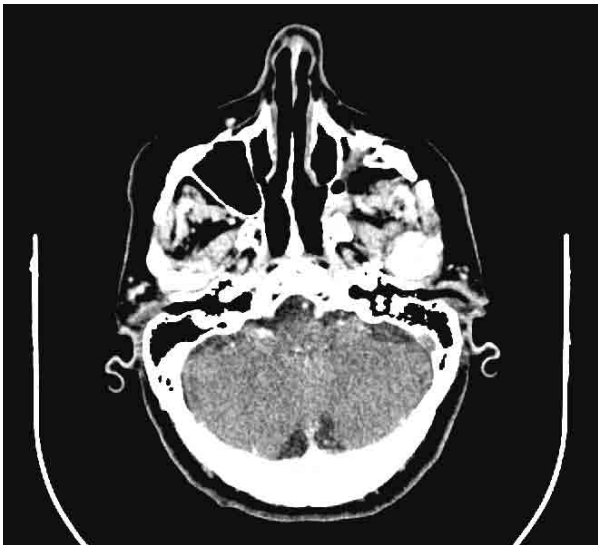
Nakon preoperativne pripreme u opštoj anesteziji odstranjena je tumorska masa u celini. Izabran je transfacijalni-transzigomatični pristup tumoru uz incizioni rez po Veber-Fergusonu koji je produžen supcilijarno. Nakon oslobađanja prednjeg zida maksile, načinjena je osteotomija u predelu infraorbitalne ivice, zigomatično-maksilarne suture i tela jagodične kosti, te je dobijeni koštani fragment u potpunosti uklonjen uz ligiranje infraorbitalnih krvnih sudova što je omogućilo pristup zadnjem zidu maksilarnog sinusa **(Slika 2)**. Na njemu je načinjen osteotomski otvor i identifikovana tumorska masa koja je u celosti odstranjena. Načinjena je revizija maksilarnog sinusa. Kroz formiranu nazoantrostomu, u defekt nastao nakon uklanjanja tumora, plasirana je jodoform gaza. Fragment kosti nakon osteotomije vraćen je na mesto i fiksiran pomoću osteosintetičkog materijala (dve mini-pločice i 8 šrafova) **(Slika 3)**.

Slika 2. Šematski prikaz osteotomije
Fig. 2. *Schematic view of osteotomy*

Patohistološkim nalazom identifikovan je švanom (*ancient type*).

Postoperativni tok prošao je bez komplikacija. Ordinirana je antibiotska terapija. Šestog postoperativnog dana uklonjena je jodoform gaza.

Preoperativna simptomatologija u vidu parestezija u predelu leve polovine lica nestala je nakon operativnog lečenja.



Slika 3. Postoperativni nalaz na snimku CT-a
Fig. 3. *Postoperative findings on CT image*

Konci su skinuti desetog postoperativnog dana, rana je zarasla uredno. Na kontrolnom pregledu nakon mesec dana pacijentkinja je bila bez subjektivnih tegoba.

Diskusija

U infratemporalnoj jami najčešće se javljaju tumori iz okolnih regija. Manji broj tumora potiče iz tkiva infratemporalnog prostora i oni se terminološki označavaju kao primarni tumori [3].

Na Klinici za maksilofacijalnu hirurgiju Kliničkog centra Vojvodine u periodu 1996–2012. godine operisano je 13 tumora infratemporalne jame, od kojih je 12 bilo malignih i jedan benigni. Od 12 malignih tumora infratemporalne regije, tri su bila primarna i to: dva osteosarkoma i mukoepidermoidni karcinom. Devet tumora je bilo metastatskih i to: dva metastatska tumora porekla karcinoma dojke, dva metastatska adenokarcinoma nepoznatog porekla, jedan metastatski tumor adenokarcinoma bubrega, jedna metastaza seminoma, jedna metastaza adenoid-cističnog karcinoma i po jedna metastaza melanoma nepoznatog porekla i planocelularnog karcima nepoznatog porekla. Jedan tumor je bio dobroćudan i to švanom opisan u ovom prikazu slučaja. Radi se o primarnom tumoru infratemporalne regije koji je patohistološkim pregledom identifikovan kao švanom. Švanom je benigna inkapsulirana neoplazma sa retkom incidencijom [4]. Javlja se obično u predelu glave i vrata, retko u drugim delovima tela. Histološki postoje varijacije švanoma kao što su: celularni tip, *ancient* tip, glandularni i epiteloidni tip. *Ancient* švanomi pokazuju pleomorfizam bez mitoza kao rezultat celularne degeneracije što može dovesti do pogrešnog dijagnostikovanja ovih tumora kao malignih. Njihova maligna alteracija je retka.

Za dijagnostikovanje veliki značaj imaju anamneza i klinički pregled kao i CT i NMR dijagnostika [5]. Pacijenti sa tumorom ove regije javljaju se sa simptomima neuropatija kranijalnih živaca koji se nalaze u infratemporalnoj regiji. Pacijenti mogu da imaju problem sa gutanjem i sa govorom (hipernazalni govor), nazalnu regurgitaciju, disfagiju, aspiraciju i disfoniju (uključenje IX, X kranijalnog nerva). Na disfunkciju i specifične kranijalne neuropatije ukazuje sledeći nalaz u fizikalnom pregledu: smanjenje elevacije ipsilateralnog nepca, smanjenje pokretljivosti i snage jezika (devijacija na zahvaćenu stranu), smanjenje supraglotične senzitivnosti, ipsilateralna paraliza glasnih žica i paraliza sternokleidomastoidnog mišića i trapezijusa (oštećen XI kranijalni nerv). Pacijentkinja u prikazanom slučaju javila se s parestezijama u predelu leve polovine lica što je ukazivalo na neuralgiju *n. infraorbitalis*, završne grane *n. maxillaris*.

Terapija ovih tumora je hirurška. Postoje razne varijante hirurških pristupa infratemporalnoj jami od transantalnog koju je Sewal uveo 1926. godine [6], preko maksilektomije, maksilarnog svinga, transzigomatičnog pristupa, do transpalatinalnog i endoskopskog pristupa uvedenih poslednjih dekada prošlog veka [7–9], a hirurgu je prepušteno da odabere odgovarajuću tehniku koja će obezbediti maksimalnu ekspoziciju tumora sa minimalnim posledicama po pacijenta uz očuvanje kvaliteta života pacijenta. Kada se sumnja na intrakranijalnu ekspanziju tumora potrebno je konsultovati neurohirurga.

Hirurški pristup infratemporalnoj jami, da bi obezbedio radikalnu resekciju tumora, može biti kombinovan: transkranijalni-suptemporalni, *Le Fort I*, transmaksilarni ili prednji frontalni pristup dok je za biopsiju (*fine-needle aspiration* biopsija ili *true cut* biopsija) endonazalni endoskopski pristup povoljniji u odnosu na konvencionalne pristupe [10,11].

Naravno da izbor hirurške metode zavisi od lokalizacije i dimenzija tumora [12,13]. S obzirom da se u našem slučaju radilo o tumoru smeštenom u predelu iza zadnjeg zida maksile, transfacijalni-transzigomatični pristup, uz prezervaciju koštanih strukura, bio je metoda izbora kojom su pošteđene neurovaskularne strukture ove regije.

Zaključak

Primarni tumori infratemporalne jame su retki tumori koji zahtevaju hirurško lečenje. Zbog anatomskog položaja i sadržaja infratemporalne jame, hirurški pristupi su složeni i zahtevaju preciznu preoperativnu dijagnostiku i izbor odgovarajućeg hirurškog pristupa koji bi obezbedio potpuno uklanjanje tumora i očuvanje neurovaskularnih elemenata. Prikazan je slučaj pacijentkinje sa švanomom infratemporalne regije koji je primenom transfacijalno-transzigomatičnog hirurškog pristupa uspešno odstranjen.

Literatura

1. Guinto G, Abello J, Molina A, Gallegos F, Oviedo A, Nettel B, Lopez R. Zygomatic-transmandibular approach for giant tumors of the infratemporal fossa and parapharyngeal space. Neurosurgery 1999;45:1385-98.

2. Prades JM, Timoshenko A, Merzougui, Martin C. A cadaveric study of combined trans-mandibular and trans-zygomatic approach to the infratemporal fossa. Surg Radiol Anatomy 2003;25(3-4):180-7.

3. Tiwari R, Quak J, Egeler S, Smeele L, Waal I, Valk P, Leemans R. Tumors of the infratemporal fossa. Skull Base Surgery 2000;10(1):1-8.

4. Honda K, Asato R, Tanaka S, Endo T, Nishimura K, Ito J, Smith R. Vidian nerve schwannoma with middle cranial fossa exedtension resected via a maxillary swing approach. Head Neck 2008;30(10):1389-93.

5. Boyle JO, Shah K, Shah J, Craniofacial resection for malignant neoplasms of the skull base: an overview**.** J Surg Oncol 1998;69:275-84.

6. Sewall EC. An operation for the removal of the sphenopalatine ganglion. Ann Otol Rhinol Laryngol 1926;79:967-9.

7. Sekhar LN, Schramm VL, Jones NF. Subtemporal-preauricular infratemporal fossa approach to large lateral and posterior cranial base neoplasms. J Neurosurg 1987;67:488-99.

8. Janecka IP, Sen CN, Sekhar LN, Arriaga M. Facial translocation: a new approach to the cranial base. Otolaryngol Head Neck Surg 1990;103:413-9.

9. Wei WI, Lam KH, Sham JST. New approach to the nasopharynx. The maxillary swing approach. Head Neck 1991; 13:200-7.

10. Mansour OI, Carrau RL, Snyderman CH, Kassam AB. Preauricular infra-temporal fossa surgical approach: modifications of the technique and surgical indications. Skull Base 2004;14:143-51.

11. Kiralj A, Ilić MP, Markov B, Dedić S, Pejaković B, Nalić B. Hondrom baze lobanje i gornje vilice. Med Pregl 2007;60(11-12):649-51.

12. Khan M, Bashir A. Advances in lateral scull and infratemporal fossa surgery. Pak J Neurol Sci 2007;2(2):111-5.

13. Branovan DI, Schaefer SD. Lateral Craniofacial approaches to the skull base and the infratemporal fossa. Otolaryngol Clin North Am 2001;34(6):1175-95.

Rad je primljen 15. II 2013.
Recenziran 20. II 2013.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:250-253.

Clinical Center Niš, Serbia
Centre of Radiology[1]
Department of Gynecology and Obstetrics[2]

Prikaz slučaja
Case report
UDK 618.33:616-006.2]-073
DOI: 10.2298/MPNS1306254M

ULTRASOUND AND MAGNETIC RESONANCE IMAGING IN PRENATAL DIAGNOSIS OF SACROCOCCYGEAL TERATOMA – CASE REPORT

ULTRASONOGRAFIJA I MAGNETNOREZONANTNI IMIDŽING U PRENATALNOJ DIJAGNOZI SAKROKOKCIGEALNOG TERATOMA – PRIKAZ SLUČAJA

Ivana MARKOVIĆ[1], Snežana STAMENOVIĆ[2], Zoran RADOVANOVIĆ[1], Petar BOŠNJAKOVIĆ[1], Dragana ILIĆ[1] and Dragan STOJANOV[1]

Summary

Introduction. Fetal tumors are relatively rare and the early prenatal diagnosis enables the prediction of possible complications and decision for appropriate treatment. This paper deals with the role of ultrasonography and magnetic resonance imaging in the early prenatal diagnosis of sacrococcygeal teratoma. **Case report.** A 21-year-old primigravida was found to have a large sacrococcygeal tumor measuring 25x30mm, presented mainly as a solid mass, when she underwent the initial ultrasound examination on the first day of 19th week of gestation. There were no other associated anomalies. The second ultrasound examination was obtained after 6 days and revealed that the tumor had doubled its size. The prominent enlargement raised suspicion of immature sacrococcygeal teratoma and thus, fetal magnetic resonance imaging was performed in the 20th gestation week. The examination showed a crococcygeal teratoma presented as a large solid mass with small microcystic areas, the largest diameter being 60mm, completely externally positioned with no intra-pelvic extension. Rapid tumor growth posed a threat to the fetal circulation and it was the main reason when opting for the termination of pregnancy at 20 weeks of gestation. Pathohystological examination confirmed the diagnosis of immature sacrococcygeal teratoma. **Discussion.** In the prenatal period the magnetic resonance imaging of a fetal tumor initially diagnosed by ultrasound examination is an additional part of diagnostic procedure, and it is not contraindicated during pregnancy. Magnetic resonance imaging improves the delineation of the tumor. The prompt prenatal diagnosis of sacrococcygeal teratoma, as well as the detection of possible associated anomalies, is important for the pregnancy management, prediction of possible complications and choice of appropriate treatment. **Conclusion.** Ultrasonography and magnetic resonance imaging are noninvasive, compatible and complementary diagnostic modalities in evaluation of sacrococcygeal teratoma in prenatal period.

