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Adresa redakcije: Vojnomedicinska akademija, Institut za naučne informacije, Crnotravska 17, poštanski fah 33–55, 11040 Beograd, Srbija. Telefoni: glavni i odgovorni urednik 3609 311, glavni menadžer časopisa 3609 479, pretplata 3608 997. Faks 2669 689. E-mail (redakcija): **vsp@vma.mod.gov.rs**

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U Beogradu je, od 29. maja do 1. juna ove godine, održan 17. kongres Balkanskog komiteta vojne medicine koji trenutno okuplja šest zemalja: Albaniju, Bugarsku, Grčku, Rumuniju, Srbiju i Tursku. Na Kongresu su razmatrane aktuelne teme iz oblasti vojne medicine i medicine uopšte (vidi str. 636).

The 17th of the Balkan Military Medical Committee was held from May 29 to June 1 this year in Belgrade. At the moment, The Balkan Military Medical Committee assembles six countries: Albania, Bulgaria, Greece, Romania, Serbia and Turkey. Numerous current topics of military medicine and medicine, in general, were discussed at the Congress (see page 637).

ORIGINALNI ČLANCI

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Dijagnostička pouzdanost citoloških nalaza nodularnih lezija štitaste žlezde iz uzoraka dobijenih aspiracijom tankom iglom

Diagnostic relevance of fine needle aspiration cytology in nodular thyroid lesions

Slavica Knežević-Ušaj*, Živka Eri†, Milana Panjković†, Ištvan Klem†, Tomislav Petrović‡, Tatjana Ivković-Kapicl*, Aleksandra Karapandžić†, Jasmina Jelić‖

***Odeljenje za patologiju i citodijagnostiku, ‡Hirurška klinika, Institut za onkologiju Vojvodine, Sremska Kamenica, Srbija; †Centar za patologiju, Institut za plućne bolesti Vojvodine, Sremska Kamenica, Srbija; ‖Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija**

Apstrakt

Uvod/Cilj. Citološki pregled lezija štitaste žlezde iz uzoraka dobijenih aspiracijom tankom iglom (*fine needle aspiration cytology* – FNAC) je brza, jeftina, tehnički jednostavna i pouzdana ali u Srbiji nedovoljno prihvaćena dijagnostička metoda. Cilj rada bio je da se prikažu sopstvena iskustva u primeni FNAC u nodularnim lezijama štitaste žlezde i utvrdi senzitivnost ove metode, njena pozitivna prediktivna vrednost i dijagnostička pouzdanost. **Metode.** U periodu maj, 2008 – maj, 2009. godine izvršen je citološki pregled materijala dobijenog aspiracijom štitaste žlezde tankom iglom pod kontrolom ultrazvuka kod 266 bolesnika. Operativno lečenje primenjeno je kod 69 bolesnika. Citološki nalaz kod operisanih bolesnika upoređivan je sa kliničkim podacima, ultrazvučnim i patohistološkim nalazima. **Rezultati.** Prisustvo karcinoma u citološkom materijalu dijagnostikovano je kod 10 bolesnika, a patohistološkom analizom kod 12. Kod dva bolesnika dobijen je lažno negativan citološki nalaz. Pokazana je statistički značajna korelacija između citološke i patohistološke dijagnoze u nodularnim lezijama štitaste žlezde. Dobijena je senzitivnost od 83%, specifičnost 100% i dijagnostičku pouzdanost 97% **Zaključak.** Naši rezultati potvrđuju da je FNAC jednostavna, brza i pouzdana dijagnostička metoda koju treba uvek primeniti u dijagnostičkom algoritmu čvorova u štitastoj žlezdi.

Ključne reči:
gušavost, nodozna; citologija; biopsija iglom; histologija; osetljivost i specifičnost.

Abstract

Background/Aim. Fine needle aspiration cytology (FNAC) of the thyroid gland has been used as an initial investigative procedure of thyroid nodule(s) in the Department of Pathology at the Institute of Oncology of Vojvodina for more than 20 years. This procedure is rapid, inexpensive and technologically simple, yet it has found only limited, albeit increasing acceptance in medical practice in Serbia. The aim of the study was to evaluate our FNAC findings by correlating cytological results with histological diagnosis and to define the sensitivity, diagnostic accuracy and positive predictive value of FNAC. **Methods.** A total of 266 patients with thyroid swellings were aspirated in one year investigated period at our Institute out of whom 69 underwent surgery between May 2008 and May 2009. The cytological results correlated with clinical features, ultrasound investigations (US) and subsequent histopathological examination of the resected tissue. **Results.** By the use of cytology we found out thyroid carcinoma in 10 patients, and by histopathological examination in 12. We obtained 83% sensitivity, 100% specificity and 97% of diagnostic accuracy of FNAC. **Conclusion.** The obtained results confirm the importance of FNAC in preoperative assesment of thyroid nodule.

Key words:
goiter, nodular; cytological techniques; biopsy, fine-needle; histology; sensitivity and specificity.

Uvod

Čvorovi u štitastoj žlezdi čest su klinički nalaz i većina ih je benigna. Ultrazvučni (UZ) pregled, najčešće, nije dovoljan za procenu biološke prirode čvorova [1]. Citološki pregled nodularnih lezija štitaste žlezde aspiracijom tankom iglom (*fine needle aspiration cytology* – FNAC) trenutno je najmanje invazivan i najprecizniji u identifikaciji visokorizičnih i malignih lezija u štitastoj žlezdi [2]. S obzirom na to da više od 50% odraslih ima jedan ili više čvorova u štitastoj žlezdi i da je maligno

Correspondence to: Slavica Knežević-Ušaj, Institut za onkologiju Vojvodine, Institutski put 4, 21 000 Sremska Kamenica, Srbija. Tel.: +381 21 480 5481, +381 63 245 752. E-mail: susaj0613@yahoo.com, slavica.usaj@onko.onk.ns.ac.rs

manje od 5% čvorova kod odraslih, hirurško odstranjenje svih čvorova ne bi bilo ni poželjno, a ni praktično, kako sa medicinskog, tako i sa ekonomskog stanovišta [3, 4]. Uvođenje minimalno invazivne dijagnostičke metode FNAC, omogućilo je da na hiljade bolesnika izbegne nepotreban rizik od hirurške intervencije, a da se oni sa karcinomom pravilno selektuju za odgovarajuću terapiju [5]. Pregled FNAC smatra se prvom linijom dijagnostičkog testa za analizu strume i, što je još važnije, za preoperativnu, ali i intraoperativnu dijagnostiku posebnih (usamljenih) čvorova u štitastoj žlezdi (*solitary thyroid nodule* – STN). Zahvaljujući širokoj primeni ove metode, značajno je smanjen broj hirurških intervencija na posebnim čvorovima [6]. Prediktivna vrednost FNAC, kao i njena senzitivnost, specifičnost i efikasnost u dijagnostici tumora veći su od 90%. Ova dijagnostička metoda obezbeđuje bržu, jeftiniju i pouzdaniju dijagnozu STN nego bilo koja druga kombinacija kliničkih i laboratorijskih testova [7].

Godinama je smatrano da citologija ima manji dijagnostički značaj od histopatologije. Tokom poslednjih 15 godina postignut je napredak i citologija je počela da se penje na lestvici dijagnostičkih metoda [8]. U Srbiji je citološka dijagnostika, generalno, nedovoljno prihvaćena i još uvek se smatra *screening*, a ne dijagnostičkom metodom [9]. Razlog za nedovoljnu primenu citologije u dijagnostici leži u malom broju edukovanih citopatologa u našoj zemlji. Supspecijalizacija iz citopatologije je u Srbiji uvedena tek 2007. godine [10, 11]. Sa povećanjem broja obrazovanih citopatologa očekuje se da citologija zauzme i u našoj zemlji mesto koje u svetu odavno zauzima.

U Institutu za onkologiju Vojvodine citologija kao dijagnostička metoda u različitim lezijama štitaste žlezde primenjuje se više od 20 godina. Ova studija imala je za cilj da prikaže sopstvena iskustva u primeni FNAC u nodularnim lezijama štitaste žlezde i korelacijom sa definitivnim patohistološkim nalazima na operativnom materijalu utvrdi senzitivnost i specifičnost, prediktivnu vrednost i dijagnostičku pouzdanost ove metode.

Metode

Ispitivanjem je bilo obuhvaćeno 266 bolesnika lečenih u Institutu za onkologiju Vojvodine, odabranih metodom slučajnog izbora, kod kojih je urađena punkcija štitaste žlezde u periodu maj, 2008 – maj, 2009. godine. Podaci o bolesnicima dobijeni su iz baze podataka Instituta. Punkcije su vršene tankom iglom, veličine 22 gauga pod kontrolom ultrazvuka. Nakon izvršene punkcije, pravljeno je 4–7 direktnih razmaza (konvencionalnih preparata) koji su sušeni na vazduhu i bojeni May-Grünwald-Giemsa metodom, ili su odmah fiksirani u 95% alkoholu i bojeni Papanicolaou metodom, a zatim analizirani svetlosnim mikroskopom. Citološki preparati najpre su procenjivani u odnosu na kvalitet preparata prema preporukama Clarka i Faquina [3]. Zadovoljavajućim uzorcima smatrani su oni koji sadrže najmanje pet grupa ćelija sa po najmanje 10 folikularnih ćelija u svakoj grupi. Citološki nalazi bili su grupisani prema preporukama Clarka i Faquina [3] u: neadekvatne (nezadovoljavajuće) uzorke, benigne lezije, neodređene lezije – verovatno benigne (NVB), neodređene lezije – verovatno maligne (NVM) i maligne.

U kategoriju „malignih lezija“ svrstane su one sa nesumnjivim citološkim karakteristikama papilarnog ili medularnog karcinoma. U slučaju medularnog karcinoma, nalaz je bio potvrđen imunohistohemijskom analizom na kalcitonin. Kod ovog bolesnika uzorak je nakon fiksacije u 95% alkoholu, tretiran straptavidin-biotin metodom (*labeled strepatavidin-biotin* – LSAB) prema standardnoj proceduri, uz primenu monoklonskog antitela na kalcitonin, proizvodnje Dakocytomation^{R}, u optimalnoj koncentraciji. Kao hromogeni supstrat korišćen je 3-amino-9-etilkarbazol (AEC), a preparat je analiziran svetlosnim mikroskopom.

U ispitivanoj grupi nije bio nijedan anaplastični karcinom niti limfom.

Kod 69 bolesnika podvrgnutih operativnom lečenju, nakon *ex tempore* analize odabranog uzorka, urađena je optimalna hirurška intervencija. Nakon makroskopskog pregleda reseciranog materijala odabran je reprezentativan broj tkivnih uzoraka koji su zatim fiksirani u formalinu i ukalupljeni u parafin, a zatim analizirani svetlosnim mikroskopom. Finalne histopatološke dijagnoze upoređivane su sa citološkim dijagnozama.

U pozitivne citološke nalaze svrstani su oni kod kojih je histološkim pregledom potvrđena maligna priroda bolesti. Lažno pozitivnim smatrani su citološki nalazi kod kojih je citološkim pregledom postavljena dijagnoza malignog tumora, a histološki je nađen benigni tumor, inflamacija ili benigna (multi)nodularna struma. U negativne nalaze svrstani su svi nalazi kod kojih je citološkim pregledom nađena folikularna proliferacija bez sumnje na malignitet, cistično degenerisani koloidni nodus, benigna (multi)nodularna struma ili inflamacija, a histološki je potvrđena benigna priroda bolesti. Lažno negativnim smatrani su svi razmazi bez elemenata malignog tumora, kod kojih je histološki, na operativnom materijalu, postavljena dijagnoza malignog tumora.

Citološki nalazi koji su označeni kao „neodređeno, verovatno maligno“, uključeni su u grupu malignih lezija, s obzirom na to da je na osnovu takvog nalaza doneta odluka o hirurškoj resekciji žlezde.

U obradi i analizi dobijenih podataka, primenjene su metode deskriptivne statistike, tabele kontigencije i korelacije. Da bi se utvrdilo da li postoji povezanost među varijablama, izračunati su koeficijenti korelacije. U zavisnosti od prirode podataka, odnosno, mernih skala sa kojih dolaze, korišćeni su Spirmanov i Pirsonov koeficijent korelacije. Za statističku obradu podataka korišćen je statistički program SSPS 15.0.

Rezultati

Analizom je bilo obuhvaćeno 239 žena i 27 muškaraca. Odnos polova iznosio je 9 : 1. Prosečna starost bolesnika iznosila je 53,4 godine, (53,5 godina za žene i 55,1 za muškarce). U grupi operisanih bolesnika, dominirao je ženski pol, tj. 66 (95,65%) ispitanika činile su žene, a samo 3 (4,35%) muškarci.

U tabeli 1 prikazane su kliničke i ultrazvučne karakteristike lezija samo za populaciju operisanih bolesnika. Nije bilo statistički značajne razlike u distribuciji lezija po režnje-

Tabela1

Kliničke i ultrazvučne (UZ) karakteristike operisanih bolesnika

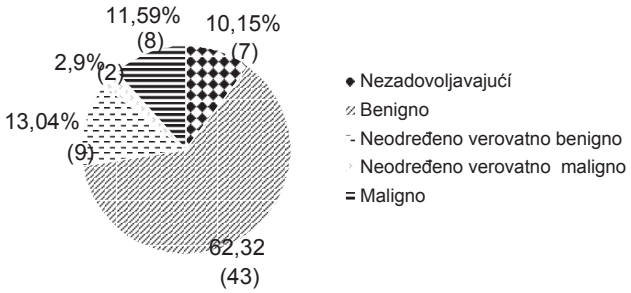
Posmatrano obeležje	Procenat ispitanika	Statistička značajnost
Distribucija po režnjevima		
desni	39,13	
levi	31,88	ns
oba	23,19	
np	5,80	
Ultrazvučni nalaz		
izoehogeni	23,19	
hipoehogeni	14,49	
heteroehogeni	47,83	ns
np	14,49	
Veličina lezija (UZ)		
do 2cm	18,84	
2–5 cm	56,52	no
preko 5cm	2,90	
np	21,74	
Makroskopski tip lezije (UZ)		
nodularne		
solitarne	87,40	
multiple	55,07	
difuzne	33,33	no
np	2,90	
	8,7	
Preoperativna dijagnoza		
struma	81,16	
Hashimotoov tireoiditis	7,25	
adenom	5,80	no
karcinom	2,90	
drugo	1,45	
np	1,45	

np – nema podataka; no – nije određivano; ns – nije signifikantno

vima. Neznatno veći procenat bolesnika imao je zahvaćen desni u odnosu na levi režanj (39,13%, nasuprot 31,88%). Najveći procenat ispitanika imao je pri ultrazvučnom pregledu heteroehogene (47,83%) i nodularne lezije (87,4%), češće solitarne, nego multiple (55,07% i 33,33%). Nodularne lezije, izmerene ultrazvučnim pregledom, najčešće su bile veličine 2–5 cm (56,52%), a najčešća klinička preoperativna dijagnoza bila je struma, čak kod 81% bolesnika. Karcinom je kliničkim i ultrazvučnim pregledom bio dijagnostikovan samo kod 2,9% bolesnika.