Key words: Ultrasonography, Prenatal; Magnetic Resonance Imaging; Prenatal Diagnosis; Teratoma; Sacrococcygeal Region; Diagnosis; Fetus

Sažetak

Uvod. Fetalni tumori su relativno retki i rana prenatalna dijagnoza omogućava predviđanje mogućih komplikacija i odluku o odgovarajućem tretmanu. U ovom radu prikazana je uloga ultrasonografije i magnetnorezonantnog imidžinga u ranoj prenatalnoj dijagnozi sakrokokcigealnog teratoma. **Prikaz slučaja.** Kod dvadesetjednogodišnje prvorotke prvog dana 19. nedelje gestacije inicijalni ultrasonografski pregled otkrio je veliki, pretežno solidni sakrokokcigealni tumor, dimenzija 25 x 30 mm. Nije bilo drugih pridruženih anomalija. Nakon šest dana, kontrolni ultrasonografski pregled pokazao je da je veličina tumora udvostručena zbog čega je indikovan pregled magnetnom rezonacijom. U 20. nedelji gestacije ovaj pregled je pokazao sakrokokcigealni teratom u vidu velike solidne mase sa malim mikrocističnim zonama, najvećeg dijametra 60 mm, u potpunosti lokalizovanu ekstrapelvično, bez širenja u malu karlicu. Kompromitovana fetalna cirkulacija zbog brzog rasta tumora bila je razlog za odluku o prekidu trudnoće. Patohistološki pregled je potvrdio dijagnozu nezrelog sakrokokcigealnog teratoma. **Diskusija.** U prenatalnom periodu, nakon ultrasonografski otkrivenog fetalnog tumora, magnetnorezonantni imidžing omogućava dalje bolje sagledavanje tumora i njegovog odnosa prema okolnim strukturama. Pravovremena prenatalna dijagnoza sakrokokcigealnog teratoma, kao i sagledavanje potencijalno udruženih razvojnih anomalija veoma su bitni za vođenje trudnoće, predviđanje mogućih komplikacija i donošenje odluke o odgovarajućem tretmanu. **Zaključak.** Ultrasonografija i magnetnorezonantni imidžing su neinvazivne, kompatibilne i komplementarne dijagnostičke metode u sagledavanju sakrokokcigealnog teratoma u prenatalnom periodu.

Ključne reči: Prenatalna ultrasonografija; Magnetna rezonanca; Prenatalna dijagnoza; Teratom; Sakrokokcigealna regija; Dijagnoza; Fetus

Corresponding Author: Dr Ivana Marković, Cenatr za radiologiju, Klinički centar Niš, 18000 Niš, Bulevar Zorana Đinđića 48, Serbia E-mail: ivanadidi@yahoo.com

Abbreviations

HQ – high quality
MRI – magnetic resonance imaging
SCT – sacrococcygeal teratoma
TE – time of echo
TR – time of repetition
T2W – T2 weighted
US – ultrasonography

Introduction

Fetal tumors are relatively rare and the early prenatal diagnosis enables the prediction of possible complications and decision for appropriate treatment. Teratomas are usually present at birth, but the small ones are often not discovered until much later in life. Congenital teratomas most frequently occur in the sacrococcygeal region. The incidence of sacrococcygeal teratoma (SCT) is 1-2 per 35 - 40000 newborns [1]. The prevalence is 0.25-0.5 : 10 000 live births for any fetal teratoma, with sacrococcygeal accounting for over 50%, cranial 40% and cervical 5.5%. SCT is more common in female than in male fetuses (1:4) [1,2].

The diagnosis of SCT is usually made by obstetric ultrasonography (US) performed as a screening procedure or to assess the uterine size too large for the dates. A detailed ultrasonographic evaluation aided by color flow Doppler allows a more accurate diagnosis. Magnetic resonance imaging (MRI) contributes significantly to the diagnosis after ultrasound examination [3]. Ultrasound examination and MRI are of great importance in diagnosing fetal teratomas because they allow the correct assessment of the tumor size, localization and its relation to surrounding structures. This paper presents the role of ultrasonography and MRI in the early prenatal diagnosis of SCT.

Case report

A 21-year-old primigravida was admitted to the Department of Gynecology and Obstetrics of the Clinical Centre of Nis (the Ward for High Risk Pregnancy) on the first day of 19th week of gestation for severe pain and high suspicion of imminent abortion. It was a low risk pregnancy and her personal and family history did not contribute significantly. On initial ultrasound examination (Toshiba 4D) we found single fetus corresponding to the period of gestation with polyhydramnios and breech presentation. In addition, a large sacrococcygeal tumor was visualized, measuring 25x30mm, presented mainly as a solid mass **(figures 1 and 2)**. There were no other associated anomalies.

The second ultrasound examination was obtained after 6 days. This examination showed a significant increase in size of tumor, which doubled its size since the first ultrasonography. Amniocentesis was also done and the analysis of the amniotic fluid showed that the caryotype was 46XX.

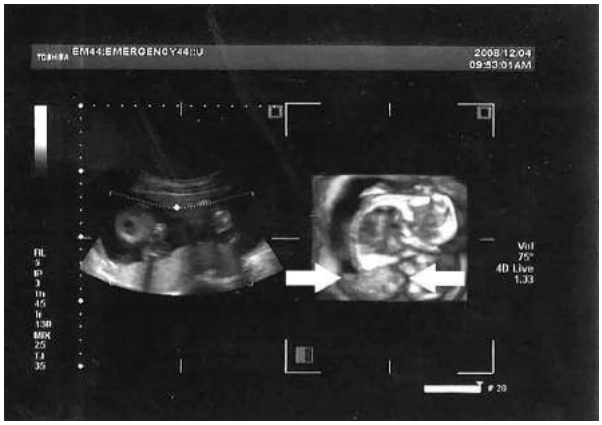


Fig. 1. Female fetus at 19 weeks with type I sacrococcygeal teratoma. Sagittal sonogram (4D) of fetus with sacrococcygeal teratoma (arrows)
Slika 1. *Ženski fetus gestacijske starosti 19 nedelja sa sakrokokcigealnim teratomom tip I. Sagitalni sonogram (4D) fetusa sa sakrokokcigealnim teratomom (označen strelicama)*

The prominent enlargement raised suspicion of an immature or malignant SCT and we decided to perform a fetal MRI.

Two days later, at the beginning of 20th gestation week, MRI was performed with 1.5 T magnet (Avanto, Siemens) equipped with a phased-array body coil. The non-sedated mother was put in supine position. The following imaging sequences were performed: T2 trufi HQ, T2 trufi FAST and T2 trufi single shot real time (TR 214.1ms, TE 1.76ms, section thickness 3mm) in the sagital, coronal and axial planes relative to the fetus. MRI study was reviewed and interpreted by the radiologist, who was aware of sonography results and clinical information. MRI results were compared with sonography results.

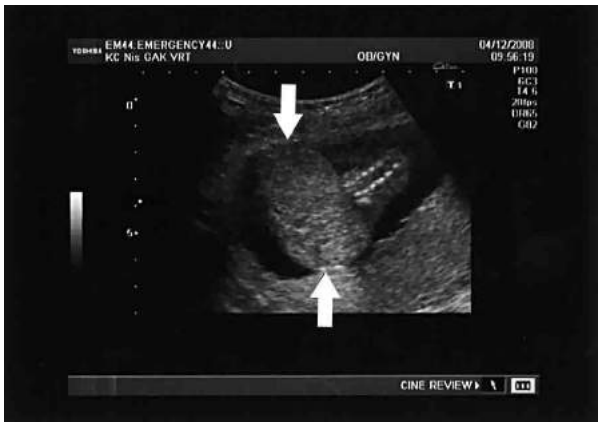


Fig. 2. Coronal sonogram shows a tumor external to the fetus with echogenic tumoral content (arrows)
Slika 2. *Koronalni sonogram pokazuje tumor sa ehogenom strukturom koji se širi van fetusa (označeno strelicama)*

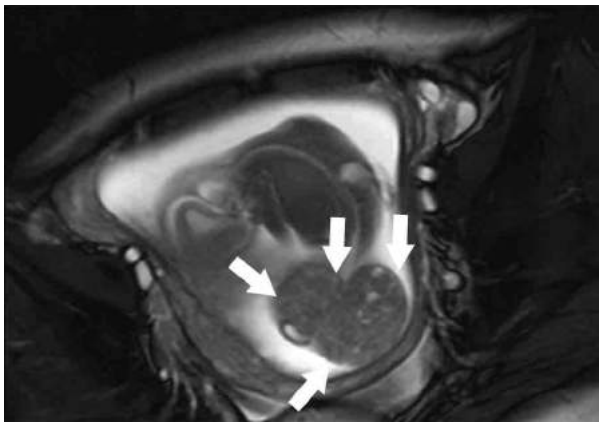


Fig. 3. Fetal MR imaging at 20 weeks with type I sacrococcygeal teratoma. Coronal T2-weighted trufi HQ MR image (TR 214.1ms, TE 1.76ms) shows large caudal extrapelvic mass (arrows) in sacrococcygeal region
Slika 3*. MRI fetusa gestacijske starosti 19 nedelja sa sakrokokcigealnim teratomom tip I. Koronalni T2W trufi HQ MR tomogram (TR 214.1 ms, TE 1.76 ms) pokazuje veliku ekstrapelvičnu masu (označeno strelicama) u sakrokokcigealnoj regiji*

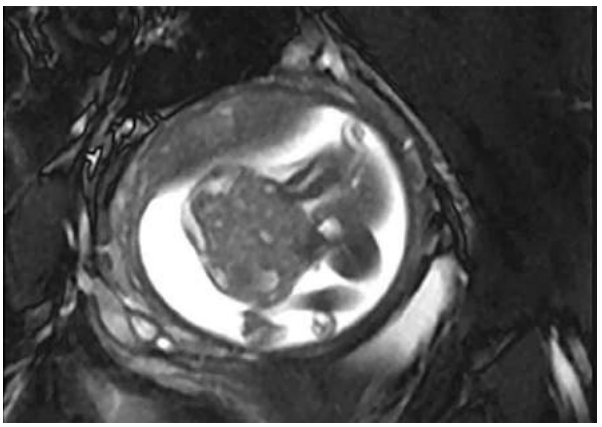


Fig. 4. MR image T2-weighted trufi HQ (TR 214.1ms, TE 1.76ms) in the axial plane shows a mainly solid tumor tissue with small areas of microcystic content
Slika 4. *MR T2W trufi HQ tomogram (TR 214.1ms, TE 1.76ms) u aksijalnoj ravni pokazuje dominantno solidno tumorsko tkivo sa manjim zonama mikrocističnog sadržaja*

The presence, size, signal intensity, characteristics, extent and compressive effect of the SCT were determined. Screening MRI at the beginning of 20th gestational week showed a SCT presenting as a large solid mass in the sacrococcygeal region with small microcystic areas, completely externally positioned with no intrapelvic extension. The largest diameter of the tumor measured on MR imaging was 60 mm **(figures 3 and 4)**.

Rapid tumor growth posed a threat to the fetal circulation, which could be seriously compromised. This was the main reason for the commission to opt for the termination of the pregnancy at 20th gestational week. The fetus exited after delivery due to immaturity.

The pathologic examination of the fetus was performed afterwards according to the hospital protocol. This examination confirmed the presence of a tumor in the sacrococcigeal region, with the largest diameter measuring 62mm. The tumor mass was clearly demarcated, and there was no propagation into the pelvis. The pelvic organs were intact. On macrosopic pathologic examination the tumor was described as predominately solid with multiple small cysts. On examination no other associated congenital anomalies were detected. The tumor was classified as immature SCT type I, which confirmed US and MRI findings.

Discussion

Magnetic resonance imaging is a complementary modality in diagnosing SCT and is always obtained after ultrasound examination. Characteristic findings are of a caudal or intrapelvic mass, which can be routinely identified during the second and third trimester. Other important information from ultrasound and magnetic resonance imaging includes the presence of abdominal or pelvic extension, evidence of bowel or urinary tract obstruction, assessment of the fetal spine integrity and lower extremity function [4,5].

Possible fetal complications include spontaneous hemorrhage into the SCT, nonimmune hydrops fetalis, malignancy, renal calyceal dilatation and bladder outlet obstruction. The resulting fetal anemia may initiate or exacerbate the effects of the vascular steal.

The major differential diagnosis includes myelomeningocele, meconium pseudocyst and obstructive uropathy. Features that may exclude these possibilities include the presence of normal kidneys, absence of solid component and calcifications within the mass, presence of spinal dysraphic features and the lack of a meconium appearance to the fluid contained within the cysts [6]. All these features can be revealed on US and magnetic resonance examination.

The prognosis is related to the size of the mass and surgical operability. Other prognostic factors include gestational age of the fetus at the time of delivery, presence or absence of associated fetal malformation and fetal hydrops, and the availability of resuscitation team to secure a neonatal airway following delivery [7,8]. The risk of malignancy depends on the child's age. SCT diagnosed at the age of less than 2 months, one year and two years is malignant in 7-10%, 37% and 50%, respectively [9].

The prenatal diagnosis of a SCT allows us to predict possible complications and to make decision for the appropriate treatment. Since these tumors are generally not malignant, most fetuses with SCT do well with surgical treatment after birth. Babies with

small tumors that can be removed along with the coccyx bone after birth can be expected to have a normal life. Fetuses with very large tumors, which can reach the size of the fetus itself, pose a difficult problem both before and after birth [10,11].

Conclusion

Magnetic resonance imaging is a valuable adjunct to obstetric sonography for the prenatal evaluation of sacrococcygeal teratoma. The team approach is the imperative in providing an organized and coordinated care plan. An obstetrician and/or perinatologist, pediatric radiologist, neonatologist and pediatric surgeon should all be available when making the final decision about the pregnancy outcome.

References

1. Bhat RA, Kusthagi P, Bhat AK. Fetal sacrococcygeal teratoma. Int J Gynecol Obstet. 2005;4:120-2.

2. Shinjiro H, Diana LF. Fetal surgery for sacrococcygeal teratoma. Clin Perinatol. 2003;30:493-506.

3. Novakov-Mikić A, Koprivšek K, Lučić M, Stojić S. Ultrasonography and magnetic resonance imaging in prenatal diagnosis of tumour of the foetal head and neck. Srp Arh Celok Lek. 2012;140(1-2):97-9.

4. Danzer E, Hubbard AM, Hedrick HL, et al. Diagnosis and characterization of sacrococcygeal teratoma with prenatal MRI. AJR 2006;187(4):350-6.

5. Avni FE, Guibard L, Robert Y, Segers V, Ziereisen F, Delaet MH, et al. MR Imaging of fetal sacrococcygeal teratoma: diagnosis and assessment. AJR 2002;178:179-83.

6. Jelin E, Jelin AC, Hanmin L. Sacrococcygeal teratoma with spinal canal invasion prenatally diagnosed. J Pediatr Surg. 2009;44:9-11.

7. Walton JM, Rubin SZ, Soucy P, et al. Fetal tumors associated with hydrops: the role of pediatric surgeon. J Pediatr Surg. 1993;28:1151-3.

8. Hedric HL, Flake AW, Crombleholme TM, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. J Pediatr Surg. 2004;39:430-8.

9. Feldman M, Byrne P, Johnson MA, Fischve J, Lees G. Neonatal sacrococcygeal teratoma: multiimaging modality assessment. J Pediatr Surg. 1990;25(6):675-8.

10. Chen YH, Chang CH, Chen KC, Diau GY, Loh IW, Chu CC. Malignant transformation of a well-organized sacrococcygeal fetiform teratoma in a newborn male. J Formos Med Assoc 2007;106(5):400-2.

11. Mann JR, Gray ES, Thornton C, Raafat F, Robinson K, Collins GS, et al. Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol. 2008;26(21):3590-7.

Rad je primljen 5. VII 2012.
Recenziran 30. XII 2012.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:254-257.

SEMINAR ZA LEKARE U PRAKSI
SEMINAR FOR PHISICIANS

Klinički centar Vojvodine, Novi Sad
Klinika za urologiju
Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad[1]
Kliničko-bolnički centar „Dragiša Mišović", Beograd, Klinika za urologiju[2]

Seminar za lekare u praksi
Seminar for phisicians
UDK 616.65-006.6:577161.2
DOI: 10.2298/MPNS1306259M

VITAMIN D I KARCINOM PROSTATE

VITAMIN D AND PROSTATE CANCER

Goran MARUŠIĆ[1], Dimitrije JEREMIĆ[1], Saša VOJINOV[1], Nataša FILIPOVIĆ[2] i Milan POPOV[1]

Sažetak

Pored od ranije poznate i jasno definisane metaboličke uloge vitamina D, danas se sve više hipotetiše sa njegovom antiproliferativnom i proapoptotskom ulogom. **Epidemiologija i značaj karcinoma prostate.** Karcinom prostate je prema učestalosti na drugom mestu u odnosu na ostale karcinome kod muškaraca. Dug period kancerogeneze, raspoloživi tumorski markeri i velika incidencija čine karcinom prostate idealnim za primenu preventivnih mera. **Fiziološka uloga vitamina D i dejstvo na ćelije karcinoma prostate.** *In vitro* i *in vivo* ispitivanja pokazala su postojanje antiproliferativne i proapoptotske uloge vitamina D. Poremećaji u fiziologiji vitamina D uočeni su na nivou gena za vitamin D, receptora vitamina D, elemenata responzivnih za vitamin D i androgenih receptora. **Zaključak.** Dosadašnja istraživanja koja se bave posmatranjem nivoa vitamina D u serumu, tkivu prostate, akivnosti enzima koji učestvuju u metabolizmu vitamina D, kao i promenama na genima, predstavljaju početak istraživanja i otkrivanja značaja vitamina D u razvoju karcinoma prostate.

Ključne reči: D vitamin; Karcinom prostate; Muško; Proliferacija ćelija + efekat lekova; Apoptoza; Genetika; Metabolizam; Epidemiologija

Summary

In addition to the metabolic role of vitamin D, which is well known and clearly defined, there have been many hypotheses regarding its anti-proliferative and pro-apoptotic role. **Epidemiology and Significance of Prostate Cancer.** Prostate cancer is the second most common malignancy in men. Long period of cancerogenesis, available tumor markers and high incidence make this cancer ideal for preventive measures. **Physiological Role of Vitamin D and its Effect on Prostate Cancer Cells.** In vitro and in vivo studies have shown the anti-proliferative and pro-apoptopic role of vitamin D. Disorders of vitamin D metabolism are noted in vitamin D gene level, vitamin D receptor, vitamin D responsive elements and androgen receptors. We present the most important effect of those changes on vitamin D metabolism. **Conclusion.** Available studies on vitamin D level in serum, prostate tissue, observed activity of vitamin D enzymes and genetic changes give us only a slight insight into the basic mechanisms of vitamin D action in the development of prostate cancer; therefore, further investigations are needed.

Key words: Vitamin D; Prostatic Neoplasms; Male; Cell Proliferation + drug effects; Apoptosis; Genetics; Metabolism; Epidemiology

Uvod

U protekloj deceniji, pored ranije definisane uloge vitamina D u homeostazi kalcijuma i fosfora [1], pojavilo se shvatanje da vitamin D ima značajnu ulogu u kancerogenezi. Epidemiološke, *in vitro* i *in vivo* studije pokazale su da postoji povezanost između nivoa vitamina D, učestalosti i mortaliteta od karcinoma debelog creva, prostate i dojke [2,3]. Postoji veliki broj studija koje se bave ulogom vitamina D u razvoju karcinoma prostate, neke sa pozitivnom, dok druge ukazuju na postojanje negativne korelacije, te se na osnovu ovih istraživanja ne može formirati defintivni stav. Pored uloge u kancerogenezi, hipotetiše se i sa potencijalnom ulogom vitamina D i njegovih analoga u terapiji malignih bolesti. Karcinom prostate predstavlja najčešću nekutanu malignu promenu od koje tokom života oboli 16,72% muškaraca; istovremeno je on uzrok smrti kod 2,57% muškaraca [4]. Bolest ima dug period progresije i preživljavanja, što stvara mogućnosti za različite dijagnostičke, preventivne i terapijske mere. Pokušaćemo da, na osnovu raspoložive literature, utvrdimo trenutno mesto i značaj vitamina D kod karcinoma prostate.

Epidemiologija i značaj karcinoma prostate

Karcinom prostate je bolest koja se javlja u starijem životnom dobu, 63% pacijenta oboleva nakon 65. godine. Kumulativni rizik za razvoj kli-

Adresa autora: Prof. dr Goran Marušić, Klinika za urologiju, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: gmarusic@neobee.net

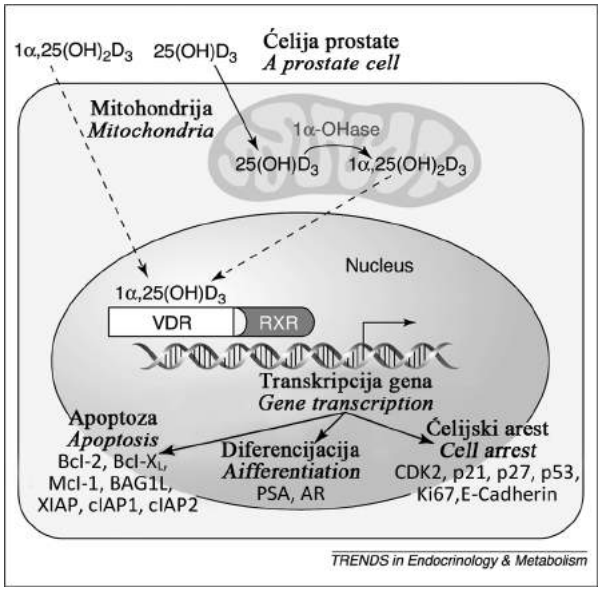
Skraćenice

VDR	– receptor vitamina D
VDREs	– elementi responzivni za vitamin D
[25(OH)D]	− 25–hidroksivitamin D
[1,25(OH)2D]	− 1,25-dihidroksivitamin D
PTH	− paratiroidni hormon
FGF-23	– *Fibroblast growth factor* 23
RXR	− retinoična kiselina
PSA	– antigen specifičan za prostatu
LNCaP ćelije	– androgent senzitivne ćelije dobijene iz metastaze karcinoma prostate u levu supraklavikularnu žlezdu
AR	– androgeni receptori
GS	– *Gleason scor*
BHP	– benigna hiperplazija prostate

nički manifestne bolesti je 17,3% do 85. godine [5]. Incidencija obolevanja u svetu znatno varira, najniža je u Aziji, dok je u Skandinavskim zemljama, Severnoj Americi i naročito u područjima naseljenim Afroameričkom populacijom, znatno veća. *Cancer survival in five continents: a worldwide population-based study* (CONCORD) ustanovila je i da je mortalitet varijabilan i u zavisnosti je od geografskih i rasnih parametara, odnosno, najveći je kod Afroamerikanaca i na većim geografskim širinama [6]. Upotrebom antigena specifičnog za prostatu (PSA) došlo je do povećanja broja pacijenata kod kojih se dijagnoza postavlja u ranom kliničkom stadijumu bolesti. Nepalpabilni karcinomi prostate danas čine 60–75% novootkrivenih slučajeva [7]. Rana dijagnostika i lečenje doveli su do produženja petogodišnjeg i desetogodišnjeg preživljavanja na 99% odnosno 91%, kombinovano za sve stadijume bolesti [8]. Dug period kancerogeneze, tumorski markeri i velika incidencija čine karcinom prostate idealnim za primenu preventivnih mera. Najznačajniji faktori rizika za razvoj karcinoma prostate su: godine starosti, geografska širina, rasna pripadnost, nasleđe. U starosti, nivo vitamina D se fiziološki smanjuje [9], dok se učestalost karcinoma prostate povećava. Oboljenje se češće javlja na većoj geografskoj širini gde je insolacija i izloženost ultraljubičastom zračenju manja. Melanin u koži Afroamerikanaca blokira sunčeve zrake i smanjuje sintezu vitamina D. Smatra se da ishrana bogata kalcijumom smanjuje nivo vitamina D i dovodi do uslova za razvoj karcinoma prostate, dok ishrana bogata ribljim uljima ima protektivno dejstvo, što potvrđuje veoma niska incidencija karcinoma prostate u Japanu. Studija koja je analizirala nivo vitamina D kod pacijenata u Finskoj, pokazala je da postoji povećan rizik za razvoj karcinoma prostate kod muškaraca sa nižim vrednostima 1,25-dihidroksivitamina D [1,25$(OH)_2$D], posebno kod mlađih osoba [3,10]. Druga studija, iz 2003. godine, pokazala je da je unošenje uobičajene količine kalcijuma (700 mg dnevno) bilo povezano sa relativnim rizikom od 1,2, dok je unošenje veće količine kalcijuma (2 000 mg dnevno) bilo povezano sa relativno većim rizikom, od 1,6 [11]. Pored nivoa vitamina D, smatra se i da receptor vitamina D (VDR) i 25(OH) D1α-hidroksilaza imaju ulogu u onkogenezi karcinoma prostate.

Fiziološka uloga vitamina D i dejstvo na ćelije karcinoma prostate

Vitamin D_3 (*cholecalciferol*) stvara se iz 7-dehidroholesterola pod uticajem ultravioletnog B zračenja, talasne dužine 290–315 nm, preko međuprodukta − provitamina D_3 u epidermalnom sloju kože. Prekomerno izlaganje suncu dovodi do razgradnje provitamina D_3 i vitamina D_3. Hranom uneti vitamin D_2 (*ergocalciferol*) i D_3 apsorbuju se u tankom crevu i hilomikronima transportuju do adipocita. Vitamin D_2 i D_3 su u krvi vezani za vitamin D-vezujući protein, kojim se transportuju do jetre, gde se pod dejstvom enzima vitamin D 25-hidroksilaze, dobija 25–hidroksivitamin D [25(OH)D]. Ova forma vitamina određuje se merenjem u serumu i biološki je inaktivna. Fiziološka vrednost je 30–60 ng/ml. Vrednosti ispod 10 ng/ml predstavljaju deficijenciju, insuficijencija postoji kod pacijenata sa nivoom 25(OH)D 20–30 ng/ml, dok se intoksikacija javlja ukoliko je vrednost veća od 150 ng/ml. Enzim 25(OH)D 1-α hidroksilaza pretvara ga u bubrezima u aktivnu formu: 1,25$(OH)_2$D. Premda je bubreg primarno mesto konverzije u 1,25$(OH)_2$D, enzim 25(OH)D 1-α hidroksilaza nalazi se i u drugim organima i žlezdama, uključujući i prostatu [12]. Nivo 1,25$(OH)_2$D kontrolisan je negativnom povratnom spregom spostvenom koncentracijom, kao i koncentracijom serumskih fosfata i kalcijuma. Paratiroidni hormon (PTH) takođe reguliše nivo vitamina D. Biološko dejstvo posredovano je VDR, koji je nuklearni receptor, nalazi se kako u zdravom tako i u tumorskom tkivu. Dokazano je da se dejstvom preko VDR, tumorska ćelija diferencira i uvodi u G_0 fazu ćelijskog ciklusa. Nakon vezivanja 1,25$(OH)_2$D za VDR, formira se heterodimer sa retinoičnim X receptorom (RXR) i aktiviraju specifični delovi DNK poznati kao elementi responzivni za vitamin D (VDREs). Transkripcijom ovih gena ćelija ostaje u G_0 fazi, prolazi senescencu (fiziološko starenje ćelije) i podleže apoptozi **(Slika 1).** Visok nivo 1,25$(OH)_2$D dovodi do stvaranja 25-hidroksivitamin D-24-hidroksilaze (24-OHase), koja ga razgrađuje. Kao produkt javlja se kalcitroička kiselina koja se izlučuje preko žuči. U tankom crevu 1,25$(OH)_2$D dovodi do poboljšanja intestinalne resorpcije kalcijuma i fosfora od 20% [12]. Na kosti deluje indirektno preko osteoblasta i medijatora koji pretvaraju preosteoklaste u osteoklaste što dovodi do mobilizacije kalcijuma i fosfora iz kosti. Primarni mehanizam dejstva 1,25$(OH)_2$D je transkripcija gena iz VDREs. Nakon vezivanja 1,25$(OH)_2$D za VDR dolazi do interakcije sa RXR, koja je neophodna za transkripciju. Kada se formira kompleks 1,25$(OH)_2$D -VDR-RXR dolazi do vezivanja za VDREs i započinje transkripcija [13]. Da bi 1,25$(OH)_2$D ispoljio svoje diferencijaciono, antiproliferativno i proapoptopsko dejstvo, funkcija VDR, VDREs i odgovara-



Slika 1. Mehanizam dejstva vitamina D na ćelije karcinoma prostate (preuzeto od Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. Trends in Endocrinology and Metabolism. 2003;14(9):423-30.)