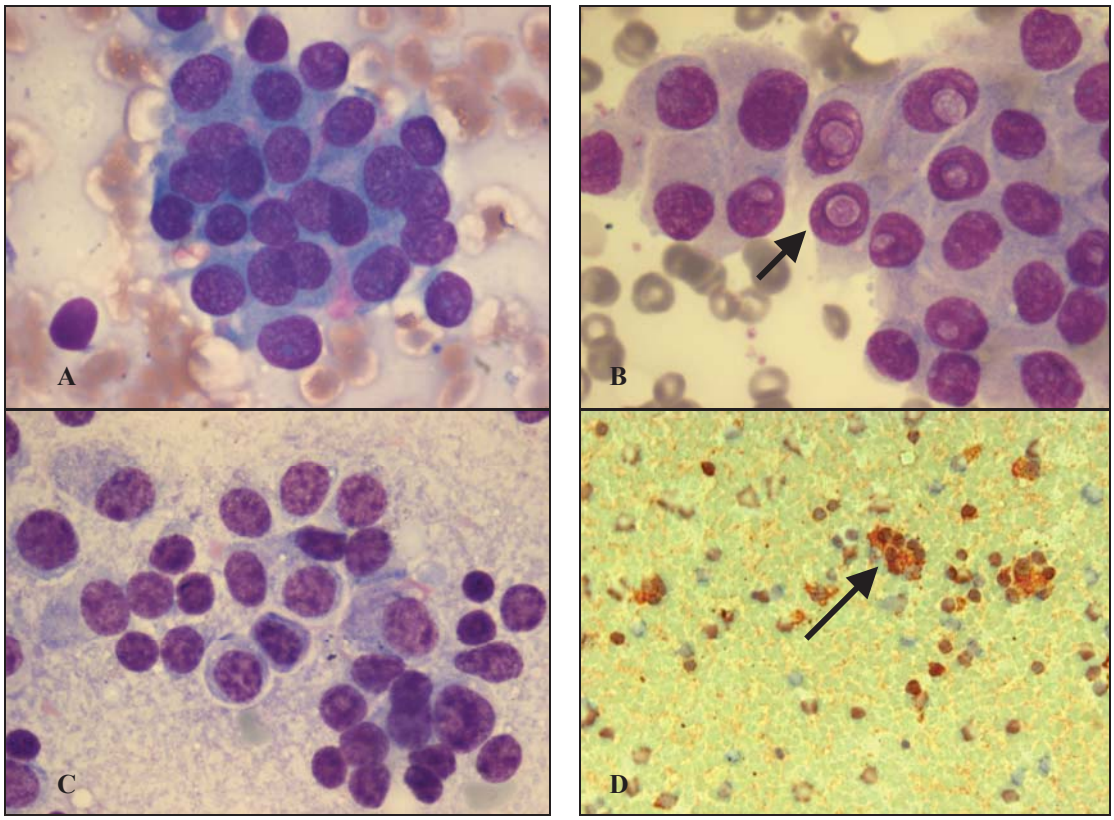
Citološkim pregledom svih 266 bolesnika dobijeno je ukupno 35 neadekvatnih razmaza (13,15%). U grupi operisanih bolesnika, bilo je 7 (10,14%) uzoraka nezadovoljavajućeg kvaliteta za citološku analizu.

U grupi operisanih, najveći broj ispitanika pri preoperativnom citološkom pregledu imao je benigni tip lezije (43 bolesnika – 62,32%), kod devet (13,4%) bolesnika bila je postavljena dijagnoza NVB, kod dva (2,9%) bolesnika nalaz je bio NVM, a citološkim pregledom kod osam (11,59%) bolesnika dijagnostikovan je karcinom (slika 1). Kod sedam (10,14%) bolesnika kvalitet razmaza bio je tehnički nezadovoljavajući za citološku analizu. Kada su u grupu sa malignim nalazima uključena i dva bolesnika čiji su citološki razmazi bili suspektni na maligno, ukupan broj bolesnika sa citološki dijagnostikovanim karcinomom iznosio je 10 (14,49%). Od 11 folikularnih lezija označenih kao „neodređena“ citološka kategorija (NVB i NVM), patohistološkom analizom karcinom je utvrđen kod dva (22%) bolesnika. Ova dva (2,9%) bolesnika su citološkim pregledom svrstana u kategoriju NVM.



Sl. 1 – Struktura uzorka prema citološkim preoperativnim dijagnozama

Najviše ispitanika (43 – 62,32%) imalo je benignu leziju. Folikularna lezija dijagnostikovana je kod 11 (15,95%) bolesnika uključujući i dva označena kao „neodređeno, verovatno maligno“ (slika 2a), dok je sedam (10,14%) bolesnika imalo papilarni karcinom (slika 2b) i jedan (1,45%) bolesnik medularni karcinom (slike 2c i 2d). Ostatak su činili neadekvatni razmazi (10,14%).



Sl. 2 – A) Grupa suspektnih folikularnih ćelija sa preklapanjem i nukleolusima (MGG, ×1000); B) Papilarni karcinom sa intranuklearnim inkluzijama (strelica) (MGG, ×1000); C) medularni karcinom (MGG, ×1000); D) Medularni karcinom. Kalcitonin u tumorskim ćelijama (strelica), imunocitohemija (LSAB, ×400)

Postoperativnom patohistološkom analizom, benigne lezije bile su zastupljene kod 57 (82,61%) ispitanika, papilarni karcinom kod devet (13%), kod dva (2,9%) bolesnika folikularni karcinom i kod jednog (1,45%) medularni karcinom. Karcinom je dijagnostikovan, bez obzira na histološki tip, kod ukupno 17,39% operisanih.

Stadijum tumorske bolesti određivan je prema 6. reviziji tumor nodus metastaza (TNM) sistema klasifikacije [12]. Šest bolesnika bilo je u stadijumu pT2, po dva bolesnika u stadijumu pT1 i pT3, i jedan je imao papilarni mikrotumor.

Svi operisani bolesnici, tj. oni kod kojih je postojala patohistološka verifikacija bolesti u štitastoj žlezdi, bili su podeljeni u kategorije: stvarno pozitivni (SP) – pozitivna FNAC dijagnoza malignog oboljenja potvrđena patohistološkim pregledom operativnog materijala; stvarno negativni (SN) – negativan citološki nalaz potvrđen i patohistološki kao benigno oboljenje štitaste žlezde; lažno pozitivni (LP) – pozitivan FNAC nalaz koji nije potvrđen patohistološkim pregledom operativnog materijala; lažno negativni (LN) – negativan FNAC nalaz, a patohistološki dokazano maligno oboljenje štitaste žlezde.

Na osnovu ovih vrednosti izračunati su, prema navedenim formulama, senzitivnost i specifičnost, pozitivna i negativna prediktivna vrednost i dijagnostička pouzdanost.

Senzitivnost (SN) je verovatnoća da bolesnici sa pozitivnim citološkim nalazom zaista imaju malignu bolest potvrđenu patohistološki: S = SP/SP + LN.

Specifičnost (SP) je verovatnoća da bolesnici sa negativnim citološkim nalazom nemaju dokazano maligno oboljenje ni patohistološkim pregledom: SP = SN/SN + LP .

Pozitivna prediktivna vrednost (PPV) označava proporciju bolesnika sa pozitivnim citološkim nalazom i histološkom potvrdom: PPV = SP/SP + LP, dok negativna prediktivna vrednost (NPV) označava proporciju bolesnika sa negativnim citološkim nalazom i histološki potvrđenim odsustvom karcinoma: NPV = SN/SN + LN).

Dijagnostička pouzdanost (DP) odnosi se na proporciju bolesnika dijagnostikovanih korektno primenjenim metodama DP = (SP + SN) / (LN + LP + SP + SN).

Korelacija sa histopatološkim nalazima pokazala je da je 82,61% ispitanika bilo „stvarno negativno“, 14,49% ispitanika „stvarno pozitivno“, a 2,9% ispitanika „lažno negativno“. Nije bilo ispitanika koji pripadaju kategoriji „lažno pozitivni“.

Na osnovu odnosa citoloških i patohistoloških dijagnoza izračunata senzitivnost iznosila je 83%, specifičnost 100%, pozitivna prediktivna vrednost 100%, negativna prediktivna vrednost 97% i dijagnostička pouydanost 97%. Međutim, kada se iz kategorije „stvarno pozitivnih“ isključe dva bolesnika sa neodređenim citološkim, ali suspektnim nalazima, senzitivnost je iznosila 80%.

Poređenjem nalaza dobijenih citološkom i patohistološkom analizom, od 43 ispitanika koji su pri citološkoj analizi imali benignu leziju, kod dva bolesnika patohistološki je dijagnostikovan karcinom. Kod svih sedam bolesnika kod ko-

jih je citološkom analizom dijagnostikovan karcinom, nalaz je bio potvrđen patohistološkim pregledom. Od 11 bolesnika kod kojih je citološkim pregledom dijagnostikovana folikularna lezija, kod dva je konačna patohistološka dijagnoza bila folikularna varijanta papilarnog karcinoma. Jednom bolesniku sa citološki dokazanim medularnim karcinomom, nalaz je potvrđen i patohistološki na operativnom materijalu. Sedam ispitanika se nalazilo u kategoriji „neadekvatan uzorak", pri čemu su kod svih patohistološkom analizom utvrđene benigne lezije. Citološkom analizom imali smo dva bolesnika s lažno negativnim nalazima kod kojih je patohistološkim pregledom utvrđeno prisustvo folikularnog karcinoma. Testovi korelacije pokazali su da je dobijena statistički značajna pozitivna korelacija između citoloških nalaza i patohistoloških dijagnoza ($r = 0,56$, $p < 0,01$).

Diskusija

Čvorovi u štitastoj žlezdi najčešća su makroskopska prezentacija različitih oboljenja ovog endokrinog organa [4]. Za terapiju i kontrolu ovih bolesnika od vitalnog je značaja razlikovati tipove čvorova u štitastoj žlezdi. Od uvođenja FNAC kao dijagnostičke procedure u proceni lezija štitaste žlezde, došlo je do značajne redukcije broja bolesnika koji se podvrgavaju hirurškoj resekciji zbog benignih čvorova u štitastoj žlezdi i do povećanja udela malignih tumora u hirurškom materijalu nakon parcijalne ili totalne tireoidektomije [13, 14].

Prosečna starost bolesnika u populaciji koju smo analizirali iznosila je 53 godine, a u grupi operisanih 49 godina, što znači da su ispitivani bolesnici stariji nego u većini studija drugih autora, izuzev malobrojne grupe muškaraca (ukupno tri operisana) čija je prosečna starost iznosila 34 godine, slično nalazima drugih autora [15, 16]. Razlog za ovakvu razliku nije jasan, ali je moguće da relativno nizak stepen zdravstvene svesti naših bolesnika, pogotovo u odsustvu kliničkih manifestacija, kasnije dovodi bolesnike lekaru, onda kada već dođe do značajnog uvećanja žlezde i kompresivnih smetnji, a za šta je ipak potreban izvestan vremenski period koji se meri godinama. Odnos polova uglavnom se podudarao sa podacima iz literature. Naime, poznato je da su oboljenja štitaste žlezde gotovo 10 puta češća u ženskoj populaciji [17].

U našem materijalu od 266 bolesnika sa FNAC odabranih metodom slučajnog izbora, hirurška intervencija izvedena je, bez obzira na citološki nalaz, kod nešto više od 25% bolesnika. Nije postojala statistički značajna razlika u pogledu učestalosti obolevanja po režnjevima. Nije bilo statistički značajne razlike u učestalosti solitarnih i multiplih nodusa (55% bolesnika sa solitarnim nasuprot 33% bolesnika sa multiplim nodusima). Kada se posmatraju samo bolesnici sa karcinomom, odnos je bio 7 : 5 u korist solitarnih nodusa. U velikim serijama bolesnika sa hladnim čvorom nije bilo statistički značajne razlike u učestalosti karcinoma u solitarnim i multipnim čvorovima (5% i 4,9%) [18]. Međutim, Khan i sar. [15] su dobili veću učestalost karcinoma u multinodularnim lezijama, što su autori pripisali kasnoj prezentaciji bolesnika doktoru.

U našoj populaciji većina bolesnika imala je solidne čvorove (62,32%). Od bolesnika sa malignom bolešću štitaste žlezde, tri su imala cističan nodus. Prema podacima iz literature, rizik prisustva karcinoma u cističnom nodusu je nizak, i iznosi manje od 4% u kompletno cističnom nodusu, ali raste do 14% za mešovite solidno-cistične lezije i ciste veće od 3 do 4 cm [3, 13, 18, 19]. Najčešće se u cističnom čvoru nađe papilarni karcinom. Nešto veći procenat karcinoma u cističnim lezijama u našoj populaciji (25%) može se objasniti malim uzorkom, te se ne može porediti sa rezultatima većih serija.

U ispitivanoj grupi bilo je oko 10% nekvalitetnih razmaza na kojima nije bilo moguće izvršiti pouzdanu citološku analizu. Kada se posmatraju svi bolesnici (operisani i neoperisani), neupotrebljivih razmaza je bilo oko 13,5%. Procenat neupotrebljivih razmaza, prema literaturi kreće se između 2 i 25%. Rabb i sar. [20] su pokazali da suboptimalni citopreparati mogu biti značajan izvor lažno negativnih nalaza. Gharib i sar. [21] imali su u svojoj studiji oko 10% malignih tumora kod bolesika sa suboptimalnim ili neupotrebljivim razmazima, što prema mišljenju autora, opravdava ponavljane FNAC u ovakvim slučajevima. Međutim, u slučajevima kada je razmaz nezadovoljavajućeg kvaliteta, a citološkim pregledom se nađu malobrojne ćelije sa nesumnjivim citološkim karakteristikama karcinoma, nalaz se ne svrstava u neupotrebljive, već se postavlja citološka dijagnoza karcinoma [13]. Ni u jednom od neadekvatnih razmaza, patohistološkim pregledom nismo identifikovali postojanje karcinoma.