Fig. 1. *Mechanism of vitamin D action on the prostate cancer cells (taken from Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. Trends in Endocrinology and Metabolism. 2003;14(9):423-30.)*

juća signalizacija, moraju biti očuvane. Ukoliko je gen CYP27B1, koji kodira 25(OH)D 1-α hidroksilazu mutiran, povećava se mortalitet kod karcinoma prostate [14,15]. Ukoliko se kod humane kulture malignih ćelija prostate dobijenih biopsijom prostate tokom radikalne prostatektomije (ALVA 31), pomoću $1,25(OH)_2D$, ćelija uvede u G_0 fazu, a nakon toga antisense oligonukleotidima blokira transkripcija VDR, može doći do ponovne proliferacije koja je prethodno zaustavljena pomoću $1,25(OH)_2D$ [13]. Ćelije kulture androgent senzitivnih ćelija dobijenih iz metastaze karcinoma prostate u levu supraklavikularnu žlezdu (LNCaP) nemaju 25(OH)D 1-α hidroksilazu i ne reaguju na 25(OH)D. $1,25(OH)_2D$ deluje tako što dovodi do diferencijacije i apoptoze LNCaP [16,17].

Analog vitamina D, EB1089, *in vivo* takođe, dovodi do inhibicije rasta LNCaP [18]. Nakon prenosa plazmida koji sadrži cDNK za 25(OH)D 1-α hidroksilazu u LNCaP, ispoljena je aktivnost koja je dovela do inhibicije rasta [19]. U istom istraživanju ustanovljena je odsutna aktivnost 25(OH)D 1-α hidroksilaze kod kulture ćelija adenokarcinoma prostate PCA-3, kao i pozitivni antiproliferativni i proapoptotski efekti nakon prenosa plazmida sa genom koji kodira 25(OH)D 1-α hidroksilazu (transfekcija). Takođe je ustanovljeno da je aktivnost 25(OH)D 1-α hidroksilaze deset puta manja u ćelijama karcinoma nego u benignim ćelijama, što može poslužiti kao parametar za otkrivanje malignih ćelija.

Dejstvo vitamina D povezano je i sa postojanjem andorgenih receptora (AR) u kulturama ćelija. Dokazano je da kulture ćelija adenokarcinoma prostate, LNCaP i CWR2RR, koje su pozitivne na AR, imaju jače izraženu inhibiciju rasta nego kulture PCA-3 i DU 145, koje nemaju eksprimirane AR [21]. Isti autori ustanovili su da $1,25(OH)_2D$ zaustavlja CWR22R i LNCaP u G_0/G_1 pri čemu je inhibicija proliferacije znatno sporija kod LNCaP (1 vs. 3 dana). Na AR negativne ćelijske kulture PCA -3 i DU 145, $1,25(OH)_2D$ nema značajniji efekat. Istovremeno sa akumulacijom ćelija u G_0/G_1 uočena je povećana ekspresija AR u LNCaP tokom prvog dana nakon primene $1,25(OH)_2D$, dok je kod CWR22R došlo do ekspresije AR u prva tri dana nakon primene $1,25(OH)_2D$, iz čega se vidi da su neophodna dalja istraživanja u smislu određivanja tačne korelacije AR, VDR i $1,25(OH)_2D$.

Gen za VDR (ranije NR1I1) nalazi se na 12q13.11. Fiziološka ekspresija VDR postoji u nukleusima epitelnih i stromalnih ćelija prostate. Prisustvno i funkcionalnost VDR je preduslov za fiziološko dejstvo $1,25(OH)_2D$, što je potvrđeno studijama koje su proučavale VDR „null" miševe i ustanovile da je VDR neophodan za antiproliferativne efekte $1,25(OH)_2D$ [21,22]. Ustanovljeno je da se ekspresija gena za VDR smanjuje tokom života; sa najvišim nivoom nalazi se u petoj deceniji, nakon čega postepeno opada [23]. Nekonzistentni nalazi studija o ulozi vitamina D u razvoju karcinoma prostate mogu biti uzrokovani polimorfizmima u genu za VDR. Analiza polimorfizama sekvenci gena za VDR − ApaI, TaqI, BsmI, poliadenin (A), FokI, nije ukazala na postojanje veze sa razvojem karcinoma prostate. Funkcija VDR se takođe menja ukoliko ćelije ispoljavaju SV40 T-antigen, protoonkogen koji može da transformiše različite ćelije.

Hendrickson i saradnici posmatrali su odnos VDR ekspresije, PSA, *Gleason* skora (GS) i TMPRSS2:ERG fuzije, koja je čest genski poremećaj kod karcinoma prostate. Ustanovili su da pacijenti sa izraženijom ekspresijom VDR imaju niže vrednosti PSA prilikom dijagnoze (17,5 ng/ml najniža kvartila vs. 8,8 ng/ml naviša kvartila) [24]. Lokalizovani karcinom prostate prilikom radikalne prostatektomije bio je češći kod pacijenata kod kojih je ekspresija VDR bila veća (60,4% najniža kvartila vs 75.4% najviša kvartila). U odnosu na GS, VDR ekspresija je bila najviša kod pacijenata sa GS 3+3, dok je u odnosu na porast GS bila obrnuto proporcionalna. Pedeset i četiri posto pacijenata sa TMPRSS2:ERG bilo je u najvišoj kvartili za ekspresiju VDR, a u najnižoj svega 29% pacijenata. Takođe, ustanovljeno je postojanje inverznog odnosa VDR i smrtnog ishoda bolesti.

Enzim koji je odgovoran za pretvaranje 25(OH)D u $1,25(OH)_2D$, 25(OH)D 1-α hidroksilaza, nalazi se u ćelijama normalnog, benigno hiperplastičnog (BHP) i karcinomskog tkiva prostate. Normalno tkivo ima najvišu aktivnost 25(OH)D 1-α hidroksilaze, dok se sukcesivno niže vrednosti mogu videti kod BHP i

karcinoma prostate. Chen i saradnici su proučavali odnos LNCaP i 25(OH)D 1-α hidroksilaze. $1,25(OH)_2D$ ne ispoljava dejstvo na LNCaP. Da bi ispitali da li je za odsustvo inhibicije odgovoran nedostatak 25(OH)D 1-α hidroksilaze, u ćelije LNCaP unet je plazmid sa genom za 25(OH)D 1-α hidroksilazu. Ćelije su konvertovale 25(OH)D u 1,25(OH)2D i ispoljeno je antiproliferativno dejstvo. Aktivnost renalne 25(OH)D 1-α hidroksilaze je pod kontrolom paratiroidnog hormona, dok je prostatična 25(OH)D 1-α hidroksilaza pod autokrinom kontrolom. Ovo ukazuje da 25(OH)D 1-α hidroksilaza ima važnu ulogu u metabolizmu $1,25(OH)_2D$ i razvoju karcinoma prostate.

Zaključak

Vitamin D ima značajnu ulogu u razvoju karcinoma prostate. Dosadašnja istraživanja kroz posmatranje nivoa vitamina D u serumu, tkivu prostate, akivnosti enzima koji učestvuju u metabolizmu vitamina D, kao i promenama na genima, predstavljaju početak otkrivanja značaja vitamina D u razvoju ovog oboljenja. U skladu sa preventivnim tendencijama savremene medicine, a imajući u vidu sporu evoluciju karcinoma prostate, postoji potencijalna uloga vitamina D kao hemopreventivnog elementa u razvoju raka prostate.

Literatura

1. Naumović N. Vitamin D: physiological importance. Med Pregl. 2010;63(5-6):301-4.
2. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006;98:451-9.
3. Ahonen MH, Tenkanen L, Teppo L, et al. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. 2000;11:847-52.
4. Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology, 10th ed. Philadelphia: Elsevies Saunders; 2012.
5. Grönberg H. Prostate cancer epidemiology. Lancet Oncol. 2003;8:859-64.
6. Coleman MP, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 2008;9:730-56.
7. Gallina A, Chun FK, Suardi N. Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer. BJU Int 2008;101:1513-8.
8. American Cancer Society. Cancer facts and figures 2010. Atlanta: American Cancer Society; 2010.
9. Orwoll E, Nielson CM, Marshall LM. Vitamin D deficiency in older men. J Clin Endocrinol Metab. 2009;94:1214-22.
10. Rodriguez C, McCullough ML, Mondul A, et al. Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United states men. Cancer Epidemiol Biomarkers Prev. 2003;12:597-603.
11. Schwartz GG, Whitlatch LW, Chen TC, Lokeshwar BL, Holick MF. Human prostate cells synthesize 1,25-dihydroxyvitamin D 3 from 25-hydroxyvitamin D 3. Cancer Epidemiol Biomarkers Prev 1998;7:391-5.
12. Haussler MR, Whitfield GK, Haussler CA, et al. The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. J Bone Miner Res. 1998;13:325-49.
13. Holt SK, Kwon ME, Koopmeiners SJ, et al. Vitamin D pathway gene variants and prostate cancer prognosis. Prostate 2010;70:1448-60.
14. Ma JF, Nonn L, Campbell MJ, et al. Mechanisms of decreased vitamin D 1α hydrixilase activity in prostate cancer cells. Mol Cell Endocrinol. 2004;221:67-74.
15. Hedlund TE, Moffatt KA, Miller GJ. Vitamin D receptor expression isrequired for growth modulation by 1α, 25-dihydroxyvitamin D3 in the human prostatic carcinoma cell line ALVA-31. J Steroid Biochem Mol Biol 1996;58:277-88.
16. Feldman D, Zhao XY, Krishnan AV. Vitamin D and prostate cancer. Endocrinology 2000;141:5-9.
17. Chen TC, Schwartz GG, Burustein KL. The in vitro evaluation of 25-hydroxyvitamin D3 and 19-nor-1,25-dihydroxyvitamin D2 for prostate cancer therapy. Clin Cancer Res. 2000;6:901-8.
18. Blutt SE, Polek TC, Stewart LV. A calcitriol analogue, EB1089, inhibits the growth of LNCaP tumors in nude mice, Cancer Res. 2000;60:779-82.
19. Whitlatch WL, Young VM, Schwartz GG. 25-Hydroxyvitamin D-1-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer. J Steroid Biochem Mol Biol 2002;81:135-40.
20. Zinser GM, McEleney K, Welsh J. Characterization of mammary tumor cell lines from wild type and vitamin D3 receptor knockout mice. Mol Cell Endocrinol. 2003;200:67-80.
21. Maund SL, Barclay WW, Hover LD, et al. Interleukin-1α mediates the antiproliferative effects of 1,25-dihydroxyvitamin D3 in prostate progenitor/stem cells. Cancer Res. 2011;71:5276-86.
22. Bao BY, Hu YC, Ting HJ, et al. Androgen signaling is required for the vitamin D-mediated growth inhibition in human prostate cancer cells. Oncogene. 2004;23:3350-60.
23. Hayes VM, Severi G, Padilla EJD, et al. Genetic Variants in the Vitamin D receptor gene and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2005;14:997-9.
24. Hendrickson WK, Richard F, Kasperzyk JL, et al. Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. J Clin Oncol. 2011;29:2378-85.

Rad je primljen 12. X 2012.
Recenziran 30. XII 2012.
Prihvaćen za štampu 14. III 2013.
BIBLID.0025-8105:(2013):LXVI:5-6:259-262.

ISTORIJA MEDICINE
HISTORY OF MEDICINE

Institute for Children and Youth Health Care of Vojvodina, Novi Sad
Department of Pediatric Surgery

Istorija medicine
History of medicine
UDK 616.5-001.17-08(091)

BURNS TREATMENT IN ANCIENT TIMES

LEČENJE OPEKOTINA U DREVNA VREMENA

Marija PEĆANAC, Zlata JANJIĆ, Aleksandar KOMARČEVIĆ, Miloš PAJIĆ, Dušanka DOBANOVAČKI and Sanja SKELEDŽIJA MIŠKOVIĆ

Summary
Discovery of fire at the dawn of prehistoric time brought not only the benefits to human beings offering the light and heat, but also misfortune due to burns; and that was the beginning of burns treatment. Egyptian doctors made medicines from plants, animal products and minerals, which they combined with magic and religious procedures. The earliest records described burns dressings with milk from mothers of male babies. Goddess Isis was called upon to help. Some remedies and procedures proved so successful that their application continued for centuries. The Edwin Smith papyrus (1500 BC) mentioned the treatment of burns with honey and grease. Ebers Papyrus (1500 BC) contains descriptions of application of mud, excrement, oil and plant extracts. They also used honey, Aloe and tannic acid to heal burns. Ancient Egyptians did not know about microorganisms but they knew that honey, moldy bread and copper salts could prevent infections from dirt in burns healing. Thyme, opium and belladona were used for pain relief. In the 4th century BC, Hippocrates recorded that Greek and Roman doctors used rendered pig fat, resin and bitumen to treat burns. Mixture of honey and bran, or lotion of wine and myrrh were used by Celsus. Honey was also known in Ayurveda (Indian medicine) time. Ayurvedic records Characa and Sushruta included honey in their dressing aids to purify sores and promote the healing. Burn treatment in Chinese medicine was traditional. It was a compilation of philosophy, knowledge and herbal medicine. The successful treatment of burns started in recent time and it has been made possible by better knowledge of the pathophysiology of thermal injuries and their consequences, medical technology advances and improved surgical techniques.
Key words: Burns + therapy; History, Ancient; History of Medicine; Honey; Ceremonial Behavior

Sažetak
Otkriće vatre u praskozorju praistorije pružilo je tadašnjem čovekolikom stvorenju koristi od svetla i toplote i istovremeno označilo početak lečenja opekotina koje su se zadesno dešavale. U Starom Egiptu doktori su pripremali lekove od biljaka, derivata životinja ili minerala ali su svi postupci bili praćeni magijskim ili nekim religioznim postupcima. Najraniji podaci o lečenju opekotina opisuju lečenje mlekom majke koja je rodila muško dete. Boginja Izis je pri tome moljena za pomoć. Neki lekovi i postupci su imali toliko zadovoljavajućih rezultata da su se koristili vekovima. U papirusu Edvina Smita (1 500 pre nove ere) spominje se lečenje opekotina medom i mašću. Ebersov papirus (datira iz istog perioda) sadrži opise o primeni blata, izlučevina, ulja i biljnih ekstrakta. Takođe se koristio med, aloja i taninska kiselina u lečenju opekotina. Stari Egipćani nisu znali za mikroorganizme ali su znali da med, plesniv hleb ili bakarni prah mogu sprečiti zagađenje opekotina. Za smanjenje bola koristili su majčinu dušicu, opijum i beladonu. U grčkoj i rimskoj medicini stavljanje zavoja natopljenog svinjskom mašću, smolama i bitumenom korišćeno je prema zapisima Hipokrata iz 4. veka pre nove ere. Mešavima meda i mekinja, kao i tečni rastvor izmira u vinu koristio je još Celzus. Med je bio poznat u ajurvedsko vreme indijske medicine. Ajurvedski zapisi Čarake i Susrute uključuju medom natopljene zavoje kao pomoć za čišćenje gnojavih rana i ubrzanje zarašćivanja. Lečenje opekotina u kineskoj medicini bilo je tradicionalističko. To je bila kompilacija filozofije, nauke i herbalne medicine. Zadovoljavajuće lečenje opekotina je počelo tek u novije vreme. Tome je doprinelo poznavanje patofoziologije povreda izazvanih toplotom i njihovih posledica, savremena medicinska tehnologija i napredak hirurške tehnike.
Ključne reči: Opekotine + terapija; Drevna istorija; Istorija medicine; Med; Obredi

Introduction

One of the turning points in the history of mankind was the discovery of fire, which resulted in many good points. However, negative effects produced by fire and high temperature left reminders of the injuries to the early men –burns. Skin injuries caused by fire, which could be of various degrees, always resulted in some complications, whether minor or major ones, or even death. The prehistoric men, who lived in nomadic tribes, were exposed to all forms of trauma. Since nobody had knowledge or

Corresponding Author: Dr Marija Pećanac, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: marion.pec@gmail.com

any ideas how to treat those injuries, some individuals began to help in such situations with prays, spells and various forms of magic, thus standing out from the crowd of the "equals" [1].

Fire caused accidental trauma in external environments (the invaders burned villages, there were spontaneous forest fires) or in dwellings (hearths in huts and houses during food preparation, or other domestic manufacturing processes). Red-hot metal was used to punish enemies by blinding them or to burn wounds inflicted by venomous animals. With the development of medicine, fire became a method of cauterization to stop bleeding and was usually applied in the limb amputations [2].

Treatment of burns started as folk medicine, however, there are no written records about it. Having gained basic knowledge about plants and their effects (vegetable oil, apples, onion, leaves of various plants), animal products (honey, milk, fat, butter, eggs) [3], minerals and various chemicals (copper, malachite, etc.), men started to use them.

Experience gained over centuries showed that treatment of burns required local application of fats and oils, special coatings, removal of decay products, anti-infection therapy, as well as rehydration and alleviation or elimination of pain [4]. All experience and knowledge about helping the injured and the sick was conveyed orally up to the time of invention of writing.

The beginning of human civilization is considered to have started in the valley of two great rivers the Tigris and the Euphrates. The witnesses of that time are the numerous clay tablets with the data on the treatment of illness and injuries found in the library of Asurbanipal in Nineveh (Assyria), preserved now in British museum in London, and deciphered [5]. The practice of the "doctors" was to perform physical examination, make a diagnosis and prognosis, and recommend remedies. Application of creams, dressings and bandages to treat injuries and burns was a part of everyday life in those times.

Egypt

According to an Ancient Egyptian legend about the origin of the world, the goddess Isis treated burns of her son Horus [6] by nursing him **(Figure 1)**. This story influenced the treatment of burns for many centuries.

Medicine in Ancient Egypt began to develop in the temples where highly educated people, who were priests – wound healers - doctors – surgeons at the same time, learned and taught the science of diseases and trauma, and where they recorded their own observations, successes or failures. From the first dynasty of kings 3000 BC, many institutions were set up to treat the sick and injured, and to study medicine. Prayers to gods and magic rituals accompanied medical treatment regularly. Long time before 2500 BC, burns were treated with milk of mothers who had male children. Treatment was

Fig. 1. Goddess Isis nursing Horus
Slika 1. *Boginja Izis doji Horusa*

accompanied by prayers to goddess Isis [7]. According to Herodotus' records, Egyptian doctors-priests often focused and specialized in certain fields of medicine and disease [8], but there are no data on physicians dedicated to burns treatment.

Invention of writing enabled the doctors of Ancient Egypt to write their observations down on papyrus scrolls, some of which are available now and having been deciphered, they revealed some of that ancient knowledge and experience [9]. The Smith papyrus, known by the name of its discoverer and owner Edwin Smith, was written around 1500 BC and it is considered to be one of the oldest records on medical treatment.

It is believed that the original data come from the period 3000 BC [10,11]. Today, the papyrus scroll is the property of the Academy of Medicine in New York, and it is exhibited in the Room of Rare Books. This 5-meter-long papyrus is mostly devoted to surgical problems and treatment; it contains descriptions of 48 injuries on the body as well as recommendations on the treatment of burns by packs of honey [12].

Fig. 2. Egyptian medical text: Georg Ebers papyrus
Slika 2. *Egipatski medicinski tekst: Ebersov papirus*

Another papyrus, known as Ebers papyrus after its first owner George Ebers, belongs now to the University Library in Leipzig. It contains many guidelines for surgical intervention [13,14] **(Figure 2)**. One of the tips is "... if the wound is bleeding (from blood vessel) it must be burnt with fire." It was treated with a knife heated in the fire. Cauterization as a method of stopping bleeding and wound treating has remained for next 4000 years up to the present [2].

Burns and scalds were very frequent in households during food preparation. The Ebers papyrus contains an important section (paragraph 482-509) with the title "Beginning of the remedies for a burn" (paragraphs 482-509). It begins with suggestions for a series of different remedies to be applied as follows:

– day 1 – black mud (perhaps to cool the burn for a short time and relieve the pain)
– day 2 – excrement of small cattle (sheep, etc) (not logical because the excrement increases the risk of serious infection)
– day 3 – resin of acacia, barley dough, carob (it is a beanlike Mediterranean plant), oil (for its soothing effect)
– day 4 – wax, oil, cooked unwritten papyrus
– day 5 – carob, red ochre, part of ima (today unknown name) tree, copper flakes (clean the burns)

This recipe, if translation from hieroglyphics is correct, seems completely illogical nowadays. Besides, there are no recorded results of this treatment.

Cooling of burned areas is described in paragraph 484 of papyrus, but it is not stated whether this refers to the initial or subsequent cooling medicated dressings. There are also records of recipes, but without specific sequence of ingredients by days of application, such as:

– honey was used in several recipes to reduce swelling and because of its antibacterial effect
– paragraph 491 mentions the application of copper flakes and malachite (antibacterial effect !)
– oil was an integral part of most recipes
– some recipes contained some plants not recognized for their positive effect on burns treatment or animal excreta (skepticism of today may not be entirely justified),
– in the last paragraph (509) it is written: "Mix barley bread, oil/grease and salt into one and apply this mixture until the patient feels well. This works - I have often seen it happen."

The Ebers parpyrus also contains two magical rituals that had to accompany the treatment prescribed [15].

Paragraph 491 of the Ebers papyrus suggested malachite powder to be used for dressing in soiled and infected burns [16]. Later, copper carbonate and hydroxide as the main ingredients of malachite, proved as inhibitor of proliferation of Staphylococcus aureus and Pseudomonas aeruginosa [17].

The papyrus Hearst (Hearst Medical Papyrus) is a collection of medical prescriptions, which is owned by Hearst Museum of the University Library in California. According to the Hearst prescriptions 34 and 90, 95 and 249, translated by Walter Wreszinskom in 1912, tannic acid, obtained from the seeds and fruits of Acacia herb, was used to treat burns [18-20].

Although they did not know anything about microorganisms that caused infection, the Egyptians used antiseptics in the treatment of wounds and burns to prevent complications. Dressing of willow leaf wraps reduced the possibility of infection, as well as honey, moldy bread, and wraps with garlic [7,21]. Solutions of copper salts and wine were used for antisepsis. According to the papyrus Ipsinger [22], cedar oil was used as an antiseptic.

Patients with burns were in a lot of pain and upset, and since Egyptian doctors knew about analgesic and sedative agents, they gave the patients drugs with opium and belladonna. If a person was injured and bleeding heavily, red-hot metal was applied to the burn to stop bleeding [21].

Honey was used for wound dressing as a natural antibiotic [23,24] and it proved to be effective in the treatment of burns. Today we know that honey reduces swelling by its osmotic effect, and the bacteria do not grow in honey [23]. Aloe Vera was also used for the treatment of burns [23].

Greece

In Greece, the practice of medicine, as a treatment of diseases and injuries by trained people, began about 1000 BC. Asclepius was mentioned in the 8th century BC as the first recorded doctor who was both adored and deified. He and his son Machaon were mentioned in the Iliad poem as doctors and

wound healers. Later, many temples were built in the name of god Asclepius throughout Greece and they were actually organized sanatoriums. In the epic poem the Iliad, which is said to have been written by Homer, the injured soldiers were trained by a doctor in military camps to help themselves and to offer the first aid to the others [2]. The Greek doctors were taught medicine at medical schools organized within healing temples of Asclepius at Epidaurus, Pergamum, Kos, Knidos and elsewhere. In the 4th century BC, a medical school, which was in the range of university, was established in Alexandria, and henceforward, medical knowledge and experience was transferred from Egyptian doctors to Greek doctors,

The most famous Greek doctor is Hippocrates from the island of Kos (the period 460-360 BC). According to his writings, burns were treated by dressings impregnated with pork fat, resin and bitumen [25]. Local therapy of burns by applying slices of lemon (citric acid as an antiseptic), various oil formulations and blends of tea leaves (tannic acid as an antiseptic) was in practice in the time of Hippocrates around 430 BC. Grease or pig's fat were often used in the preparation of drugs [26].

Roman times

The Romans studied medicine mainly from conquered people: Egyptians, Etruscans, Persians, and mostly, from Greeks. Before the arrival of doctors from Greece, medicine in Rome was empirical and magical, and then medicine became more and more scientific. Since many wars were waged in that time, military hospitals were places where all injuries, particularly war wounds, were treated.

In the ancient Rome, burns were treated by the mixture of honey and bran as recommended by Aulus Cornelius Celsus [25] as well as by wine and lotion from Izmir [19]. Galen (129-199 AD) is said to have introduced cold water in burns treatment although there is no written evidence in his papers [19].

Medicine in Rome was responsible for establishing and organization of medical schools, public and military hospitals, and systems for clean water supply [21].

India, China and the East Asian Countries

Ayurveda, a part of Vedic system in medicine that promotes health as harmony of body, soul and spirit, appeared in India around 3000 BC. Some written documents described the beneficial effect of honey known in East Asian countries for centuries. Ayurveda (sometimes translated as a science of life) is the ancient Indian medicine. Ayurvedic documents describe honey as the nectar of life and recommend it to be used in a variety of diseases **(Figure 3)**. Charaka and Sushruta, preachers of Ayurvedic Science, used honey to dress wounds and burns [12,27].

The records of Traditional Chinese Medicine, which was based mostly on empirical observation, give two recipes for the local treatment of burns known in the ancient times: one suggested dressings with a mixture of vegetable oils, and the other one contained mature forms of sponges from the family calcarea Sulphurica or lard boiled with willow bark. Bandages impregnated with this mixture reduced the possibility of infection of wounds successfully [28].

Fig. 3. Indian medical text: a manuscript of the Atharva veda
Slika 3. *Ajurvedski medicinski zapis: rukopis iz Atarva vede*

Ancient civilizations of the American continent

For centuries, extensive burns were bandaged or left untreated so that the organism itself had to fight with deformed scars and such burns often resulted in death. There are only scarce data on the application of red-hot metals, usually knives, to stop bleeding after amputations or other surgical interventions. People of the central and southern American continent knew about the analgesic and anesthetic effects of the plant Coco, but there are no surviving records that it was applied for that purpose [29].

Conclusion

The overall knowledge of burns originating from old medicine of the Babylonians, Etruscans, Egyptians, Greeks, Romans and other peoples of Asia, Africa and America was rather modest but applicable. The new history has brought additional forms of burns that appeared in the medieval wars (hot oil containers were used in the defense of occupied towns) and damage from electrical current (modern era and electrocution). Successful treatment of burns started in recent time. Until the 1940s, a patient with burn covering over one third of the body would probably have died. Nowadays, modern centers are equipped to treat burns covering 65% of the body. Advances in bacteriology and pharmacology, surgery and intensive care have enabled successful treatment of severe and deep burns. A significant reduction in mortality and consequences of burns are the positive achievements of modern medicine and related sciences.