Citološkom analizom 69 operisanih bolesnika utvrđeno je da preko 60% ima benignu leziju, dok je karcinom citološki dijagnostikovan kod 11,59% bolesnika. Ukoliko u „maligne" nalaze uvrstimo i dve folikularne lezije koje su označene kao „neodređeno – verovatno maligno", procenat pozitivnih citoloških nalaza iznosio je 14,49. Učestalost karcinoma od 17,39%, nakon definitivne patohistološke dijagnoze u našoj studiji, slična je nalazu Mahar i sar. [19] i Nayar i Ivanović [18] koji su analizom citoloških nalaza svrstanih u grupu „nedeterminisanih lezija" utvrdili učestalost karcinoma, nakon patohistološke verifikacije operativnog materijala kod 12% bolesnika. Međutim, pomenuti autori su koristili novi, Bethesda sistem klasifikacije citoloških lezija, koji podrazumeva šestostepeni sistem gradiranja tireoidnih lezija [17]. Ovaj sistem, pored kategorija „atipičnih folikularnih lezija neodređenog značaja", ima i kategoriju „suspektno na maligno" i u ovoj kategoriji je nakon resekcije, u studiji Nayar i Ivanović [18], učestalost karcinom iznosila 53%. U našoj studiji bila su dva bolesnika sa nalazom „neodređeno – verovatno maligno" i u oba slučaja (100%) je histološki dijagnostikovana folikularna varijanta papilarnog karcinoma.

U analiziranoj grupi bila su dva bolesnika sa citološki lažno negativnim nalazima kod kojih je nakon patohistološkog pregleda postavljena dijagnoza folikularnog karcinoma. Lažno negativan FNAC nalaz može biti rezultat pogrešnog uzorka (lažno „praznog" uzorka), ili pogrešne interpretacije od strane citopatologa. Ovakvi nalazi su od posebnog značaja jer su potencijalan izvor „propuštanja" da se blagovremeno postavi dijagnoza maligne bolesti štitaste žlezde, a time i dovede do neadekvatnog lečenja pacijenta sa dalekosežnim posledicama [21, 22]. Međutim, prilično je teško utvrditi stvarnu frekvenciju lažno negativnih nalaza, zbog toga što se u sredinama sa dugotrajnom tradicijom citologije i razvijenom citopatološkom službom, samo oko 10% bolesnika sa

negativnim, odnosno benignim citološkim nalazima podvrgava hirurškoj resekciji [23]. U našoj studiji operisano je 22% bolesnika sa negativnim citološkim nalazima (57 od 254 bolesnika sa negativnom citologijom), slično kao u studiji Mahar i sar. i Nayar i sar. [18, 19]. Jedan broj bolesnika operisan je zbog kompresivnih smetnji, a drugi, zbog toga što je hirurgu, i pored negativnog citološkog nalaza, lezija štitaste žlezde klinički bila suspektna. Većina autora smatra da bi prava stopa lažno negativnih nalaza bila ispod 5% ukoliko bi se svi bolesnici sa negativnim FNAC nalazom podvrgli resekciji i patohistološkoj verifikaciji [23, 24]. Procenat lažno negativnih nalaza u značajnoj meri zavisi od iskustva i znanja citopatologa. Zbog toga kvalitetna citologija zahteva edukovane i dobro „istrenirane" patologe sa supspecijalizacijom iz citologije i dugogodišnjim iskustvom.

Procenat lažno negativnih nalaza od 2,9% u našem radu podudara se sa nalazima drugih autora kod kojih se ovaj procenat kreće između 2 i 7% [25]. Međutim, u pojednim studijama lažno negativnih nalaza bilo je znatno više i ovaj se procenat kreće i do 16% [26, 27].

Dijagnostička aspiraciona punkcija tankom iglom danas se smatra jeftinom, brzom i pouzdanom metodom za testiranje nodularnih lezija štitaste žlezde. Senzitivnost ove metode kreće se od 65 do 98%, specifičnost od 72–100% [19, 20]. U našem radu senzitivnost je iznosila 83%, a specifičnost 100%. Razlike u ovim vrednostima zavise od kategorizacije suspektnih nalaza. Ukoliko se suspektan nalaz kategorizuje u grupu pozitivnih (odnosno malignih) senzitivnost je veća nego ako se ovakvi nalazi smatraju negativnim. Ikram i sar. [28] imali su specifičnost i senzitivnost 100%, ali oni nisu imali lažno negativne ni lažno pozitivne nalaze. Grupa autora sa Aga Khan univerziteta imala je senzitivnost 61,9% i specifičnost od 99,31%, PPV 92,86%, NPV 94,74% i DP 94,58% [29]. U našem radu PPV iznosila je 100%, NPV 97% i DP 97%. Ovakvi nalazi se razlikuju od nalaza pomenutih autora, možda zbog toga što su Ikram i sar. [28] suspektne slučajeve alternativno stavljali u grupu pozitivnih ili negativnih. Kada smo iz stvarno pozitivnih citoloških nalaza isključili one koje smo inicijalno svrstali u grupu „neodređeno – verovatno maligno", kalkulacija je pokazala nižu senzitivnost od 80%, NPV od 93% i DP od 94%. Ovako visok stepen senzitivnosti i specifičnosti u našoj studiji može se pripisati malom broju slučajeva. Dva suspektna nalaza uvrstili smo u kategoriju pozitivnih što je uticalo na PPV od 100%.

Citopatološki izveštaji među sobom se prilično razlikuju u pogledu kategorizacije nalaza. Wang [30] je 2006. objavio pregled literature o citološkom izveštavanju štitaste žlezde i našao široku lepezu kategorizacija, od dvostepene podele na benigno/maligno do šest ili više kategorija u kojima postoji jedna ili više kategorija neodređenih benignih, odnosno malignih karakteristika. Upravo ovakva šarolikost u kategorizaciji može biti uzrok širokih varijacija u kalkulacijama senzitivnosti i specifičnosti.

Najproblematičnije za citopatologa su folikularne lezije. Sa sve širim prihvatanjem citologije kao pouzdane dijagnostičke metode, poslednjih godina raste primena FNAC u praćenju bolesnika sa određenim folikularnim lezijama štitaste žlezde, bez obzira na ograničenja FNAC kod ovog tipa lezija [18, 5]. Suštinski, FNAC predstavlja skrining metodu za folikularne lezije. Iako se ne može napraviti razlika između folikularnog adenoma i folikularnog karcinoma, iskusan citopatolog može odvojiti folikularne lezije/lezije Hürthleovih ćelija sa dominacijom jedne ćelijske populacije, kao neoplazme [18]. Za ovakve lezije NCI (*National Cancer Institute*) terminologija preporučuje termin „suspektno na folikularnu neoplazmu" [13]. Ukoliko su u citološkom materijalu prisutne samo pojedine karakteristike papilarnog karcinoma, takva folikularna neoplazma može se svrstati u kategoriju „suspektno na karcinom" ili ostaviti u kategoriji folikularnih neoplazmi, zavisno od stepena suspektnosti [17].

Prema NCI vodičima, preporučeno je da se za heterogenu grupu lezija, koje obuhvataju citološke preparate sa arhitekturalnom ili citološkom atipijom, i tzv. lezije sive zone sa karakteristikama folikularnih lezija i lezija Hürthleovih ćelija, koristi termin „atipija neodređenog značaja" [24]. U ovu kategoriju mogu se svrstati i suboptimalni citološki uzorci (osušeni, niske celularnosti), ciste obložene atipičnim epitelom, postterapijske promene i druge nespecifične citološke promene. Preporuka je da se u ovakvim slučajevima napravi korelacija sa kliničko-radiološkim nalazima i, ukoliko je potrebno, ponovi FNA [13]. Primena standardizovanih kriterijuma i terminologije, praćenje ovih bolesnika kao i konačni ishod zahtevaju još dosta vremena i iskustva pre nego što se realno proceni koje sve FNAC promene treba svrstati u kategoriju „atipija neodređenog značaja". Početkom 2010. godine, objavljena je publikacija NCI o standardizaciji terminologije u vidu atlasa i web sajta, koja bi trebalo da predstavlja glavni korak ka standardizaciji izveštavanja citoloških lezija štitaste žlezde [24].

Zaključak

Naši rezultati potvrđuju da je aspiracija tankom iglom brza, jeftina, vrlo senzitivna i pouzdana metoda, sa visokim stepenom prediktivne vrednosti u dijagnostici i kontroli bolesnika sa oboljenjima štitaste žlezde koju bi trebalo primeniti kao rutinsku metodu kod svih lezija štitaste žlezde, a posebno kod lezija nodularnog tipa. Ukoliko se dobra laboratorijska praksa i minimalni set podataka kombinuju, korektna dijagnoza se može postići u većini slučajeva i time izbeći nepotrebno izlaganje bolesnika operativnom riziku.

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Otpornost na lom cirkonijumskih keramičkih kruna izrađenih na bazi linijske preparacije zuba

Fracture toughness of zirconia ceramic crowns made by feather-edge tooth preparation design

Nemanja Mirković*, Aleksandra Špadijer Gostović†, Zoran Lazić*, Branka Trifković †

***Klinika za stomatologiju, Vojnomedicinska akademija, Beograd, Srbija;**
†Stomatološki fakultet, Beograd, Srbija

Apstrakt

Uvod/Cilj. Otpornost na lom uslovljava čvrstoću krune u toku funkcionalnih opterećenja i sprečava oštećenje keramike u toku mastikacije. U literaturi nema podataka o otpornosti na lom kruna izrađenih na bazi linijske preparacije. Mehaničkim testiranjem keramičkih uzoraka treba pokazati da li se linijska preparacija zuba može primeniti bez rizika od degradacije mehaničkih osobina keramičkih kruna. Ovo istraživanje sprovedeno je sa ciljem da se utvrdi uticaj linijske preparacije zuba na otpornost na lom pojedinačnih cirkonijumskih keramičkih kruna. **Metode.** Istraživanje je obavljeno kao eksperimentalna studija. Izrađeno je ukupno 60 keramičkih kruna na nekarioznim ekstrahovanim humanim premolarima. Ukupno 30 kruna izrađeno je na bazi linijske preparacije (prva eksperimentalna grupa), dok je u drugoj grupi izrađeno 30 kruna na osnovu preparacije oblika pravouglog stepenika sa unutrašnjim zaobljenjem. Za izradu kruna korišćen je kopir-frez sistem "Zirkonzahn" (Zirkonzahn GMBH, Gais, Germany). Za određivanje otpornosti na lom primenjen je test pritiska sa sferičnim opterećenjem – keramičkom kuglom prečnika 6 mm. Sila potrebna da dovede do loma keramičke krune zabeležena je na univerzalnoj mašini za testiranje materijala Zwick, tipa 1464, koja se kretala brzinom od 0,05 mm/min. **Rezultati.** Rezultati ovog ispitivanja ukazali su na značajne razlike između otpornosti na lom dve ispitivane grupe kruna. Prosečna otpornost na lom obe grupe kruna bila je iznad 2 000 N, što je dvostruko više od preporučene vrednosti. Krune na bazi linijske preparacije imale su prosečnu vrednost otpornosti na lom od 2 090 N, dok je u drugoj grupi otpornost iznosila 2 214 N. **Zaključak** Eksperimentalnim ispitivanjem utvrđena je visoka otpornost na lom cirkonijumskih keramičkih kruna izrađenih na osnovu linijske preparacije zuba. Ispitivane krune imale su otpornost na lom na dovoljnoj distanci u odnosu na minimalne vrednosti funkcionalnog opterećenja. Neophodna su dalja istraživanja funkcionalnog opterećenja ovakvih kruna u uslovima *in vivo* kao i ispitivanje rubnog zaptivanja cementiranih kruna i inflamatornog odgovora gingive.

Ključne reči:
krune; cirkonijum; zub, preparacija; biomehanika.

Abstract

Background/Aim. Fracture toughness determines functional crown strenght and prevents damages on ceramics during mastication. There is a lack of relevant literature data about fracture toughness of crowns made by feather-edge preparation. Mechanical testing of ceramic samples is supposed to show if feather-edge tooth preparation is a successful method for making ceramic crowns without any risk of reduction of their mechanical properties. This research was done to establish effects of feather-edge tooth preparation on fracture toughness of single zirconia ceramic crowns. **Methods.** The research was performed as an experimental study. Sixty (60) ceramic crowns were made on non-carious extracted human premolars. Thirty (30) crowns were made on the basis of feather-edge preparation (experimental group I). The group II included 30 crowns made on 1 mm rounded shoulder. Crowns fabrication was executed on a copy mill production system "Zirkonzahn" (Zirkonzahn GMBH, Gais, Germany). The spherical compression test was used to determine fracture toughness, using 6 mm diameter ceramic ball. Fracture load for damaging ceramic crown was recorded on a universal testing machine – Zwick, type 1464, with the speed of 0.05 mm/min. **Results.** The results of this research introduced significant differences between fracture toughness of ceramic samples in every examined group. However, fracture toughness of crowns from both group was above 2 000 N, what was double beyond a recommended value. The mean value of fracture toughness in the feather-edge group was 2 090 N, and in shoulder group it was 2 214 N. **Conclusion.** This research showed a high fracture toughness of zirconia crowns made on feather-edge preparation. The examined crowns showed a fracture resistance at a sufficient distance in relation to the minimum values of functional loads. Further research of functional loads of these crown is necessary, as well as research of marginal adaptation of cemented crowns and gingival inflammatory response.

Key words:
crowns; zirconium; tooth preparation; biomechanics.

Correspondence to: Nemanja Mirković, Vojnomedicinska akademija, Klinika za stomatologiju, Crnotravska 17, 11 000 Beograd, Srbija. Tel.: +381 11 360 8322. E-mail: doktorno@neobee.net

Uvod

Keramičke krune predstavljaju fiksne zubne nadoknade čija mehanička otpornost zavisi prevashodno od čvrstoće materijala od koga su izrađene [1]. U poređenju sa metalnim legurama, dentalna keramika ima neuporedivo manju čvrstoću, što sužava indikaciono područje bezmetalne keramike na izradu pojedinačnih kruna prednjih zuba – sekutića i očnjaka [2]. Razvoj novih keramičkih materijala pokušao je da proširi polje njihove primene i na izradu pojedinačnih kruna bočnih zuba – premolara i molara [3].

Najreprezentativniji keramički materijal danas je keramika od cirkonijum-dioksida (cirkonijumska keramika). Ova vrsta keramike ulazi u stomatološku praksu u poslednjih nekoliko godina kao novi materijal sa izuzetno velikom čvrstoćom na savijanje i otpornošću na lom. Cirkonijumska keramika, u pravom smislu reči, omogućava trenutnu revoluciju u stomatologiji zasnovanu na upotrebi CAD-CAM tehnologije. Sistemi CAD-CAM pojednostavljuju proces izrade zubnih nadoknada eliminišući pojedine konvencionalne kliničke i laboratorijske faze [4, 5].

Demarkacija oblika stepenika širine 1 mm bila je najzastupljeniji oblik demarkacije u početku razvoja keramičkih materijala. Ovakva demarkacija jasno ukazuje zubnom tehničaru na lokalizaciju gingivalnog ruba krune, pri čemu debljina ruba krune od 1 mm daje kruni potrebnu mehaničku otpornost.

Demarkacija oblika polužleba širine 0,5–1 mm je alternativa demarkaciji oblika stepenika zbog bržeg i jednostavnijeg izvođenja u kliničkim uslovima. Razni autori uvrdili su da demarkacija oblika polužleba uslovljava manju čvrstoću gotovih keramičkih kruna [6–9]. Ako se keramičke krune cementiraju adhezivnim načinom, uz upotrebu savremenog kompozitnog cementa, demarkacija oblika polužleba nema uticaja na čvrstoću keramičkih kruna [10, 11].

Demarkacija oblika linije (linijska demarkacija preparacije) je najčešće izvođena vrsta demarkacije u svakodnevnoj stomatološkoj praksi kod nas [12]. Razlozi za to su: lako izvođenje, nedovoljna obučenost stomatologa za izvođenje demarkacije oblika stepenika i polužleba i strah stomatologa od povrede zubne pulpe u toku brušenja zuba. Linijska preparacija uklanja najmanju količinu zubne supstance, posebno u gingivalnoj trećini brušenog zuba. Time se zdravo zubno tkivo čuva od preteranog brušenja. Ipak, gingivalni rub krune je tanji nego kod prethodna dva oblika demarkacije, pa je mehanička otpornost ovakvih kruna manja prilikom funkcionalnih opterećenja [13–15]. Ovakav tip preparacije je indikovan u slučajevima rotiranih i lingvalno nagnutih zuba, kao i zuba za jako produženom kliničkom krunom. Demarkaciona linija preparacije nije dovoljno jasna, pa se kao česta greška dešava da su gotove krune ili predugačke – kada prekrivaju i nebrušeni deo zuba, ili prekratke – kada ne prekrivaju brušene površine [12]. Metal-keramičke krune izrađene prema ovom tipu preparacije najčešće imaju predimenzioniran rub, jer na tanak metalni rub treba naneti keramički sloj i zatim kompletan rub smestiti u zonu gingivalnog sulkusa, što može provocirati hroničnu inflamatornu reakciju gingive. Zato se linijska demarkacija može primeniti ako je rub krune izrađen samo od metala [16].

Mogućnost za izradu keramičkih kruna na bazi linijske demarkacije pomenula je firma "Wolceram" (WDT, Ludwigshafen, Nemačka). Sistem je predstavljen javnosti 1999. godine, a kod nas se pojavio krajem 2004. Specifičnost ovog sistema je primena koloidnog rastvora *in-ceram alumina* ili *in-ceram zirconia* keramičkog materijala koji se putem elektroforeze nanosi na gipsani model brušenog zuba [17].

„Kopir-frez" sistem za izradu keramičkih kruna na bazi linijske demarkacije pod nazivom "Zirkonzahn", istoimene nemačke firme (Zirkonzahn GMBH, Gais, Germany) razvijen je 2005. godine. Sistem koristi sopstvene predsinterovane (polusinterovane) keramičke blokove, od kojih se postupkom manuelnog kopirajućeg frezovanja dobijaju keramičke supstrukture – kapice. Nakon osmočasovnog sinterovanja u specijalnoj peći, ove supstrukture dobijaju definitivni oblik i čvrstoću sinterovanog cirkonijum-dioksida. Sistem "Zirkonzahn" veoma je ekonomičan i pojednostavljen sistem, koji uz minimalnu obuku zubnih tehničara omogućava izradu različitih keramičkih nadoknada, od pojedinačnih kruna do višečlanih mostova.

Cilj ovog rada bio je da se na eksperimentalnom modelu utvrdi otpornost na lom keramičkih kruna izrađenih na osnovu linijske demarkacije preparacije, i izvrši komparativna analiza u odnosu na eksperimentalne vrednosti otpornosti na lom keramičkih kruna izrađenih na osnovu preparacije oblika pravouglog stepenika sa unutrašnjim zaobljenjem.

Metode

Nosači keramičkih kruna izrađeni su od nekarioznih ekstrahovanih prvih premolara, koji su izvađeni iz ortodontskih razloga (slika 1). Do početka ispitivanja ekstrahovani zubi su čuvani na sobnoj temperaturi u 0,1% rastvoru timola, kao antibakterijskom i antioksidativnom sredstvu, ne duže od tri meseca. Ukupno 60 premolara podeljeno je u dve eksperimentalne grupe: grupu A u kojoj se nalazilo 30 zuba planiranih za linijsku preparaciju i grupu B sa 30 zuba planiranih za preparaciju oblika stepenika pod uglom od 90°, sa unutrašnjim zaobljenim uglom.

Sl. 1 – Premolari ekstrahovani iz ortodontskih razloga

Da bi se imitirala fiziološka pokretljivost zuba, zubni korenovi su obloženi tankim slojem gumaste smole do nivoa 2 mm ispod cementnogleđne granice. Ovaj sloj, debljine 0,25

mm, dobija se kao imitacija periodontalne membrane premazivanjem korena gotovim fabričkim preparatom – Anti-Rutsch-Lack (Wenko-Wenselaar GmbH, Germany). Zubni korenovi zatim su uronjeni u samovezujući akrilat "Technovit" (Heraeus Kulzer GmbH, Germany), koji imitira koštanu potporu zuba. Zamešani akrilat stavljen je u posebne plastične kalupe – posude, i zubi su uronjeni u njega pomoću nosača do potpunog vezivanja akrilata (slika 2).

Sl. 2 – Premolar postavljen u autopolimerizujući akrilat

Preparacijom (brušenjem) zuba obezbeđuje se prostor za buduću keramičku krunu. Većina proizvođača CAD-CAM sistema daje sledeće smernice za redukciju zubne supstance: okluzalna redukcija od 1,5 do 2 mm, aksijalna redukcija od 1 do 2 mm, demarkaciona linija preparacije u vidu pravouglog stepenika sa unutrašnjim zaobljenjem, ili u vidu polužleba.

Preparaciju zuba za prihvatanje krune izvršio je jedan operator – kliničar, koristeći odgovarajući komplet bušilica za uklanjanje zubne supstance i postizanje željene forme preparacije – komplet oznake 800-841-4522 (Brasseler, USA). Preparacija je izvedena turbinskim radnim nastavkom modela Sirona T1 (Siemens, Germany) uz hlađenje vodenim sprejom. Kod oba tipa preparacije aksijalna konvergencija iznosila je 6°, dok je stepenik prepariran pod uglom od 90° sa unutrašnjim zaobljenjem ukupne širine od 1mm (slika 3).

Sl. 3 – Ispreparisani premolari: uzorak levo – preparacija sa stepenikom; uzorak desno – linijska preparacija

Preko ispreparisanih zuba uzet je finalni otisak dvofaznom metodom pomoću silikonskih otisnih masa tipa Express (3M Espe, St. Paul, USA). Otisci su izliveni tvrdim gipsom tipa Fujirock (GC, Europe).

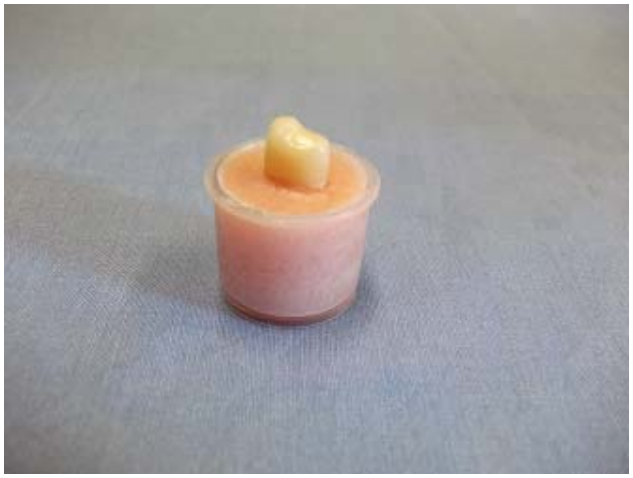
Kod obe eksperimentalne grupe, keramičke krune izrađene su od dve vrste gradivnih keramičkih materijala: cirkonijumske keramike za izradu supstrukture i kompatibilne feldspatne keramike za prekrivanje supstrukture i dobijanje definitivne morfologije krune premolara. Tehnička aparatura predstavlja „kopir frez" sistem za izradu keramičkih kruna na bazi linijske demarkacije pod nazivom „ZirkonZahn", istoimene nemačke firme (slika 4). Fabrički blokovi cirkonijum-dioksida pod nazivom „ICE Zirconia Blanks" (ZirkonZahn GMBH, Gais, Germany) izrađuju se u različitim veličinama prema postojećoj indikaciji – za izradu pojedinačnih kruna pa sve do jednokomadnih mostova od 16 članova. Blokovi se veoma lako mašinski obrađuju jer cirkonijum nije prethodno sinterovan, već je samo tvrdo presovan i ima veoma visoku primarnu gustinu. Blokovi se dobijaju postupkom hladnog izostatskog presovanja čime nastaju keramičke preforme, koje svojim izgledom podsećaju na kredu i nazivaju se svež ili sirovi cirkonijum.

Sl. 4 – Uređaj za kopirajuće frezovanje keramičkih blokova, tipa "Zirkograph" (ZirkonZahn, Germany)

Debljina sinterovanog jezgra izrađenog od cirkonijumske keramike iznosila je 0,5 mm što je preporuka proizvođača za izradu pojedinačnih kruna premolara. Ova debljina izrađivana je uniformno na svim površinama brušenih zuba. Debljina jezgra kontrolisana je meračem debljine materijala marke Renfert. Merena je debljina kompozitnih supstruktura (služe kao model za kopiranje), koja je uvećana za iznos kasnije kontrakcije sinterovanja cirkonijumske keramike. Debljina gotovih cirkonijumskih supstruktura kontrolisana je istim meračem i po potrebi korigovana prikladnim dijamantskim rotirajućim brusnim elementima.

Materijal za prekrivanje keramičkih supstruktura (fasetna keramika) distribuira se pod imenom "ICE Zirconia Ceramics". Materijal se koristi za definitivno modelovanje i sinterovanje zubne nadoknade pri čemu se dobija željena morfologija zuba koji se nadoknađuje.

Gotove krune cementirane su za zube nosače upotrebom kompozitnog adhezivnog sistema sa dvostrukim (svetlosnim i hemijskim) vezivanjem. Korišćen je adhezivni cement "Panavia F" proizvođača "Kuraray" (Tokyo, Japan). Posle nanošenja cementa uzorci su držani pod statičkim pritiskom od 40 N u trajanju od 7 min što predstavlja vreme vezivanja ovog cementa (slika 5).

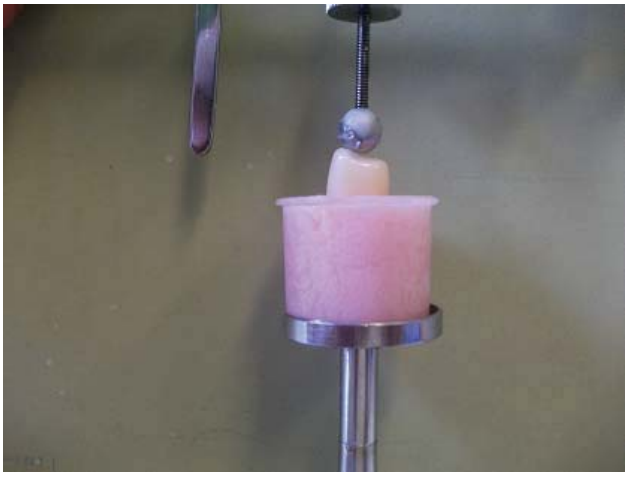


Sl. 5 – Keramička kruna cementirana na ispreparisanim premolarima

Za procenu mehaničke otpornosti korišćen je test pritiska sa sferičnim opterećenjem. To je najčešće korišćeni test za procenu čvrstoće keramičkih kruna, blizak realnoj kliničkoj situaciji. Univerzalna elektromehanička mašina za testiranje materijala firme Zwick, tip 1464 (Ulm, Germany) kretala se brzinom 0,5 mm/min do pojave loma keramičkih kruna (slika 6).

Sl. 6 – Uređaj za ispitivanje otpornosti materijala tipa "Zwick 1464" (Zwick, Germany)

Oštećenje koje se registrovalo podrazumevalo je potpun lom ispitivanih kruna, što se odnosilo na lom fasetne keramike i samog jezgra kruna izrađenog od cirkonijumske keramike. Dinamometar Zwick ima mogućnost registrovanja najveće sile otpornosti koja nastaje u materijalu pre potpunog loma krune što predstavlja meru otpornosti na lom ispitivanih kruna izraženu u njutnima (N). Na glavi mašine je montirana keramička kuglica prečnika 6 mm, koja je delovala normalno na centralnu zonu grizne površine svake ispitivane krune preko folije od kalaja debljine 1 mm da bi se postigla homogena distribucija napona u materijalu (slika 7). Sila pritiska potrebna da dovede do potpunog loma krune je automatski beležena na displeju uređaja, posle čega su oštećene krune fotografisane (slika 8). Klinički prihvatljivom mehaničkom otpornošću smatrale su se vrednosti veće od 1 000 N (100 kg).



Sl. 7 – Test vertikalnog opterećenja do loma keramičke krune (u alatu za mehaničko testiranje)

Sl. 8 – Lom keramičke krune pod dejstvom opterećenja

Istraživanje je sprovedeno kao eksperimentalna studija. U statističkoj obradi je primanjen deskriptivni statistički metod, a rezultati su predstavljeni kao srednja vrednost i standardna devijacija. Značajnost razlika između obeležja posmatranja utvrđena je Studentovim *t*-testom i prihvatana na nivou od 0,05 i većem.

Rezultati

Rezultati određivanja otpornosti na lom cirkonijumskih keramičkih kruna izrađenih na bazi linijske demarkacije preparacije i demarkacije oblika stepenika prikazani su u tabeli 1.

Tabela 1

Otpornost na lom keramičkih kruna izrađenih na osnovu linijske demarkacije i demarkacije (A) oblika stepenika (B) iskazana u Njutnima (N)

Grupa uzoraka	Broj merenja	$\bar{x} \pm SD$	(min–max)
A	30	2 214 ± 149*	(1 947–2 352)**
B	30	2 090 ± 164	(1 855–2 204)

SD – standardna devijacija; min – minimalna vrednost; max – maksimalna vrednost
***p* < 0,01; ** *p* < 0,05**

Obe grupe ispitivanih uzoraka demonstrirale su srednju vrednost otpornosti na lom veću od 2 000 N.

Prosečna vrednost otpornosti na lom keramičkih kruna u grupi uzoraka izrađenih na osnovu preparacije sa stepenikom, iznosila je 2 214 N. U ovoj grupi izmerena je i najveća vrednost otpornosti na lom od svih ispitivanih kruna koja je iznosila 2 352 N. Najniža utvrđena otpornost u ovoj grupi kruna imala je vrednost od 1 947 N.

Krune iz grupe uzoraka izrađenih na osnovu linijske preparacije pokazale su manju prosečnu vrednost otpornosti na lom u odnosu na prethodnu grupu, i ona je iznosila 2 090 N. U ovoj grupi izmerena je najmanja vrednost otpornosti na lom od svih ispitivanih uzoraka – 1 855 N. Maksimalna vrednost otpornosti na lom u ovoj grupi kruna bila je 2 204 N.