References

1. Dobanovački D, Milovanović LJ, Slavković A, Tatić M, Skeledžija Mišković S, Škorić Jokić S, et al. Surgery before common era (B.C.E.). Arch Oncol 2012;20(1-2):26-33.

2. Ignjatović M. Istorijski pregled razvoja ratne hirurgije: 1. deo. Vojnosanit Pregl 2006;63(6):619-24.

3. Ahmed AKJ, Hoekstra MJ, Hage JJ, Karim RB. Honey-medicated dressing: transformation of an ancient remedy into modern therapy. Ann Plast Surg 2003;50(2):143-8.

4. Lewis SRMD. The treatments of burns. J Trauma Injury Infect Crit Care 1965;5(2):307-8.

5. Scurlock JA, Anderson BR. Diagnoses in Assyrian and Babylonian medicine: ancient sources, translation. Illinois: University of Illinois Press; 2005.

6. The way to eternity: Egyptian myth. Ed. Time Life Books. London: Duncan Baird Publ; 1997.

7. Davies G. The illustrated timeline of medicine. New York: The Rosen Publishing Group; 2012.

8. Herodotus histories 2,84. In: Osler W. The evolution of modern medicine: a serues of lectures delivered at Yale University on the Silliman foundatiuon 1913. Digital Collection .New York: Cornel Universitiy Library; 2010.

9. Čolović R. Kratka istorija hirurgije. U: Čolović RB. Hronika hirurgije Srbije. Beograd: Prosveta; 2002. str. 26-49.

10. Dunn Jimmy Edwin Smith Papyrus. 1996. Available from: http://www.touregypt. net/edwinsmithsurgical.htm

11. Breasted JH. The Edwin Smith surgical papyrus: facsimile plates and line for line hieroglyphic transliteration. two volumes. University of Chicago Oriental Institute publications. v.3-4. Chicago: University of Chicago Press; 1991. and Oxford: Oxford The University Press; 2010.

12. Subrahmanyam M. Honey dressing for burns: an appraisal. Ann Burns Fire Disast 1996;9:1.

13. Bryan PW. The papyrus ebers. London: Geoffrey Bles; 1930.

14. Ebbell B, tr. The papyrus ebers: the greatest Egyptian medical document. Copenhagen: Levin & Munksgaard 1937.

15. Burns: surgery, trauma and dangerous animals. In: Nunn JF. Ancient Egyptian medicine. London: The British Museum Press; 2006. p. 163-90.

16. Drug therapy. In: Nunn JF. Ancient Egyptian medicine. London: The British Museum Press; 2006. p. 136-62.

17. Estes JW. The medical skills of ancient Egypt. Canton: Science History Publication; 1989.

18. Leake CD. The old Egyptian medical papyri. Lawrence Kansas: Logan Clendening Univerity of Kansas Press; 1952.

19. Majno G. The healing hand: man and wound in tne ancient world. Cambridge: Harvard University Press; 1982. p. 86-121.

20. Bergman A, Yanal J, Weiss J, Bell D, David MP. Acceleration of wound healing by topical application of honey. Am J Surg 1983;145:374-6.

21. Ancient Egypt – 3500 BC to 100 BC. In: Duchan's history of speech – language pathology. Available from: http://www.acsu.buffalo.edu/ - duchan/new_history/ancient_history/.

22. Lichtheim M. Ancient Egyptian Literature. vol III. Berkley: University of Californisa Press; 1980. p. 199.

23. Majno G. The healing hand. Harvard Univesity Press. Cambridge 1975.

24. Altman N. The honey prescription: the Amazing power of honey as Medicine. Rochester: Inner Traditions/Bear & Company; 2010. p. 60-2.

25. Artz CP. History of burns. In: Artz CP, Moncrief JA, Pruitt BA, ed. Burns: a team approach. Philadephia, PA: W.B. Saunders Comp; 1979.

26. Pinegard MD, Pinegard FC III. History of burn care: a survey of important changes in the topical treatment of thermal injuries. Burns Incl Therm Inj 1986;12(7):508-17.

27. Grover SK, Prasad CS. Use of Madhu in Ayurveda. J NIMA 1985;10:7-10.

28. Kopp J, Wang GY,Horch RE, Pallua N, Ge SD. Ancient traditional Chinese medicine in burn treatment: a historical review. Burns 2003;29(5):473-8.

29. Thorwald J. Moć i znanje drevnih liječnika. Zagreb: August Cesarec; 1991.

Rad je primljen 19. X 2012.
Recenziran 8. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:263-267.

Klinički centar Niš, Centar za radiologiju[1]
Medicinski fakultet Univerziteta u Nišu
Klinički centar Niš, Klinika za očne bolesti[2]

Istorija medicine
History of medicine
UDK 61:929]:737

MEDICINA U NOTAFILIJI – III DEO

MEDICINE IN NOTAFILIA – PART III

Rade R. BABIĆ[1] i Gordana STANKOVIĆ BABIĆ[2]

Sažetak

Uvod. Notafilija je nauka o papirnom novcu. Samo je nekoliko država u svetu izdalo papirne novčanice sa portretima poznatih naučnika koji su svom narodu i medicini doneli svetsku slavu. **Portreti naučnika na novčanicama Jugoslavije, Srbije i Crne Gore i Republike Srbije.** Nikola Tesla i Mihajlo Idvorski Pupin bili su genijalni pronalazači i naučnici našeg doba koji su dali poseban doprinos radiologiji. Nikola Tesla (1856−1943) prvi je primenio X-zrake u medicinske svrhe, time praktično postavio temelje radiologije, rendgenografije i ukazao na postojanje štetnog dejstva X-zraka na organizam čoveka. Mihajlo Idvorski Pupin (1854−1935) bio je u svetu poznat po primeni fizike u praksi, zatim osnovama telefonske i telegrafske trasmisije. Izučavao je takođe i prirodu X-zraka i dao doprinos utemeljenju radiologije. **Portreti naučnika na novčanicama iz sveta.** Marija Sklodovska Kiri (1867−1934) bila je prva žena koja je stekla akademsku titulu pariske Akademije medicine. Zajedno sa suprugom Pjerom Kirijem (1859−1906) dala je izuzetan doprinos nauci i medicini. Otkrićem radioaktivnih elemenata uveden je novi fizički pojam – radioaktivnost, a u medicinu je uvedena nova disciplina – radioterapija. Stvoreni su uslovi za nastanak nuklearne medicine, razvoj onkologije, mobilne radiološke dijagnostike. **Zaključak.** Prikazane su novčanice sa portretima Nikole Tesle, Mihajla Idvorskog Pupina, Marije Sklodovske Kiri i Pjera Kirija, naučnika svetskog glasa, koji su dali ogroman doprinos razvoju medicine i postavili temelj radiologije.

Ključne reči: Istorija medicine; Poznate ličnosti; Radiologija + istorija; X-zraci; Radioaktivnost

Summary

Introduction. Notafilia is the study of paper money. Only a few countries in the world have issued banknotes with portraits of well-known scientists who brought international fame to their own people and medicine. **Portraits of scientists on the banknotes of Yugoslavia, Serbia and Montenegro and Serbia.** Nikola Tesla and Mihailo Pupin Idvorski were the ingenious inventors and scientists of our time who made special contributions to radiology. Nikola Tesla (1856-1943) pioneered the use of X-rays for medical purposes, thus effectively laying the foundations of radiology and radiography, and revealed the existence of harmful effects of X-rays on the human body. Mihailo Pupin Idvorski (1854-1935) was worldwide famous for applying physics in practice, as well as in the basis of telephone and telegraph transmissions. He also studied the nature of X-rays and contributed to establishing of radiology. **Portraits of scientists on the banknotes of the world.** Maria Sklodowska Curie (1867-1934) was the first woman to gain the academic title of the Academy of Medicine, Paris. Together with her husband Pierre Curie (1859-1906) she gave an outstanding contribution to science and medicine. The discovery of the radioactive elements introduced the concept of ”radioactivity” into physics and ”radiotherapy” as a new discipline in medicine, thus creating the conditions for the development of nuclear medicine, oncology, and mobile diagnostic radiology. **Conclusion.** This paper presents the banknotes featuring the portraits of Nikola Tesla, Mihailo Pupin Idvorski, Maria Sklodowska Curie and Pierre Curie, the world renowned scientists, who made enormous contributions to medicine and laid the foundation for radiology.

Key words: History of Medicine; Famous Persons; Radiology + history; X-Rays; Radioactivity

Uvod

Notafilija je nauka o papirnom novcu. Na svakoj novčanici razlikuju se: lice novčanice (avers), poleđina novčanice (revers) i obojena vlakanca koja se nalaze u novčanici (vlakanca). Pored samog katološkog broja, vrednost same novčanice se meri i po njenoj očuvanosti, koja se deli u šest kategorija [1].

U prethodno objavljenim radovima [2,3] prikazali smo papirne novčanice sa likovima poznatih lekara Srbije, Jugoslavije, Austrije, Nemačke, Francuske, Švedske, Španije, Grčke i Kine. U ovom radu prikazujemo papirne novčanice sa portretima poznatih naučnika iz Srbije, Jugoslavije, Sjedinjenih Američkih Država, Poljske i Francuske, koji su takođe naučnim pronalascima doprineli razvoju savremene medicine, a svom narodu, kao i medicini; doneli svetsku slavu.

Portreti naučnika na novčanicama Jugoslavije, Republike Srbije i Crne Gore i Republike Srbije

Socijalistička Federativna Republika Jugoslavija (SFRJ) tokom 1970. godine izdala je novčanicu od 500 dinara **(Slika 1)**. Na aversu novčanice prikazan je spomenik Nikoli Tesli podignut ispred

Adresa autora: Dr sc. med. Rade R. Babić, Centar za radiologiju,
18000 Niš, Bulevar dr Zorana Đinđića 48, E-mail: gordanasb@open.telekom.rs

Slika 1. Novčanica Narodne banke Jugoslavije od 500 dinara, sivozelene boje, sa slikom spomenika Nikoli Tesli, rad Franje Kršnića; u pozadini je spirala Teslinog transformatora.

Fig. 1. *A 500 dinar banknote issued by the National Bank of Yugoslavia, it is grey-green, with the statue of Nikola Tesla by Frano Kršinić and the spiral coil of his transformer in the background*

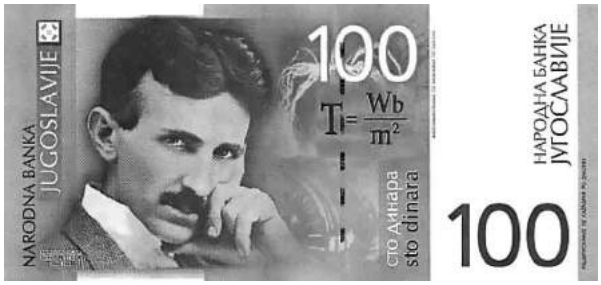
zgrade Elektrotehničkog fakulteta u Beogradu (1963), a čija se kopija nalazi i na obalama slapova Nijagarinih vodopada u Sjedinjenim Američkim Državama (SAD), rad vajara Frana Kršinića (1956).

Sa raspadom SFRJ, Narodna banka Jugoslavije štampala je novčanice sa likom Nikole Tesle u apoenima od 1 000 din (1991. i 1992. godine), 5 000 000 din. (1993), 10 000 000 000 din. (1993), 500 din (1993) i 100 din (1994. godine) **(Slika 2)**, nastale kao produkt hiperinflacije koja je tada harala našom zemljom. Da bi se obuzdala inflacija, Narodna banka Jugoslavije uvodi 1994. godine novi dinar. Na tržištu novca, tadašnji jedan novi dinar, ima vrednost jedne nemačke marke. U promet se pušta papirna novčanica od 5 novih dinara sa portretom Nikole Tesle **(Slika 2)**.

Sa raspadom Savezne Republike Jugoslavije (SRJ) i nastankom Republike Srbije i Crne Gore, još uvek aktivna Narodna banka Jugoslavije pušta u promet novčanicu u vrednosti od 100 dinara **(Slika 3)**, vizantijsko plave boje. Na aversu je lik Nikole Tesle i definicija jedinice Tesla (T): $T = Wb/m^2$. Na reversu je lik Nikole Tesle sa sijalicom u ruci, beli

Slika 2. Novčanica Narodne banke Jugoslavije od 5 novih dinara, crvene boje, sa portretom Nikole Tesle, puštena je u promet 24. januara 1994. godine

Fig. 2. *A 5 new dinar banknote issued by the National Bank of Yugoslavia on 24th of January 1994; it is red, with the portrait of Nikola Tesla*



Slika 3. Novčanica Narodne banke Jugoslavije od 100 dinara, plave boje, sa portretom Nikole Tesle, definicija jedinice magnetske indukcije tesla i asinhroni motor, puštena u promet 2000. godine

Fig. 3. *A 100 dinar banknote issued by the National Bank of Yugoslavia in 2000, it is red, with the portrait of Nikola Tesla and the definition of tesla, a unit of magnetic flux density and a detail from the Tesla's ac motor*

golub i nacrt sistema za proizvodnju naizmenične struje opisan u patentu US390721.

Sa raspadom Republike Srbije i Crne Gore, novčanica sa likom Nikole Tesle ostaje u platnom prometu sada Narodne banke Srbije.