Utvrđena je statistički značajna razlika između prosečnih vrednosti ispitivanih parametara, pri čemu je otpornost na lom kruna izrađenih na bazi preparacije sa stepenikom bila veća od kruna izrađenih na osnovu linijske preparacije ($p < 0,01$). Takođe, utvrđena je statistički značajna razlika kada se porede maksimalne i minimalne izmerene vrednosti otpornosti na lom u obe grupe uzoraka ($p < 0,05$).

Diskusija

Funkcionalna trajnost keramičkih zubnih nadoknada u prvom redu zavisi od njihove mehaničke čvrstoće – otpornosti na lom. Cirkonijumska keramika ima veliku otpornost na lom protetske konstrukcije u toku opterećenja zahvaljujući svojim strukturnim osobinama.

Veliki broj kliničkih i laboratorijskih ispitivanja do sada je bio vezan za otpornost na lom keramičkih kruna izrađenih na bazi preparacije sa stepenikom [7, 8,18–22]. Istraživanja na bazi linijske preparacije uglavnom su sprovođena u vezi sa njihovim rubnim zaptivanjem i merenjem marginalne diskrepance [23, 24].

Akesson i sar. [24] eksperimentalnim ispitivanjima pokazali su da mehanička otpornost keramičkih kruna izrađenih na linijskoj preparaciji zuba u velikoj meri zavisi od debljine cirkonijumske supstrukture.

Rezultate je potrebno dovesti u vezu sa prosečnim mastikatornim silama u bočnoj regiji (regiji premolara i molara). Većina autora sugerisala je da funkcionalna sila od 500 N predstavlja fiziološki maksimum u prirodnoj denticiji [25–27]. Autori smatraju da se mastikatorne sile kreću u rasponu od 50 do 250 N u toku normalne mastikacije, a preko 500 u slučaju parafunkcija kao što je bruksizam. Zbog toga Tinschert i sar. [28] smatraju da se keramičke krune za bočne zube mogu prihvatiti kao terapijska mogućnost jedino ako je njihova minimalna otpornost na lom 500 N. Tako se može održati sigurna distanca u odnosu na prosečne sile žvakanja u bočnoj regiji zubnog niza. Veliki broj keramičkih sistema danas može da pređe tu tehnološku granicu.

Poznato je da dentalna keramika može da podlegne degradaciji sopstvenih mehaničkih osobina što se dovodi u vezu sa starenjem materijala [29]. Ovakvo smanjenje mehaničke otpornosti cirkonijuma može biti uzrokovano boravkom nadoknade u vlažnoj sredini i uticajem periodičnog opterećenja slabijeg intenziteta [30]. Dakle, usled kombinovanog dejstva pljuvačke i cikličnog mehaničkog opterećenja funkcionalna otpornost cirkonijumskih zubnih nadoknada može opasti do 50% u odnosu na prvobitnu otpornost materijala pre izlaganja ovim faktorima [31–33]. Schmitt i sar. [34] ispitivali su otpornost na lom cementiranih cirkonijumskih keramičkih kruna prednjih zuba izrađenih na bazi linijske preparacije u uslovima funkcionalnih opterećenja kod 19 bolesnika, kroz period od tri godine, pri čemu ni u jednom slučaju nisu registrovali makroskopska oštećenja keramike.

U ovoj studiji keramičke krune iz obe grupe imale su otpornost na lom veću od 2 000 N. Ako se pretpostavi da u toku funkcionalnih opterećenja u ustima usled starenja materijala dođe do degradacije čvrstoće materijala, otpornost na lom ispitivanih kruna će se smanjiti do vrednosti nešto većih od 1 000 N. Sa ovim vrednostima i dalje će se održati dvostruko veća distanca do minimalno propisanih vrednosti od 500 N.

Dobijeni rezultati su približni rezultatima Tinscherta i sar. [35] koji su dobili vrednosti otpornosti na lom od 1 937 N za nefasetirani cirkonijum i 2 289 N za cirkonijum obložen fasetnom keramikom. Sundh i sar. [36] dobili su vrednosti od 2 237 N i 1 973 N za dve grupe cirkonijumskih kruna obloženih različitom vrstom fasetne keramike. Takođe, oni su ispitivali otpornost cirkonijumskih konstrukcija posle dinamičkog opterećenja u vodi i dobili vrednosti od 1 450 N, odnosno 1 900 N [36].

Kao posledica supkritičnog rasta pukotina u dentalnoj keramici pod uticajem opterećenja koje dovodi do zamora materijala, keramika gubi i do 50% od svoje inicijalne čvrstoće. Ova degradacija mehaničke otpornosti mora se uzeti u obzir prilikom određivanja minimalne zahtevane otpornosti na lom koja će omogućiti dugotrajnu kliničku stabilnost nadoknade [37, 38]. Zato se čini razumnim predlog da inicijalna otpornost na lom keramičkih kruna za bočne zube treba da iznosi 1 000 N.

Zaključak

Sprovedenim ispitivanjem utvrđena je visoka eksperimentalna otpornost na lom cirkonijumskih keramičkih kruna izrađenih na osnovu linijske preparacije zuba. Savremeni polikristalni cirkonijum sa sadržajem cirkonijum-dioksida približno 95%, zahvaljujući svojoj jednofaznoj homogenoj mikrostrukturi, omogućava izradu kruna velike čvrstoće. Otpornost na lom ovakvih kruna je na dovoljnoj distanci u odnosu na minimalno propisane vrednosti funkcionalnog opterećenja.

Da bi se dala preporuka za kliničku primenu cirkonijumskih keramičkih kruna na bazi linijske demarkacije preparacije potrebna su dodatna dugoročna ispitivanja ovih kruna u uslovima *in vivo*, odnosno praćenje njihove mehaničke otpornosti u uslovima realnog funkcionalnog opterećenja kroz duži vremenski period. Ovo je potrebno zbog moguće degradacije mehaničkih osobina cirkonijumske keramike pod uticajem dugotrajnog periodičnog opterećenja u vlažnoj sredini.

Potrebno je uzeti u obzir i kvalitet rubnog zaptivanja – marginalne adaptiranosti ovako izrađenih keramičkih kruna, jer je precizno izrađen rub krune sa dobrim rubnim zaptivanjem jedan od najvažnijih uslova za očuvanje zdravlja gingive. Moguće proizvoljnosti u lokalizaciji gingivalnog ruba krune kod linijske demarkacije preparacije limitiraju parodontoprotektivnu dimenziju cementirane fiksne nadoknade i potenciraju gingivalni inflamatorni odgovor.

Na osnovu svega iznetog može se očekivati suženo indikaciono područje za kliničku primenu ovako dizajniranih keramičkih kruna.

L I T E R A T U R A

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Uticaj različitih režima insulinske terapije na kvalitet života obolelih od dijabetesa melitusa tipa 1

Different insulin treatment regimens in patient with diabetes mellitus type 1: Effects on quality of life

Jelena Stojanović*, Dragoslav Milošević*, Ilija Antović†, Goran Sekulić‡, Teodora Beljić-Živković§

***Odeljenje za gerijatriju, §Odeljenje za endokrinologiju, Kliničko-bolnički centar „Zvezdara“, Beograd, Srbija; †Fakultet organizacionih nauka, Univerzitet u Beogradu, Beograd, Srbija; ‡Ministarstvo odbrane, Univerzitet odbrane u Beogradu, Beograd, Srbija**

Apstrakt

Uvod/Cilj. Uprkos savremenom lečenju dijabetesa melitusa (DM), jedna polovina bolesnika ne postiže optimalnu metaboličku kontrolu. S obzirom na veliko psihičko opterećenje obolelih od DM, cilj ovog rada bio je da ispita uticaj različitih režima insulinske terapije, kvaliteta glikoregulacije i prisustva vaskularnih komplikacija na subjektivnu procenu bolesnika o njihovom kvalitetu života. **Metode.** Bolesnici lečeni od DM tipa 1 (n = 122) kontrolisani u endokrinološkoj ambulanti Kliničko-bolničkog centra „Zvezdara“ svrstani su u četiri grupe prema režimima insulinske terapije: 26 bolesnika bilo je na kontinuiranoj supkutanoj insulinskoj infuziji insulinskom pumpom, 30 bolesnika na konvencionalnoj insulinskoj terapiji, 33 na intenziviranoj terapiji humanim insulinima, a 33 na intenziviranoj terapiji insulinskim analozima. Procena kvaliteta života vršena je pomoću tri upitnika: WHO-5 (za procenu emocionalnog blagostanja), SF-36 (opšta zdravstvena anketa) i ITAS upitnik (za procenu stava prema insulinskoj terapiji). Procena metaboličke kontrole vršena je analizom glikoliziranog hemoglobina (HbA1c), lipidnog statusa i prisustva glikoziliranog komplikacija. U ovoj studiji preseka korišćene su sledeće metode statističke analize: deskriptivna statistika, *t*-test, χ^2 test, tabele kontingencije, ANOVA i metode korelacije. **Rezultati.** Bolesnici na insulinskoj pumpi imali su značajno bolju metaboličku kontrolu od drugih bolesnika, naročito od onih na konvencionalnoj terapiji (HbA1c na pumpi 7,07 ± 1,48% *vs.* HbA1c na konvencionalnoj terapiji 10,04 ± 1,44; $p = 0,000$). Nije uočena razlika među grupama na intenziviranoj terapiji humanim insulinima ili insulinskim analozima. Dobra metabolička kontrola značajno je uticala na kvalitet života. Postojanje retinopatije i nefropatije značajno je umanjilo fizičko blagostanje, a polineuropatije i kardiovaskularnih komplikacija i fizičko i mentalno blagostanje. **Zaključak.** Izbor režima insulinske terapije značajno utiče ne samo na metaboličku kontrolu, nego i na kvalitet života bolesnika.

Ključne reči:
dijabetes melitus, insulin-zavisni; lečenje; kvalitet života; upitnici.

Abstract

Background/Aim. Despite of contemporary diabetes mellitus (DM) treatment, one half of patients do not achieve an optimal metabolic control. Considering great psychological burden of diabetic patients, the purpose of this study was to assess the effect of different insulin treatment regimens, glycemic control and the presence of vascular complications on self-reported well-being and quality of life (QoL) of subjects with type 1 DM. **Methods.** The patients with type 1 DM (n = 122) recruited from the outpatient Diabetes Endocrinology Clinic of Zvezdara University Medical Center were divided into 4 groups according to the specific treatment regimen: 26 were on continuous subcutaneous insulin infusion (CSII), 30 on conventional insulin therapy, 33 on multiple daily injections (MDI) with human insulins, and 33 on MDI with insulin analogues. QoL was assesed by self-reported well-being with the following questionnaires: WHO-5 item Well Being Index (WHO-5), 36 item Short Form (SF-36) survey, and Insulin Treatment Appraisal Scale (ITAS). Objective metabolic control was assessed by glycosylated hemoglobin (HbA1c), lipid levels and the presence of vascular complications. Statistical analyses used in this cross-sectional study included: descriptive statistics, Student's *t*-test, Chi-sqare test, contingency tables, ANOVA and correlation methods. **Results.** The patients on CSII had significantly better metabolic control than all other treatment groups, especially when compared to the one on conventional therapy (CSII HbA1c 7.07 ± 1.48% *vs* conventional therapy, HbA1c 10.04 ± 1.44; $p = 0.000$). No significant difference in glycemic control was observed between patients on MDI with human insulins and insulin analogues. Good glycemic control significantly influenced the reported QoL. The patients with retinopathy and nephropathy reported significantly lower physical well-being, and the patients with polyneuropathy and cardiovascular complications reported also lower psychological well being. **Conclusions.** Insulin treatment regiment selection affects not only objective metabolic control, but also QoL.

Key words:
diabetes mellitus, type 1; therapeutics; quality of life; questionnaires.

Correspondence to: Jelena Stojanović, Kliničko bolnički centar „Zvezdara“, Odeljenje za gerijatriju, Zmaja od Noćaja 14, 11000 Beograd, Srbija. Tel.: +381 63 779 32 47, +381 11 2181 868. E-mail: j.vukcevic@gmail.com

Uvod

Dijabetes melitus (DM) je jedan od ključnih zdravstvenih problema u svetu [1]. Uprkos savremenim terapijskim režimima, 50% osoba sa DM ne postigne zadovoljavajuću metaboličku kontrolu, što povećava rizik od vaskularnih komplikacija [2]. Hronične komplikacije odgovorne za visok morbiditet i mortalitet od DM, značajno umanjuju kvalitet života obolelih [3]. Rizik od mikrovaskularnih komplikacija povećava se sa dužinom trajanja hiperglikemije [4–6], mada i genetska sklonost igra izvesnu ulogu u njihovom nastajanju [7]. Za nastanak makrovaskularnih komplikacija DM, međutim, hronična hiperglikemija, dislipidemija i hipertenzija su podjednako važni [8]. Po preporukama Evropskog udruženja za proučavanje DM (EASD) i Evropskog udruženja kardiologa (ESC) vrednosti glikoziliranog hemoglobina (HbA1c) kod obolelih od DM tipa 1 trebalo bi da budu do 6,5%. Ciljne vrednosti krvnog pritiska trebalo bi da su niže od 130/80 mmHg, a kod već razvijene proteinurije (od preko 1 g/dan), niže i od 125/75 mmHg. Po ovim preporukama, vrednost ukupnog holesterola trebalo bi održavati ispod 4,5 mmol/L, triglicerida ispod 1,7 mmol/L; lipoproteina niske gustine (LDL) holesterola ispod 1,8 mmol/l; lipoproteina visoke gustine (HDL) holesterola kod muškaraca bi trebalo održavati iznad 1,0, a kod žena iznad 1,2 mmol/L [8].

Psihosocijalni teret života obolelih od DM do nedavno je bio slabo ispitivan. Prve kvantitativne podatke koji se odnose na stavove, želje i potrebe osoba sa DM obezbedila je studija *Diabetes Attitudes, Wishes and Needs* (DAWN) [9–11]. Naime, oboleli od hroničnih bolesti mnogo češće pate od depresije u odnosu na opštu populaciju i pokazuju znatno niži stepen blagostanja i kvaliteta života. Pojam „kvalitet života“ definisan je osećanjem prema fizičkom, emotivnom i socijalnom aspektu života sa tegobama nastalim usled hroničnog oboljenja [12]. Procena kvaliteta života bolesnika od strane lekara nije uvek jednaka sa subjektivnom procenom samog bolesnika. Veliki je uticaj psihosocijalnih i kulturnih faktora na subjektivnu procenu. Sve više se pokazuje potreba za prepoznavanjem patnje bolesnika sa DM i njihove porodice usled ograničenja sa kojima se suočavaju, gubitka spontanosti u svakodnevnim aktivnostima, kao i potištenosti zbog pojave komplikacija [13]. Psihosocijalna istraživanja ukazuju na zajedničku ulogu psihosocijalnih činilaca na sve aspekte lečenja DM [14, 15]. Negativni stavovi i psihološki problemi poput depresije, anksioznosti i poremećaja ishrane česti su u DM i mogu doprineti lošem ishodu lečenja [16, 17]. Psihološki tretman može poboljšati samokontrolu glikoregulacije i kvalitet života [18, 19].