Nikola Tesla (10. jul 1856, Smiljan – 7. januar 1943, Njujork), genijalni pronalazač i naučnik našeg doba, postavio je temelje nove grane medicine – radiologije [4–9]. Malo je poznato da je Nikola Tesla radio na ogledima kojima je nastojao da objasni prirodu rendgenskih zraka. Svi Teslini radovi o X-zracima bili su eksperimentalni.

Tesla je 1892. godine kod svoje sijalice za molekularno bombardovanje, registrovao „vidljivu svetlost, crnu svetlost i neko naročito zračenje". Prirodu „naročitog zračenja" Tesla nije objasnio sve do otkrića X-zraka profesora Vilhema Konrada Rendgena (Wilhelm Conrad Röntgen). Po svom običaju, Tesla je proverio eksperiment prof. Rendgena i dobio je iste rezultate, što je značilo da njegovi zraci i X-zraci imaju vrlo slične osobine, iako su dobijeni na malo drugačiji način. O svom istraživanju prirode X-zraka, Tesla je rekao sledeće: „Da kažem prvo, prvi put sam se oglasio s rizikom, posle izvesnog oklevanja i odlaganja i to tek kada sam stekao ubeđenje da je informacija koju treba da saopštim potrebna; jer, što je isto i kod drugih, nisam bio sasvim u stanju da se oslobodim i svesnog osećanja koje čovek mora da ima kada prelazi na teren koji nije njegov. "...No, ova Rendgenova otkrića, po rangu tačno jednaka teleskopu i mikroskopu, njegovo gledanje kroz neprozirnu materiju velike debljine, njegovo snimanje na osetljivu ploču predmeta koji su inače nevidljivi, bila su tako lepa, i očaravajuća, toliko puna obećanja da je prestalo svako uzdržavanje i svi su se bacili na zadovoljstva razmišljanja i eksperimentisanja. Kada bi svaka nova i vredna ideja nailazila na takav odjek!...".

Po obnovljenim eksperimentima Tesla je poslao prof. Rendgenu slike senki koje je dobio pomoću

„naročitog zračenja". Rendgen je sa oduševljenjem odgovorio: „Slike su vrlo interesantne. Ako biste hteli da budete tako ljubazni i da mi otkrijete način na koji ste ih dobili".

Prednosti Nikole Tesle u izučavanju prirode X-zraka su u tome što je on za rad svoje cevi koristio naizmeničnu struju. U to vreme samo je Tesla radio na proizvodnji X-zraka u cevi sa naizmeničnom strujom, dok su ostali radili sa jednosmernom strujom. Očigledno je to mogao samo Nikola Tesla.

Prof. Rendgen objavio je rad o X-zracima 28. decembra 1895. godine u Biltenu Akademije u Berlinu, a već 11. marta 1896, Nikola Tesla objavljuje svoj prvi rad o X-zracima, a do 11. avgusta 1897. godine, ukupno je objavio deset radova iz ove oblasti:

– O rendgenskim zracima, *Electrical Review*, 11. mart 1896.;
– O rendgenskim zracima, *Electrical Review,* 18. mart 1896.;
– O odbijenim rendgenskim zracima, *Electrical Review*, 1. april 1896.;
– O rendgenskim zračenjima, *Electrical Review*, 8. april 1896.;
– Istraživanja rendgenskih zraka, *Electrical Review,* 22. april 1896. g.;
– Jedno interesantno svojstvo zračenja X-zraka, *Electrical Review,* 8. juli 1896. g.;
– Rendgenski zraci ili mlazevi, *Electrical Review,* 12. avgust 1896.;
– O rendgenskim mlazevima, *Electrical Review*, 1. decembar 1896.;
– O štetnim dejstvima Lenardove i Rendgenove cevi, *Electrical Review*, 5. maj 1897.;
– O izvoru rendgenskih zraka i praktičnoj gradnji i bezbednom radu Lenardovih cevi, *Electrical Review*, 11. avgust 1897. godine.

O primeni X-zraka, Nikola Tesla je zapisao: „Sada je nesumljivo pokazano da se u ma kom delu tela mogu nepogrešivo otkriti mali metalni predmeti ili koštane ili krečne senke".

O vrednosti i lepoti rendgenograma, Nikola Tesla je zapisao: „Jasne senke kostiju ljudskih udova dobijene su ekspozicijom između četvrtine časa i jednog časa, a neki od snimaka pokazuju toliku količinu pojedinosti da je gotovo nemoguće poverovati da su posredi samo senke. Na primer, načinjen je snimak jedne noge sa cipelom, pa se vidi svaki nabor na koži, pantalonama, čarapi itd., dok se mišići i kosti oštro ističu."

Nikola Tesla je prvi ukazao na štetno dejstvo X-zraka na organizam čoveka, zapisavši: „No, istovremeno se ne može poreći da se jednako ne preporučuje i ignorisanje opasnosti, sada kada znamo da one, pod izvesnim okolnostima, stvarno postoje. Smatram da je sve potrebnije biti svestan tih opasnosti, pošto predviđam da će u opštu upotrebu ući novi aparati, sposobni da razviju zračenja nepredvidivo veće snage. U naučnim laboratorijama su instrumenti obično u rukama lica koja su obučena za manipulisanje njima, sposobna da približno procene veličinu dejstva, pa se pri sadašnjem

Slika 4. Novčanica Narodne banke Jugoslavije od 50 000 000 dinara, crvene boje, sa portretom Mihajla Idvorskog Pupina, u prometu od 1993. godine
Fig. 4. *A 50,000,000 dinar banknote issued by the National Bank of Yugoslavia in 1993; it is red, with the portrait of Mihajlo Idvorski Pupin*

stanju našeg znanja ne treba toliko plašiti, ako nema potrebnih mera predostrožnosti".

U proleće 1897. godine, Nikola Tesla se misteriozno razboleo, bolovao više nedelja i izjavio da su mu X-zraci prouzrokovali šok za oči i da se od njih razboleo.

Tesla je brižljivo beležio vidljive efekte štetnog dejstva X-zraka na ljudsko telo: „Prilikom izlaganja glave jakom zračenju zapaženi su neobični efekti. Na primer, našao sam da se javlja sanjivost i izgleda kao da vreme brzo prolazi. Postoji opšti efekat smirenja, a ja sam imao osećaj toplote u gornjem delu glave." Osećaj sanjivosti koji je registrovao Tesla, radiolozi zovu „radiološki mamurluk".

Radi zaštite od štetnog dejstva X-zraka, Nikola Tesla uvodi u primenu rendgenski paravan u vidu aluminijumskih ploča i ukazuje na vrednost kvadratnog zakona (sa kvadratom rastojanja, efekat jonizujućeg zraćenja se četvorostruko smanjuje).

Nikola Tesla je prvi primenio X-zrake u medicinske svrhe i time praktično, postavio temelje radiologije, rendgenografije i ukazao na postojanje štetnog dejstva X-zraka na organizam čoveka.

Na novčanici Savezne Republike Jugoslavije iz 1993. godine od 50 000 000 dinara nalazi se portret Mihajla Idvorskog Pupina **(Slika 4)**.

Mihajlo Idvorski Pupin (9. oktobar 1954, Idvor – 12. mart 1935, Njujork) u svetu je poznat po primeni fizike u praksi, osnovama telefonske i telegrafske transmisije, ali se malo zna da je radio na izučavanju prirode X-zraka i doprineo utemeljenju radiologije [9-13].

Naime, februara 1896. godine, odmah posle otkrića X-zraka, Mihajlo Idvorski Pupin započeo je svoj istraživački rad na X- zracima, X-fluoroskopiji i skraćenju ekspozicije. U sklopu ovih istraživanja, Pupin je otkrio sekundarne X-zrake, nazvavši ih „h-zracima" o čemu je 6. aprila 1896. godine obavestio Akademiju nauka SAD. Otkriveni sekunarni zraci, našli su veliku primenu u medicini i atomskoj fizici.

U autobiografskom delu „Sa pašnjaka do naučnjaka" (*From immigrant to inventor*) iz 1823. godine, Pupin iznosi detalje o svom doprinosu razvoju radiologije u poglavlju „Moj pronalazak br-

Slika 5. Novčanica Poljske od 20 000 zlota sa portretom Marije Sklodovske Kiri.
Fig. 5. *A 20,000 Polish zloty banknote with the portrait of Maria Sklodowska Curie*

zog snimanja pomoću X-zraka". Pupin je za ovo autobiografsko delo 1924. godine dobio Pulicerovu nagradu. Ovo Pupinovo delo dugo godina je bilo obavezna lektira u američkim školama.

Folije koje se danas koriste pri rendgenografiranju, emituju svetlost određene talasne dužine, tj. svetlost određene boje, na koju je rendgenski film osetljiv. Ovim se postiže prenos latentne rendgenske slike u vidljivu svetlost tj. u svetlosnu sliku, dalje na rendgenski film, čime ona postaje vidljiva. Do ovog otkrića, Pupin je došao tako što je postavio fotografsku ploču iza fluorescentnog zastora, čime je smanjio vreme ekspozicije sa jednog sata na nekoliko sekundi. Svoje otkriće, Mihajlo Idvorski Pupin je nazvao „pronalazak brzog snimanja pomoću X-zraka". Iako je do pronalaska „brzog snimanja pomoću X-zraka" Pupin došao 40 dana nakon što je prof. Rendgen otkrio X-zrake, nažalost ovo otkriće Pupin nije patentirao.

Pomoću „pronalazaka brzog snimanja pomoću X-zraka" 7. februara 1896. godine Mihajlo Idvorski Pupin je načinio rendgenogram šake kod bolesnika kojeg mu je poslao dr Bul kod kojeg je vizualizovao dramlije u šaci kao okrugle, oštro delinirane senke, intenziteta metala. To je ujedno i datum kada je u SAD učinjena prva hirurška intervencija uz pomoć rendgenskog snimka. Zato se Mihajlo Idvorski Pupin smatra ocem američke radiologije.

Mihajlo Idvorski Pupin dobitnik je mnogobrojnih naučnih nagrada i medalja. Bio je član Američke akademije nauka, Srpske kraljevske akademije i počasni doktor 18 univerziteta. Bio je i počasni konzul Srbije u SAD, osnivač i dugogodišnji predsednik Srpskog narodnog saveza u Americi. Nosilac je jugoslovenskog odlikovanja Beli orao prvog reda. Uticao je na konačne odluke Pariske mirovne konferencije kada se odlučivalo o određivanju granica buduće Kraljevine Srba, Hrvata i Slovenaca. Tada, u vrlo teškoj situaciji na pregovorima o Jugoslaviji, Pupin je lično uputio Memorandum (19. mart 1919.) predsedniku SAD, Vudrou Vilsonu, koji je na osnovu podataka dobijenih od Mihajla Pupina o istorijskim i etničkim karakteristikama graničnih područja Dalmacije, Slovenije, Istre, Banata, Međumurja, Baranje i Makedonije, nakon tri dana dao izjavu o nepriznavanju Londonskog ugovora potpisanog između saveznika sa Italijom.

Portreti naučnika na novčanicama iz sveta

Zlota (poljski – *zloty*; simbol - Zł) novčana je jedinica Poljske, koja je u upotrebi od 1924. godine. Na novčanici od 20 000 zlota, koja je bila u upotrebi od 1989. do 1. januara 1996. nalazi se portret Marije Sklodovske Kiri **(Slika 5)**.

Marija Sklodovska Kiri (francuski – *Marie Sklodowska Curie*; 7. novembar 1867, Varšava, Poljska – 4. jun 1934, Passy, Francuska) sa suprugom Pjerom Kiri otkrila je radioaktivne elemente – polonijum ($_{84}Po^{210}$), torijum ($_{90}Th^{232}$) i radijum ($_{88}Ra^{226}$) [14-17].

Marija Sklodovska Kiri je prva žena u Francuskoj koja je postala doktor nauka, profesor na Sorboni, član Medicinske akademije Francuske, a u istoriji Nobelove nagrade, prva osoba koja je bila dva puta nagrađena i jedina žena koja je Nobelovu nagradu dobila dva puta – Nobelova nagrada za fiziku (1903) i Nobelova nagrada za hemiju (1911).

Za vreme I svetskog rata, Marija Sklodovska Kiri je pokazala i u praksi primenila, da se u automobil instalira rendgen-aparat i da se dinamo koji pokreće automobil, iskoristi i za rad rendgen-aparata. Pod njenim rukovodstvom nastaju pokretna „radiološka kola". Za potrebe francuske vojske, za vreme I svetskog rata, opremila je ovakvih 20 kola i obučila 150 ljudi da na njima radi.

Marija Sklodovska Kiri je sa otkrićem radioaktivnih elemenata, u medicinu uvela novu medicinsku disciplinu – radioterapiju, omogućila nastanak nuklearne medicine i razvoj onkologije, a radiološkim kolima, medicini, tj. radiologiji, dala nešto sasvim novo – mobilnu radiološku dijagnostiku.

Francuski franak (Franc Français; simboli – F, FF, FRF i ₣) nekadašnja je valuta Francuske koja je 2002. godine povučen iz upotrebe i zamenjena novčanicama i kovanicama evra. Na novčanici od 500 francuskih franaka nalaze se portreti supružnika Marije i Pjera Kiri **(Slika 6)**.

Slika 6. Novčanica Francuske od 500 franaka sa portretima supružnika Marije i Pjera Kiri
Fig. 6. *A 500 French franc banknote with the portraits of the Curie spouses, Maria and Pierre*

Pjer Kiri (Pierre Curie; 15. maj 1859, Pariz – 19. april 1906, Pariz), francuski je fizičar i hemičar. Sa bratom Žakom i suprugom Marijom dao je doprinos nastanaku i razvoju novih grana medicine – radiologije, nuklearne medicine, onkologije [14–18]. Pjer i Žak Kiri otkrili su piozoelektricitet (1880) koji čini osnovu današnje ultrasonografske dijagnostike, dok su Pjer i Marija otkrili radioaktivne elemente polonijum ($_{84}Po^{210}$) i radijum ($_{88}Ra^{226}$) i uveli novi fizički pojam – radioaktivnost. Pjer Kiri, Marija Sklodovska Kiri i Antoan Anri Bekerel (Antoine Henri Becquerel) su 1903. godine dobili Nobelovu nagradu za fiziku.

Pjer Kiri je 19. aprila 1906. stradao u saobraćajnoj nesreći.

Zaključak

Prikazani su porteti Nikole Tesle, Mihajla Idvorskog Pupina, Marije Skolodovske Kiri i Pjera Kirija koji su našli mesto na papirnim novčanicama Jugoslavije, Srbije, Francuske i Poljske. Svojim znanjem i radom dali su doprinos razvoju savremene medicine u svetu, svom narodu i medicini doneli svetsku slavu i postavili temelje nove grane medicine – radiologije.

Literatura

1. Stojanović Ž. Nacionalni katalog novčanica Srbije i Jugoslavije. Beograd: Sanimex; 2007.

2. Babić R, Stanković Babić G. Notafilija u medicini. Med Pregl 2010;63(3-4):289-92.

3. Babić R, Stanković Babić G. Notafilija u medicini II deo. Med Pregl 2012;65(7-8):347-50.

4. Babić RR. Tesla o X zracima. Vojnosanit Pregl 2006; 63(11):979-82.

5. Milenković A. Tesla: an inventor for the third millennium. Belgrade: Beoknjiga; 2002.

6. Babić RR. Nikola Tesla and x-ray. Acta Med Median 2004;1:81-2.

7. Babić RR. Nikola Tesla and the fundamentals of radiology. Acta Med Median 2005;44(1):85-7.

8. Babić RR. Nikola Tesla about X-rays. Acta Med Median 2005;44(2):91-2.

9. Babić RR. Nikola Tesla about the adverse affects of X-rays. Acta Med Median 2005;44(3):67-9.

10. Babić RR. Povodom 155. godina od rođenja Mihajla Idvorskiog Pupina. Vojnosanit Pregl 2009;66(5):407-10.

11. Babić RR, Mihajlo Idvorski Pupin otac američke radiologije. Acta Med Median 2005;4:89-91.

12. Shampo AM, Kyle AR. Michael Idvorsky Pupin. JAMA 1981;248(22):2572.

13. Davis B. Biographical memoir of Michael Idvorsky Pupin 1858-1935. Washington: National Academy of Sciences of the USA; 1938.

14. Babić RR. Sedamdeset godina od smtri Marije Sklodovske Kiri. Acta Med Median 2044;43(3):85-6.

15. Babić RR, Stanković Babić G. Marija Sklodovska Kiri (1867-1934): dopinos razvoju ratne radiologije. Acta Med Median 2010;49(1):70-72.

16. Babić RR, Stanković Babić G. Marija Sklodovska Kiri (1867-1934): dopinos razvoju radiologije. Med Pregl 2011;64 (3-4):229-33.

17. Babić RR, Milošević Z, Stanković Babić G: Teleradiology at distance. Acta Fac Med Naiss 2012;29(3):145-51.

18. Dimić G, Ilić D, Tomić J. Fizika. Beograd: Zavod za udžbenike i nastavna sredstva; 1995.

Rad je primljen 29. X 2012.
Recenziran 8. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:5-6:268-272.

Štampu ovog časopisa ”Medicinski pregled”
pomogla je **Vlada AP Vojvodine**

Printing of this journal ”Medical Review”
has been supported by
the Government of the AP of Vojvodina

UPUTSTVO AUTORIMA

Časopis objavljuje sledeće kategorije radova:

1. Uvodnici (editorijali) – do 5 stranica. Sadrže mišljenje ili diskusiju o nekoj temi važnoj za Časopis. Uobičajeno ih piše jedan autor *po pozivu*.

2. Originalni naučni radovi – do 12 stranica. Sadrže rezultate sopstvenih originalnih naučnih istraživanja i njihova tumačenja. Originalni naučni radovi treba da sadrže podatke koji omogućavaju proveru dobijenih rezultata i reprodukovanje istraživačkog postupka.

3. Pregledni članci – do 10 strana. Predstavljaju sažet, celovit i kritički pregled nekog problema na osnovu već publikovanog materijala koji se analizira i raspravlja, ilustrujući trenutno stanje u jednoj oblasti istraživanja. Radovi ovog tipa biće prihvaćeni samo ukoliko autori navođenjem najmanje *5 autocitata* potvrde da su eksperti u oblasti o kojoj pišu.

4. Prethodna saopštenja – do 4 stranice. Sadrže naučne rezultate čiji karakter zahteva hitno objavljivanje, ali ne mora da omogući i ponavljanje iznetih rezultata. Donosi nove naučne podatke bez detaljnijeg obrazlaganja metodologije i rezultata. Sadrži sve delove originalnog naučnog rada u skraćenom obliku.

5. Stručni članci – do 10 stranica. Odnose se na proveru ili reprodukciju poznatih istraživanja i predstavljaju koristan materijal u širenju znanja i prilagođavanja izvornih istraživanja potrebama nauke i prakse.

6. Prikazi slučajeva – do 6 stranica. Obrađuju *retku* kazuistiku iz prakse, važnu lekarima koji vode neposrednu brigu o bolesnicima i imaju karakter stručnih radova. Prikazi slučajeva ističu neuobičajene karakteristike i tok neke bolesti, neočekivane reakcije na terapiju, primenu novih dijagnostičkih postupaka ili opisuju retko ili novo oboljenje.

7. Istorija medicine – do 10 stranica. Pišu se na poziv uredništva Medicinskog pregleda i obrađuju podatke iz prošlosti sa ciljem održavanja kontinuiteta medicinske i zdravstvene kulture, a imaju karakter stručnih radova.

8. Druge vrste publikacija (feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih ustanova, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novine u medicini, pitanja i odgovori, stručne i staleške vesti i *In memoriam*).

Priprema rukopisa

Propratno pismo

– Mora da sadrži svedočanstvo autora da rad predstavlja originalno delo, kao i da nije objavljivan u drugim časopisima, niti se razmatra za objavljivanje u drugim časopisima.

– Potvrditi da svi autori ispunjavaju kriterijume za autorstvo nad radom, da su potpuno saglasni sa tekstom rada, kao i da ne postoji sukob interesa.

– Navesti u koju kategoriju spada rad koji se šalje (originalni naučni rad, pregledni članak, prethodno saopštenje, stručni članak, prikaz slučaja, istorija medicine).

Rukopis

Za pisanje teksta koristiti *Microsoft Word for Windows*. Tekst treba otkucati koristeći font *Times New Roman*, na stranici formata A4, proredom od 1,5 (i u tabelama), sa marginama od 2,5 cm i veličinom slova od 12 pt. Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana. Naslovna strana treba da sadrži kratak i jasan naslov rada, bez skraćenica, zatim kratki naslov (do 40 karaktera), puna imena i prezimena autora (najviše 6 autora) indeksirana brojkama koje odgovaraju onima kojim se u zaglavlju navode uz pun naziv i mesta ustanova u kojima autori rade. Na dnu ove stranice navesti titulu, punu adresu, e-mail i broj telefona ili faksa autora zaduženog za korespondenciju.

2. Sažetak. Sažetak treba da sadrži do 250 reči, bez skraćenica, sa preciznim prikazom problematike, ciljeva, metodologije, glavnih rezultata i zaključaka. Sažetak treba da ima sledeću strukturu:

– originalni naučni radovi: uvod (sa ciljem rada), materijal i metode, rezultati i zaključak;

– prikaz slučaja: uvod, prikaz slučaja i zaključak;

– pregled rada: uvod, odgovarajući podnaslovi koji odgovaraju onima u tekstu rada i zaključak.

U nastavku navesti do deset ključnih reči iz spiska medicinskih predmetnih naziva (*Medical Subjects Headings, MeSH*) Američke nacionalne medicinske biblioteke.

3. Sažetak na engleskom jeziku. Sažetak na engleskom jeziku treba da bude prevod sažetka na srpskom jeziku, da ima istu strukturu i da sadrži do 250 reči, bez upotrebe skraćenica.

4. Tekst rada

– Tekst originalnih članaka mora da sadrži sledeće celine:

Uvod (sa jasno definisanim ciljem rada), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su korišćene u tekstu) i eventualna zahvalnost autora onima koji su pomogli u istraživanju i izradi rada.

– Tekst prikaza slučaja treba da sadrži sledeće celine: Uvod (sa jasno definisanim ciljem rada), Prikaz slučaja, Diskusija i Zaključak.

– Tekst treba da bude napisan u duhu srpskog jezika, oslobođen suvišnih skraćenica, čija prva upotreba zahteva navođenje punog naziva. Skraćenice ne upotrebljavati u naslovu, sažetku i zaključku. Koristiti samo opšte prihvaćene skraćenice (npr. DNA, MRI, NMR, HIV,...). Spisak skraćenice koje se navode u radu, zajedno sa objašnjenjem njihovog značenja, dostaviti na poslednjoj stranici rukopisa.

– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http:// www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

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

∗ *Organizacija kao autor*

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

∗ *Nisu navedena imena autora*

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

∗ *Volumen sa suplementom*

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

∗ *Sveska sa suplementom*

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

∗ *Sažetak u Časopisu*

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

Knjige i druge monografije:

∗ *Jedan ili više autora*

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

∗ *Urednik(ci) kao autor*

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

∗ *Poglavlje u knjizi*

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

∗ *Rad u zborniku radova*

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.

∗ *Disertacije i teze*

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

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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

∗ *Monografije u elektronskoj formi*

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

∗ *Kompjuterski dokument (file)*

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

6. Prilozi (tabele, grafikoni, sheme i fotografije).

Dozvoljeno je najviše šest priloga!

– Tabele, grafikoni, sheme i fotografije dostavljaju se na kraju teksta rukopisa, kao posebni dokumenti na posebnim stranicama.

– Tabele i grafikone pripremiti u formatu koji je kompatibilan sa programom *Microsoft Word for Windows.*

– Slike pripremiti u JPG, GIF TIFF, EPS i sl. formatu

– Svaki prilog numerisati arapskim brojevima, prema redosledu njihovog pojavljivanja u tekstu.

– Naslov, tekst u tabelama, grafikonima, shemama i legendama navesti na srpskom i na engleskom jeziku.

– Objasniti sve nestandardne skraćenice u fusnotama koristeći sledeće simbole: *, †, ‡, §, | |, ¶, **, ††, ‡ ‡.

– U legendama mikrofotografija navesti korišćenu vrstu bojenja i uvećanje na mikroskopu. Mikrofotografije treba da sadrže merne skale.

– Ukoliko se koriste tabele, grafikoni, sheme ili fotografije koji su ranije već objavljeni, u naslovu navesti izvor i poslati potpisanu izjavu autora o saglasnosti za objavljivanje.

– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

7. Slanje rukopisa

Prijem rukopisa vrši se u elektronskoj formi na stranici: **aseestant.ceon.rs/index.php/medpreg/**. Da biste prijavili rad morate se prethodno registrovati. Ako ste već registrovani korisnik, možete odmah da se prijavite i započnete proces prijave priloga u pet koraka.

8. Dodatne obaveze

Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net

INFORMATION FOR AUTHORS

Medical review publishes papers from various fields of biomedicine intended for broad circles of doctors. The papers are published in Serbian language with an expanded summary in English language and contributions both in Serbian and English language, and selected papers are published in English language at full length with the summary in Serbian language. Papers coming from non-Serbian speaking regions are published in English language. The authors of the papers have to be Medical Review subscribers.

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

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

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

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

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

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

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

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

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

Preparation of the manuscript

The covering letter:

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

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

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

The manuscript:

Use Microsoft Word for Windows to type the text. The text must be typed in font Times New Roman, page format A4, space 1.5 (for tables as well), borders of 2.5 cm and font size 12pt. The manuscript should contain the following elements:

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

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

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

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

– review papers should have the introduction, subtitles corresponding to those in the paper and conclusion. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

3. The summary in Serbian language. The summary in Serbian should be the translation of the summary in English, it should be structured in the same way as the English summary, containing up to 250 words, without any abbreviations.

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

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

– The text should be written in the spirit of Serbian language, without unnecessary abbreviations, whose first mentioning must be explained by the full term they stand for. Abbreviations should not be used in the title, summary and conclusion. Only commonly accepted abbreviations (such as DNA, MRI, NMR, HIV…) should be used. The list of abbreviations used in the text, together with the explanation of their meaning, is to be submitted at the last page of the manuscript.

– All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C). and pressure in mmHg.

– No names, initials or case history numbers should be given.

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

Material and methods should contain data on design of the study (prospective/retrospective, eligibility

and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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

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

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

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

Articles in journals

∗ *A standard article*

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

∗ *An organisation as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *Acomputer file*

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

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

– Tables, graphs, schemes and photographs are to be submitted at the end of the manuscript, on separate pages.

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

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

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

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

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

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

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

7. Manuscript submission

The manuscripts can be submited on the web-page: **aseestant.ceon.rs/index.php/medpreg/**. The authors have to register with the journal prior to submitting their manuscript, or, if already registered, they can simply log in and begin the 5 step process.

8. Additional requirements

If the author and all co-authors have failed to pay the subscription for Medical Review, their paper will not be published.

Papers which have not met the criteria of Medical Review will not be taken into consideration. The Editorial review of the paper will be announced not later than six weeks after the submission of the paper. The Editorial Board reserves the right to make a decision regarding the publication of the paper according to the policy of Medical Review even if the review is positive. Contact the technical secretary for all additional information:

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net