Režim izbora za postizanje dobre metaboličke kontrole u DM tipa 1 je intenzivirana insulinska terapija (IIT) [20]. U svakodnevnoj praksi to je još uvek bazal-bolusni režim humanim insulinima ili insulinskim analozima, mada najbolje rezultate pokazuje kontinuirana supkutana insulinska infuzija (*continuous subcutaneous insulin infusion therapy* – CSII). Njenom primenom obezbeđuje se potpunija insulinizacija, još više se smanjuju variranja glikemije, pa i broj ozbiljnih hipoglikemija [21]. U praksi se često odlaže intenziviranje terapijskog režima, čak i u dijabetesu tipa 1, zbog psihološke barijere bolesnika [22, 23].

Cilj ovog rada bio je da ispita uticaj režima insulinske terapije, kvaliteta glikoregulacije i prisustva vaskularnih komplikacija na doživljaj kvaliteta života bolesnika sa DM tipa 1.

Metode

Ovom studijom preseka bile su obuhvaćene 122 osobe obolele od DM tipa 1, starosti od 19 do 60 godina, svrstane u četiri grupe prema režimu insulinske terapije: 33 ispitanika bilo je na IIT humanim insulinima, 30 na konvencionalnoj insulinskoj terapiji sa dve doze fiksne mešavine insulina, 33 na IIT insulinskim analozima i 26 na režimu CSII. Bolesnici prve tri grupe javljali su se na redovne kontrole u endokrinološku ambulantu Kliničko-bolničkog centra „Zvezdara“ od januara 2007. do februara 2008. Bolesnici četvrte grupe, koji su bili na insulinskoj pumpi, kontrolu svoje bolesti vršili su Klinici za endokrinologiju, dijabetes i bolesti metabolizma Kliničkog centra Srbije, a njih smo kontaktirali radi sprovođenja pomenutih procedura.

Ispitanici su zamoljeni da popune upitnike o kvalitetu života i stavu prema insulinskoj terapiji. Za procenu stava prema režimu sopstvene insulinske terapije korišćen je deo upitnika za bolesnike iz studije DAWN, tzv. *Insulin Treatment Appraisal Scale* (ITAS) upitnik[24]. Za subjektivnu procenu kvaliteta života korišćeni su indeks Svetske zdravstvene organizacije (SZO) za procenu blagostanja [*The World Health Organisation 5-Item Well-Being Index* (WHO-5 index)] [25], kao i zdravstvena anketa SF-36 [26] (36-*item Short Form survey*).

Upitnik ITAS je dvodimenzioni upitnik i sadrži 20 tvrdnji koje odražavaju pozitivan ili negativan stav bolesnika prema insulinskoj terapiji. Bolesnik na Likertovoj skali označava u kojoj meri se slaže, od „uopšte se ne slažem“ do „slažem se u potpunosti“ (od 1 do 5). Veći broj bodova označava negativniji stav, s obzirom na to da je većina tvrdnji negativno orijentisana.

Indeks WHO-5 ispituje emocionalno blagostanje. Ispitanik označava stepen do koga su dati navodi bili prisutni u poslednje 2 nedelje, od 0 (nikada), do 5 (sve vreme). Zbir se prikazuje na skali od 0–100, pri čemu veći zbir označava veće emocionalno blagostanje.

Upitnik SF-36 čini 36 pitanja podeljenih u 8 grupa, od kojih četiri grupe ispituju domen fizičkog zdravlja i to: opšti osećaj zdravlja (6 pitanja) ograničena fizička aktivnost zbog bolesti (10 pitanja), ograničeno ispunjavanje obaveza zbog somatskih problema (4 pitanja) i bol (2 pitanja). Sledeće četiri grupe čine domen mentalnog zdravlja: ograničeno ispunjavanje obaveza zbog emotivnih problema (3 pitanja), vitalnost (4 pitanja), mentalno zdravlje (5 pitanja), ograničena socijalizacija (2 pitanja). Konačni rezultat svake grupe izražen je kao procenat maksimalnog zbira (100% predstavlja osećaj najboljeg zdravlja).

Metabolička kontrola DM tipa 1 procenjivana je na osnovu laboratorijskih parametara: HbA1c, ukupnog holesterola, HDL-holesterola, LDL-holesterola, triglicerida i mikroalbuminurije. Svakom ispitaniku urađen je fizikalni pregled i elektrokardiogram (EKG).

Dijagnozu dijabetesne retinopatije postavljao je oftalmolog pregledom očnog dna. Dijagnozu polineuropatije postavljao je neurolog na osnovu smanjene osetljivosti na pritisak mikrofilament metodom i testiranjem vegetativne neuropatije *Neuropad* testom [27]. Za dijagnozu nefropatije kriterijum je bio ponavljana mikroalbuminurija preko 30 mg/dan. Za potvrdu kardiovaskularnih komplikacija uzimano je postojanje ishemijskih promena na EKG-u ili pozitivan test opterećenja. Vrednosti HbA1c manje od 7% tretirane su kao idealna glikoregulacija, od 7,1 do 8,5% kao klinički zadovoljavajuća, a HbA1c preko 8,5% kao loša glikoregulacija. Vrednosti holesterola preko 5,2 mmol/L ili LDL-holesterola preko 3,2 mmol/L tretirane su kao hiperholesterolemija, a vrednosti triglicerida preko 1,7 mmol/L kao hipertrigliceridemija [8, 28].

Prilikom statističke obrade podataka korišćene su metode deskriptivne statistike uključujući određivanje frekvencija, procenata, aritmetičkih sredina, i standardnih devijacija. Procena značajnosti razlika aritmetičkih sredina vršena je primenom Studentovog *t*-testa (značajnost na nivou $p < 0,05$). Značajnost hipoteze o normalnosti raspodele testirana je primenom χ^2 testa, kao i tabelama kontigencije. Primenjene su metode multivarijantne statistike uključujući analizu varijanse (ANOVA), a povezanost varijabli procenjivana je korišćenjem metoda korelacije. Analiza svih podataka vršena je pomoću softvera SPSS za Windows – verzija 12,0.

Uporedivost skorova na upitnicima omogućena je rekodiranjem vrednosti odgovora prema ITAS upitniku, tako da veći skor na svakom upitniku (i WHO-5 i SF-36) pokazuje negativniji stav prema postavljenoj tvrdnji.

Rezultati

Osnovne epidemiološke karakteristike svih bolesnika prikazane su u tabeli 1. Grupe ispitanika bile su slične po dobnoj strukturi, dužini trajanja DM i obrazovanju. Značajna razlika nađena je jedino u zastupljenosti polova ($\chi^2 = 18,592$, $p < 0.01$).

Mikro- i makrovaskularne komplikacije bile su ravnomerno zastupljene unutar grupa bolesnika na različitim terapijskim režimima (tabela 1).

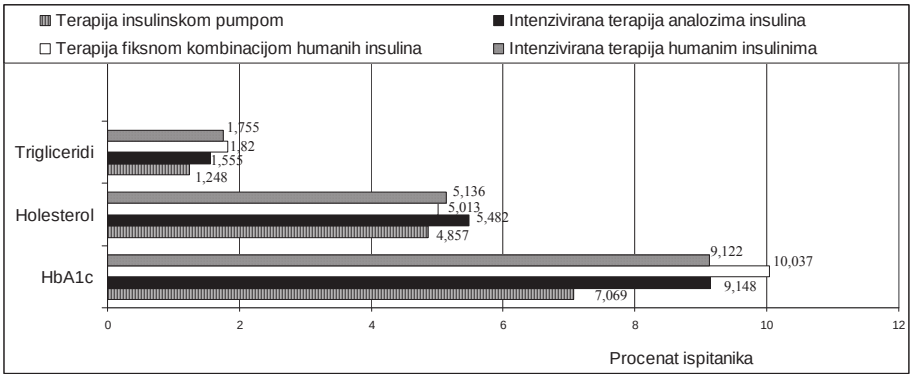
Analiza prosečnih vrednosti HbA1c pokazala je da su ispitanici na insulinskoj pumpi imali statistički značajno niži HbA1c u odnosu na ostale grupe [($F(3,118) = 9,788$; $p = 0,000$)]. Nije bilo razlike u vrednosti HbA1c među grupama na IIT humanim insulinom (9,122 ± 2,61%) i analozima insulina (9,148 ± 2,42%). Nije nađena razlika u prosečnim vrednostima holesterola i triglicerida između 4 grupe na različitim terapijskim režimima (slika 1).

Svi bolesnici popunili su sve upitnike. Upitnik ITAS, koji je analizirao stav prema insulinskoj terapiji, pokazao je da su osobe na insulinskoj pumpi osećale najveće zadovoljstvo terapijom, a najveću averziju prema terapiji imali su is-

Tabela 1

Epidemiološke i kliničko-patološke karakteristike obolelih od dijabetesa melitusa (DM) tipa 1

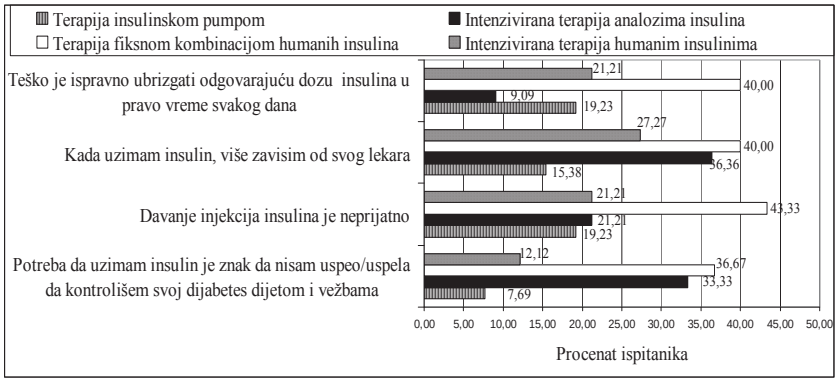
Parametri	Intenzivirana terapija humanim insulinima	Terapija fiksnom kombinacijom insulina	Intenzivirana terapija analozima insulina	Terapija insulinskom pumpom	Ukupno
Pol [n (%)]					
muški	19 (15,6)	22 (18,0)	21 (17,2)	5 (4,1)	67 (54,9)
ženski	14 (11,5)	8 (6,5)	12 (9,8)	21 (17,2)	55 (45,1)
Prosečno životno doba (god)	33,6 ± 11,1	34,2 ± 10,3	35,2 ± 10,8	30,8 ± 5,6	33,6 ± 9,9
Prosečna dužina trajanja DM (god)	13,1 ± 10,4	12,8 ± 8,6	14,9 ± 10,6	14,4 ± 6,9	13,8 ± 9,3
Komplikacije [n (%)]					
polineuropatija	12 (9,8)	15 (12,3)	10 (8,2)	6 (4,9)	43 (35,2)
retinopatija	9 (7,4)	16 (13,1)	10 (8,2)	8 (5,7)	43 (35,2)
nefropatija	7 (5,7)	12 (9,0)	8 (6,6)	7 (5,7)	34 (27,9)
kardiovaskularne komplikacije	3 (2,5)	5 (4,1)	3 (2,5)	3 (2,5)	14 (11,5)
Ukupno	33 (27,0)	30 (24,5)	33 (27,0)	26 (21,3)	122 (100)



Sl. 1 – Prosečne vrednosti glikoziliranog hemoglobina (HbA1c), holesterola i triglicerida kod bolesnika na četiri terapijska režima

pitanici na konvencionalnoj terapiji. Slika 2 prikazuje procenat ispitanika koji su na pitanja upitnika ITAS sa negativnom konotacijom prema insulinu odgovorili sa „slažem se u potpunosti".

[(F(3,118) = 3,457, p = 0,01)]. Bolesnici na konvencionalnoj terapiji ocenili su kao značajno lošije i svoje fizičko zdravlje (SF-36 za fizičko zdravlje) od drugih ispitanika [(F(3,118) = 6,586, p = 0,000)]; pokazali su i značajno lošiju ocenu svog



Sl. 2 – Odgovori na pitanja u upitniku o proceni lečenja insulinom (ITAS) sa negativnom konotacijom prema insulinskoj terapiji (pitanja br. 5, 12, 16, 20)

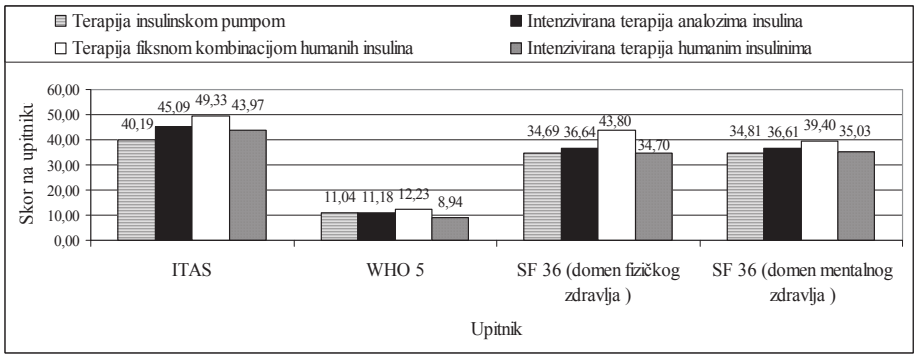
Najbolju ocenu svog mentalnog zdravlja (najmanji skor na SF-36 anketi) pokazala je grupa ispitanika na pumpi, a najlošiju grupa na konvencionalnoj terapiji. Takođe, najbolju ocenu svog fizičkog zdravlja na SF-36 anketi, kao i emocionalno blagostanje na WHO-5 indeksu, pokazale su osobe na CSII, a najlošiju osobe na konvencionalnoj insulinskoj terapiji.

Dakle, pokazana je tendencija grupe ispitanika sa insulinskom pumpom ka pozitivnijem stavu, tj. nižim zbirovima na svim upitnicima; zatim slede grupa na intenziviranoj terapiji humanim, pa na IIT insulinskim analozima, a sa najvišim prosečnim zbirovima na svim upitnicima bila je grupa na fiksnoj mešavini insulina. To odražava njen najnegativniji stav prema insulinu, najniži indeks blagostanja, kao i najlošiju procenu sopstvenog fizičkog i mentalnog zdravlja. Ovu tendenciju distribucije zbirova na upitnicima pokazali su bolesnici sa različitim režimima terapije (slika 3).

mentalnog zdravlja (SF-36 za mentalno zdravlje) nego bolesnici na insulinskoj pumpi i na IIT humanim insulinama [(F(3,118) = 3,136, p = 0,028)]. Međutim, u oceni svog emocionalnog blagostanja (WHO-5 upitnik) među ispitanicima na različitim režimima nije bilo razlike.

Uticaj komplikacija dijabetesa na parametre kvaliteta života

Ispitanici sa retinopatijom pokazali su značajno niži osećaj fizičkog zdravlja procenjenog SF-36 anketom (t = -3,036, p = 0,003). Isto su pokazale i osobe sa nefropatijom (t = -2,945, p = 0,004). Ove mikrovaskularne komplikacije nisu uticale na ocenu sopstvenog mentalnog zdravlja i emocionalnog blagostanja. Međutim, postojanje polineuropatije i kardiovaskularnih komplikacija pokazalo je uticaj na sve aspekte kvaliteta života. Naime, dijabetesna polineuropatija



Sl. 3 – Distribucija zbirova dobijenih odgovora na korišćenim upitnicima kod četiri grupe bolesnika

ITAS – Insulin Treatment Appraisal Scale
WHO 5 – The World Health Organisation 5-Item Well-Being Index
SF 36 – 36-item Short Form survey

Uticaj terapijskih režima na parametre kvaliteta života

Značajna razlika u stavu prema insulinskoj terapiji (upitnik ITAS), pokazana je između bolesnika na insulinskoj pumpi, kao najzadovoljnijih svojim režimom i onih na dve doze bifazičnim insulinima sa najnegativnijim stavom

značajno je umanjila osećaj fizičke sposobnosti (na SF-36 za fizičko zdravlje: t = -5,637, p = 0,000), osećaj mentalne sposobnosti (na SF-36 za mentalno zdravlje: t = -4,181, p = 0,000), kao i ocenu emocionalnog blagostanja (na WHO-5: t = -2,642, p = 0,009). Isto tako, postojanje kardiovaskularnih komplikacija pokazalo je značajan uticaj na ocenu sopstve-

nog fizičkog i mentalnog zdravlja (SF-36 za fizičko zdravlje: t = -5,248, p = 0,000; SF-36 za mentalno zdravlje: t = -2,763 p = 0,007), kao i na ocenu emocionalnog blagostanja (WHO-5 indeks: t = -2,109, p = 0,037).

Uticaj glikoregulacije na parametre kvaliteta života

Radi jasnijeg uvida u uticaj glikoregulacije na skorove korišćenih upitnika, vršena je dodatna analiza za koju su bolesnici svrstani u tri grupe: bolesnici koji imaju vrednost HbA1c do 7,0% činili su grupu sa idealnom glikoregulacijom; bolesnici koji su imali HbA1c između 7,1% i 8,5% činili su grupu sa zadovoljavajućom glikoregulacijom, a bolesnici sa HbA1c većim od 8,5% činili su grupu sa lošom glikoregulacijom.

Pokazano je značajno odstupanje grupe sa idealnom glikoregulacijom: na upitniku ITAS ta grupa je imala visoko pozitivniji stav prema svom terapijskom režimu [F(2,119) = 10,016; p = 0,000]; u upitniku WHO-5 [F(2,119) = 4,340; p = 0,015] pokazala je značajno viši stepen emocionalnog blagostanja, a u anketi SF-36 značajno višu procenu kako svog fizičkog zdravlja [SF-36 za fizičko zdravlje, F(2,119) = 5,823; p = 0,004], tako i mentalnog zdravlja [SF-36 za mentalno zdravlje, F(2,119) = 5,253; p = 0,007].

Diskusija

Prema našem saznanju, ovo je prvi rad koji je ispitivao stav dijabetičara sa DM tipa 1 prema insulinskoj terapiji, kao i uticaj stava prema terapiji na ocenu kvaliteta života. Ustanovili smo da izbor terapijskog režima utiče na objektivan ishod lečenja DM i može doprineti kvalitetu života. Ispitanici sa najuspešnijom glikoregulacijom imali su najpozitivniji odnos prema insulinskoj terapiji, kao i najbolji osećaj fizičkog i mentalnog zdravlja.

Do sada je mnogo studija poredilo terapijske režime u DM tipa 1, ali je samo nekoliko bilo fokusirano na aspekt kvaliteta života. U njima je korišćen upitnik *Diabetes Quality of Life Questionnaire* (DQOL), osmišljen za potrebe studije DCCT. Poredeći kvalitet života bolesnika na IIT i CSII, neke od tih studija su pokazale da među ovim grupama nema razlike u proceni kvaliteta života [29], dok su druge studije dokumentovale poboljšanje kvaliteta života kod bolesnika na insulinskoj pumpi [30–32]. Pomoću nešto senzitivnijeg upitnika, *Diabetes Specific Quality of Life Scale* (DQOLS) ustanovljeno je značajno poboljšanje kvaliteta života kod onih bolesnika koji su na insulinskoj pumpi [33].

Upitnik ITAS korišćen u ovoj studiji, osmišljen je za studiju DAWN, jednu od najvećih studija do sada sprovedenih u dijabetologiji. U njoj su, širom sveta, ispitivani nivo samokontrole bolesnika, psihološki poremećaji obolelih, kvalitet odnosa bolesnik-lekar, saradnja među onima koji sprovode lečenje, kao i teškoće u prihvatanju medikamentne terapije [11, 17]. Program DAWN, započet 2001. godine, predstavlja potpuno novi pristup DM jer mu je u centru pažnje upravo ličnost obolelog [2, 34]. Upitnik ITAS korišćen je i u istoimenoj ITAS studiji, a za procenu stava prema insulinu kod dijabetičara sa DM tipa 2. Cilj je bio analiza bespotrebnog odlaganja uvođenja insulinske terapije [24]. Validnost ITAS upitnika je u toj studiji potvrđena i to kao kratkog psihometrijskog testa koji je pokazao povezanost sa WHO-5 upitnikom za procenu emocionalnog blagostanja. Time je ITAS skrenuo pažnju na činjenicu da stav prema terapijskom režimu utiče na psihološko blagostanje obolelog.

Analizom strukture uzorka pokazano je da postoji razlika u polnoj strukturi (χ^2 = 18,592; p < 0.01). Ta razlika je uslovljena indikacijama za primenu insulinske pumpe u našoj zemlji (najčešće je dobijaju trudnice ili one žene koje žele trudnoću), zbog čega je zaključeno da je uzorak validan. Važno je napomenuti da su u studiji trudnice izostavljene zbog mogućeg uticaja trudnoće na subjektivnu procenu kvaliteta života [35].

Poređenjem parametara metaboličke kontrole među bolesnicima na različitim terapijskim režimima, utvrđena je značajna razlika u glikoregulaciji u korist grupe ispitanika na insulinskoj pumpi, sa najnižim prosečnim HbA1c, u odnosu na preostale tri grupe. Nisu uočene razlike u holesterolemiji i trigliceridemiji između grupa.

Ispitivanjem učestalosti javljanja vaskularnih komplikacija pokazano je da nema značajne razlike među grupama bolesnika na različitim terapijskim režimima, što je suprotno očekivanju da će bolesnici sa adekvatnom terapijom (na IIT ili na CSII) ređe imati komplikacije. To može biti povezano sa postojećim indikacijama za započinjanje terapije insulinskom pumpom ili insulinskim analozima. Naime, uslov za uvođenje ovih režima je verifikovana loša glikoregulacija na prethodnom terapijskom režimu, što praktično odgađa rano uvođenje optimalnog režima.

Analizom odgovora na upitnicima uočena je blago pozitivna ocena i stava prema insulinskoj terapiji i procene fizičkog i psihičkog blagostanja. U poređenju sa rezultatima studije DAWN, prikazani bolesnici imaju manji strah od hipoglikemija posle davanja insulina (45% *vs* 55% ispitanika u uzorku DAWN) i manje strahuju od povećanja telesne mase usled insulinske terapije (15% *vs* 45% DAWN ispitanika). Čak 87% naših ispitanika mišljenja je da insulin popravlja zdravlje (45% u studiji DAWN) [10, 11]. Ovi podaci su prilično ohrabrujući i skreću pažnju na činjenicu da su naši bolesnici, bar oni koji se javljaju u polikliničku službu radi praćenja, možda bolje informisani i edukovani od bolesnika iz sveta.

Odgovorima na upitnik ITAS najnegativniji stav prema insulinu pokazala je grupa bolesnika na konvencionalnoj terapiji. Ovo je očekivano, s obzirom na to da upravo ovi bolesnici često odbijaju intenziviranje terapije i uporno ostaju na dve doze insulina zbog svojih predubeđenja.

Upoređujući grupe bolesnika na IIT, grupa bolesnika na insulinskim analozima pozitivnije je odgovorila na pitanja koja su sa pozitivnom konotacijom prema insulinu i pokazala je više vere u svoj režim najsavremenijim dostupnim insulinima.

Najveća razlika nađena je između bolesnika na konvencionalnoj terapiji i onih koji imaju insulinsku pumpu. Bolesnici na insulinskoj pumpi pokazali su veliki spokoj i zadovoljstvo trenutnim načinom nadoknade insulina, a pokazali su čak i visoki stepen saradljivosti i motivisanosti da učes-

tvuju u ovom istraživanju, sa idejom da isticanjem prednosti, možda olakšaju dodelu insulinskih pumpi budućim bolesnicima. Zadovoljstvo bolesnika na insulinskoj pumpi najviše je vezano za fleksibilnost u svakodnevnim aktivnostima, dijeti i organizovanju slobodnog vremena [31, 32]. Međutim, važno je skrenuti pažnju na to da su ovi bolesnici pokazivali skoro jednaku odbojnost prema samom davanju injekcija insulina koliko i bolesnici na dve doze. Ujedno, ti bolesnici pokazali su i najveći strah od nastanka hipoglikemije posle davanja injekcija insulina (čak 57,69%), što sve može biti posledica navikavanja na lagodniji i bezbrižniji režim regulisanja glikemije insulinskom pumpom u odnosu na ranije iskustvo sa davanjem injekcija insulina.

Pokazana je značajna razlika u oceni fizičkog i mentalnog zdravlja među grupama. Za razliku od bolesnika na konvencionalnoj terapiji, bolesnici na IIT humanim insulinima i oni na insulinskoj pumpi pokazali su visoki stepen zadovoljstva svojim zdravljem. Međutim, u oceni emocionalnog blagostanja, bolesnici na različitim režimima nisu se bitno razlikovali.

Postojanje vaskularnih komplikacija pokazalo je najveći uticaj na subjektivnu ocenu fizičke spremnosti. Razumljivo je da osoba sa oštećenjem bilo kog organskog sistema ne doživljava svoje fizičko zdravlje, snagu i spremnost kao dovoljno dobro. Ali, postojanje senzitivne polineuropatije i kardiovaskularnih komplikacija pokazalo je i dodatni odraz na psihu bolesnika. To je najverovatnije vezano za konstantan osećaj bola koji ove komplikacije izazivaju, a bol je značajan faktor u nastanku depresije kod bolesnika [16, 36].

Praktično, to znači da svi bolesnici jednako nose emocionalni teret svoje bolesti, bez obzira na to kako je regulisana i koliko dobro prihvataju način lečenja.

Pokazavši da postoji značajna razlika u oceni mentalnog, emocionalnog i fizičkog blagostanja, a čak visokoznačajna razlika u stavu prema svojoj terapiji u zavisnosti od kvaliteta glikoregulacije, potvrdili smo da dobra glikoregulacija sama po sebi pozitivno utiče na kvalitet života dijabetičara [20, 37, 38].

Zaključak

Dijabetes melitus je veoma veliki psihološki teret za obolele. Pored straha od pojave komplikacija, bolesnici se suočavaju sa svakodnevnom, neprekidnom i neizbežnom insulinskom terapijom. U velikoj meri i ishod njihovog lečenja zavisi od toga kako prihvataju bolest. Potrebno je da ove osobe ne doživljavaju svoj terapijski režim kao dodatni socijalni, psihološki i emocionalni teret.

Pokazali smo da su bolesnici na insulinskoj pumpi bili najzadovoljniji svojim terapijskim režimom. Oni su, uz bolesnike na intenziviranoj terapiji analozima insulina imali najbolju metaboličku kontrolu i najbolje ocenjivali kvalitet svog života. Bolesnici na konvencionalnoj insulinskoj terapiji imali su najveću averziju prema insulinskoj terapiji, najlošiju metaboličku kontrolu i najmanje zadovoljstvo kvalitetom života. Na taj način, pokazali smo da izbor terapijskog režima utiče na objektivan ishod lečenja DM i da popravlja kvalitet života obolelih.

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Uticaj morfometrijskih osobina međukondilarne jame na povređivanje prednje ukrštene veze

The influence of the morphometric parameters of the intercondylar notch on rupture of the anterior cruciate ligament

Lazar Stijak*, Valentina Nikolić*, Miloš Mališ*, Ružica Maksimović†, Milan Aksić*, Branislav Filipović*

***Institut za anatomiju, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija;**
†Centar za magnetnu rezonancu, Klinički centar Srbije, Beograd, Srbija

Apstrakt

Uvod/Cilj. Morfometrijske osobine međukondilarne jame butne kosti predstavljaju jedan od bitnih faktora rizika od povređivanja prednje ukrštene veze (*ligamentum cruciatum anterio* – LCA). U morfometrijskim studijama kolena dva najčešće spominjana indeksa su indeks širine i indeks oblika međukondilarne jame. Cilj ovog rada bio je utvrđivanje morfometrijskih parametara međukondilarne jame kao faktora rizika od povređivanja LCA. **Metode.** Ispitivanjem je obuhvaćeno 99 bolesnika podeljenih u dve grupe. Ispitivana grupa sastojala se od 57 bolesnika koji su imali hroničnu nestabilnost kolena zbog ranije rupture LCA. Kontrolnu grupu sačinjavala su 42 bolesnika koji su u anamnezi imali povredu kolena, ali kod kojih nije dijagnostikovana ruptura LCA. Merenje širine i visine međukondilarne jame i epikondilarne širine vršeno je na snimku horizontalnog preseka dobijenog nuklearnom magnetnom rezonancom. Na osnovu tih vrednosti računati su indeks širine i indeks oblika međukondilarne jame. **Rezultati.** Utvrđeno je da je ispitivana grupa imala statistički značajno višu ($p < 0,05$) međukondilarnu jamu, kao i manji indeks oblika međukondilarne jame ($p < 0,05$) od kontrolne grupe. Razlika postaje visoko statistički značajna ($p < 0,01$) ako se posmatraju samo muškaraci, a gubi se ako se posmatraju žena ($p > 0,05$). Takođe, utvrđene su visoko statistički značajno veće vrednosti ($p < 0,01$) apsolutnih dimenzija morfometrijskih parametara distalnog okrajka butne kosti kod muškaraca nego kod žena, izuzev u slučaju međukondilarne visine unutar kontrolne grupe ($p > 0,05$). **Zaključak.** Povećana visina međukondilarne jame, kao i manja vrednost indeksa oblika udružene su sa rupturom LCA kod muškaraca ali ne i kod žena.

Ključne reči:
ligament, prednji ukršteni; koleno, povrede; femur; faktori rizika; magnetna rezonanca, snimanje.

Abstract

Background/Aim. Morpohometric parameters of the intercondylar notch of femur present one of the substantial risk factors for rupture of the anterior cruciate ligament (ACL). In morphometric studies of the knee the most often referred indexes are notch width index and notch shape index. The aim of this study was to identificate the morphometric parameters of the intercondylar notch as risk factors for ACL rupture. **Methods.** This study included 99 patients divided into two groups: the study group (n = 57) composed of patients with chronic instability of the knee because of previos rupture of the ACL, and the control group (n = 42) composed of patients with lesion of the knee, but without rupture of the ACL. Measuring the width and height of intercondylar notch and epicondylar width was observed on a horizontal MR section. According to these values notch width and notch shape indexes were calculated. **Results.** The study group had statistically significantly higher ($p < 0.05$) intercondylar notch and lesser notch shape index than the control group ($p < 0.05$). The difference was highly statistically significant ($p < 0.01$) only in males, but not in females ($p > 0.05$). Absolute dimensions of the morphometric parameters of the distal part of the femur had highly statatistically significant larger values ($p < 0.01$) in males than females, exept in case of the intercondilar height in the control group ($p > 0.05$). **Conclusion.** Enhanced height of the intercondylar notch as well as lesser value of the notch shape index are associated with rupture of the ACL in males but not in females.

Key words:
anterior cruciate ligament; knee injuries; femur; risk factors; magnetic resonance imaging.

Correspondence to: Lazar Stijak, Institut za anatomiju, Medicinski fakultet, dr Subotića 4/2, 11000 Beograd, Srbija.
Tel.: +381 63 1105 330; E-mail: lazar.stijak@gmail.com

Uvod

Na konferenciji u Hunt Valley-u, Maryland, 1999. godine *American Orthopaedic Society for Sports Medicine, the Orthopaedic Research and Education Foundation, the National Athletic Trainers Association Research and Education Foundation and the National Collegiate Athletics Association* [1] naveli su najznačajnije anatomske faktore rizika od povređivanja prednje ukrštene veze (*Ligamentum cruciatum anterius* – LCA). Oni se mogu svrstati u tri grupe: osobine međukondilarne jame (*fossa intercondylaris*) butne kosti, zadnji tibijalni nagib (*tibial slope*) i morfometrijske osobine LCA zgloba kolena. Anatomski parametri međukondilarne jame butne kosti bili su predmet izučavanja mnogih studija, ali se njihovi rezultati nisu uvek podudarali [2–8].

Međukondilarna jama nalazi se na zadnjoj strani distalnog okrajka butne kosti. Spolja je ograničavaju kondili butne kosti, a prednju granicu, krov međukondilarne jame, gradi distalni okrajak butne kosti. Proksimalnu granicu čini međukondilarna linija, a distalnu i zadnju granicu označavaju slobodne ivice kondila. Velikim brojem studija utvrđeno je da su uske međukondilarne jame povezane sa rupturom LCA [2, 4–6]. Međutim, Herzog i sar. [3] u svojoj studiji nisu potvrdili značaj međukondilarnog useka za povređivanje LCA.

Zbog velikih varijacija u telesnoj građi ispitanika, a samim tim i građe distalnog okrajka butne kosti, apsolutne veličine međukondilarne jame se uz pomoć apsolutnih veličina distalnog okrajka butne kosti relativizuju u indekse. U morfometrijskim studijama kolena dva najčešće spominjana indeksa su indeks širine međukondilarne jame i indeks oblika međukondilarne jame (*noch shape index* – NSI). Indeks širine međukondilarne jame definisali su Souryal i sar. [6] kao odnos širine međukondilarne jame, (*intercondylar width* – ICW) i širine distalnog dela butne kosti. Manja vrednost indeksa govori u prilog stenozi međukondilarne jame a samim tim i verovatnoća rupture LCA je veća. Takođe, isti autori [6] navode kritičnu vrednost ovog indeksa ispod koje je verovatnoća povređivanja LCA veća. Ona iznosi 0,2 za muškarce i 0,18 za žene.

Indeks oblika jame predstavlja odnos ICW i visine međukondilarne jame, *intercondylar height* (ICH) [9]. Hutchinson i sar. [10] na osnovu NSI podelili su jame na A-oblik i obrnuti U-oblik. Tanzer i sar. [11] smatraju da uske međukondilarne jame imaju više A-oblik, dok široke imaju obrnuti U-oblik. Anderson i sar. [12] u svojoj studiji pokazali su da oblik međukondilarne jame koreliše sa povredom LCA, odnosno da međukondilarne jame sa niskim NSI imaju veću verovatnoću povređivanja.

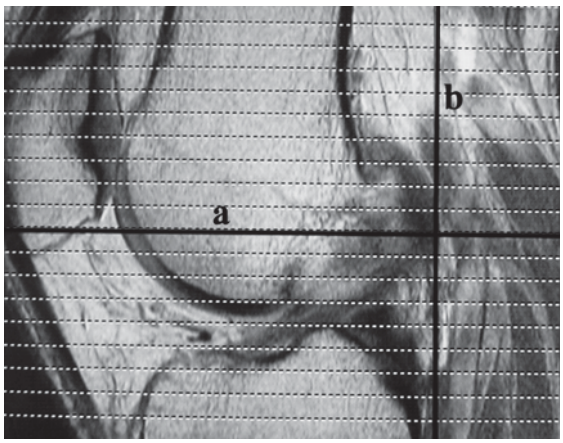
Cilj rada bio je da se utvrde morfometrijski parametari međukondilarne jame kao faktori rizika od povređivanja LCA.

Metode

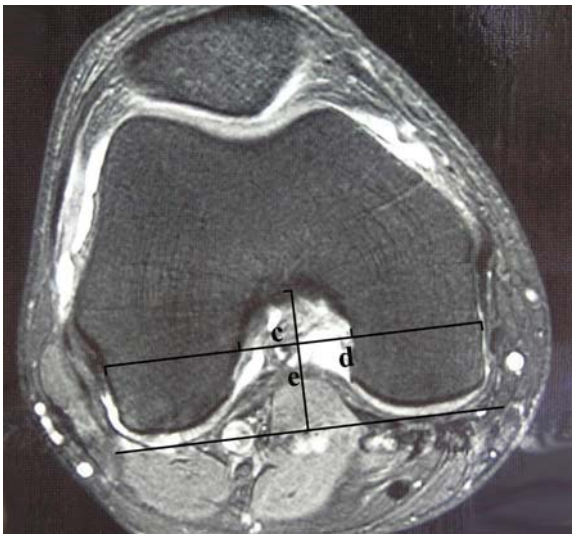
Sprovedena je retrospektivna studija u kojoj su, metodom slučajnog izbora formirane dve grupe bolesnika sa hirurškom intervencijom na zglobu kolena. Pre formiranja grupa, iz studije su bili isključeni bolesnici sa gonartrotičnim promenama i koštanim oštećenjima na zglobu kolena. Ispitivanu grupu sačinjavali su bolesnici koji su imali hroničnu nestabilnost kolena zbog ranije rupture LCA (57 bolesnika, 35 muškog i 22 ženskog pola). Kontrolnu grupu sačinjavali su bolesnici koji su u anamnezi imali povredu kolena, ali kod kojih nije dijagnostikovana ruptura LCA (42 bolesnika, 27 muškog i 15 ženskog pola). Kod svih bolesnika razlog hirurške intervencije bila je nekontaktna povreda zgloba kolena.

Prosečna starost bolesnika u ispitivanoj grupi iznosila je 30,4 ± 8,9 godina (od 15 do 48 godina), a u kontrolnoj 31,6 ± 11,4 (od 15 do 52 godine).

Merenje je vršeno na snimcima dobijenim magnetnom rezonancom (MR). Svi MR snimci napravljeni su upotrebom 1.5T MR. Merenje dimenzija međukondilarne jame vršeno je na horizontalnom snimku MR koji je prolazio kroz najposteriornije tačke unutrašnjeg i spoljašnjeg kondila butne kosti (slika 1). Na svakom snimku mereni su: ICW i epikondilarna širina (*epicondylar width* – EW) u nivou zatkolenog žleba (slika 2). Takođe, merena je i ICH kao najkraće rastojanje između najviše tačke međukondilarne jame i linije koja prolazi kroz najposteriornije tačke unutrašnjeg i spoljašnjeg kondila butne kosti (slika 2).



Sl. 1 – Izbor horizontalnog preseka (a) na sagitalnom snimku magnetne rezonance (linija „b“ prolazi kroz najposteriornije tačke butnih kondila)



Sl. 2 – Način merenja širine međukondilarne jame (c), epikondilarne širine (d) i visine međukondilarne jame (e) na horizontalnom preseku snimka magnetne rezonance

Na osnovu dobijenih vrednosti izračunate su vrednosti NWI kao odnosa ICW/EW i NSI kao odnosa ICW/ICH.

Podaci su obrađeni u programu SPSS 11.0. S obzirom na to da nije utvrđena statistički značajna razlika između ispitivane i kontrolne grupe u godinama ($p = 0,597$; $p > 0,05$), za testiranje razlike između ove dve grupe nije korišćena dvofaktorska analiza varijanse, već nezavisni Studentov *t*-test. Testirana je razlika između ispitivane i kontrolne grupe ICW, EW, ICH, NWI i NSI, a navedeni indeksi su takođe testirani i unutar polnih podgrupa. Nivo značajnosti bio je postavljen na 0,05.

Rezultati

U tabeli 1 prikazane su približno jednake vrednosti ICW i EW kod bolesnika ispitivane i kontrolne grupe. Sa druge strane, ICH bolesnika ispitivane grupe imalo je preko 1 mm veću vrednost nego ICH kontrolne grupe. Ova razlika direktno se odražavala i na NSI koji je bio „povoljniji" kod bolesnika kontrolne grupe.

Podelom ispitivane i kontrolne grupe na mušku i žensku podgrupu dobijena je statistički značajna razlika između ispitivane i kontrolne grupe za ICH i NSI. Ta razlika bila je izraženija u muškoj podgrupi ($p = 0,002$, $p < 0,01$; $p = 0,007$, $p < 0,01$; respektivno) a nije bilo u ženskoj podgrupi ($p = 0,845$, $p > 0,05$; $p = 0,498$, $p > 0,05$; respektivno). Vrednosti ICH i NSI muške podgrupe prikazane su i na slikama 3 i 4.

Uzimajući u obzir činjenicu da su muškarci značajno krupnije građe od žena, dobijene su statistički značajno više vrednosti apsolutnih parametara (ICW, EW i ICH) u podgrupama muškaraca (tabela 2). Međutim, u slučaju ICH, kontrolna podgrupa muškaraca imala je vrednosti slične podgrupi žene. Relativni parametri muške i ženske podgrupe su slični, izuzev u slučaju NSI kontrolne grupe gde muškarci beleže visoko statistički značajno veću vrednost od žena (0,749 : 0,662).

Tabela 2
Statistička značajnost razlike posmatranih parametara između podgupa muškaraca i žena

Mortometrijski parametri	Ispitivana grupa *p*	Kontrolna grupa *p*
ICW	0,001	0,000
ICH	0,000	0,271
EW	0,000	0,000
NWI	0,192	0,981
NSI	0,899	0,004

***p* < 0,05 – statistički značajno**
ICW – širina međukondilarne jame; EW – epikondilarna širina; ICH – visina međukondilarne jame, NWI – indeks širine međukondilarne jame; NSI – indeks oblika međukondilarne jame

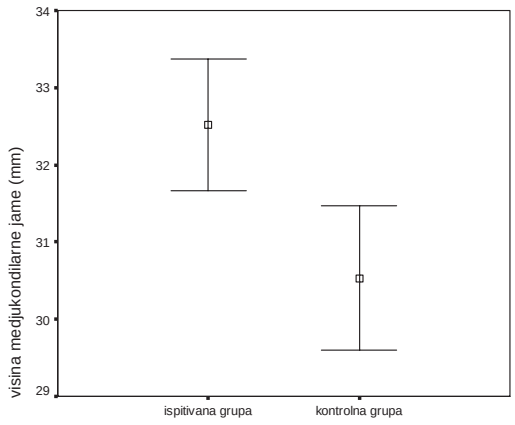
Tabela 1
Vrednosti posmatranih parametara međukondilarne jame ispitivane i kontrolne grupe

Mortometrijski parametri	Ispitivana grupa	Kontrolna grupa	*p*
ICW (mm)	21,31 ± 2,42	21,68 ± 3,01	0,493; 0,05;
EW (mm)	74,77 ± 5,78	74,19 ± 6,32	0,636; 0,05;
ICH (mm)	31,38 ± 3,09	30,25 ± 2,24	0,047; 0,05;
NWI	0,285 ± 0,025	0,292 ± 0,028	0,206; 0,05;
NSI	0,685 ± 0,089	0,720 ± 0,096	0,027; 0,05;

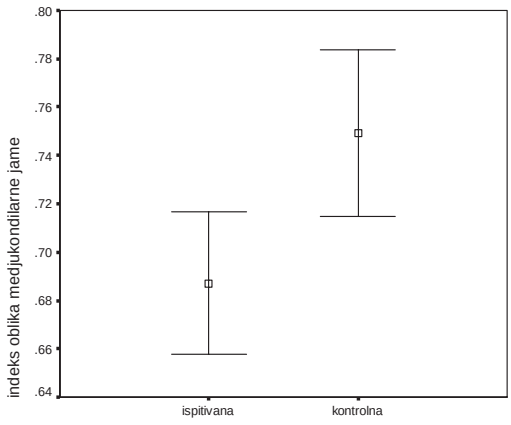
***p* < 0,05 – statistički značajno**
ICW – širina međukondilarne jame; EW – epikondilarna širina; ICH – visina međukondilarne jame, NWI – indeks širine međukondilarne jame; NSI – indeks oblika međukondilarne jame

Diskusija

Mnoge studije vršene na radiografskim i MRI snimcima pokušale su da utvrde razliku u morfometriji interkondilarne jame bolesnika sa rupturom LCA i bolesnika sa intaktnom LCA [2, 4, 6, 8, 12].



Sl. 3 – Vrednosti visine međukondilarne jame muške ispitivane i kontrolne grupe



Sl. 4 – Vrednosti indeksa oblika međukondilarne jame muške ispitivane i kontrolne grupe

Rezultati naše studije, na osnovu snimaka MR, pokazuju da se ICW ispitivane grupe (21,3 mm) i kontrolne grupe (21,7 mm) bitno ne razlikuju. Međukondilarna širina manja od 17 mm kritična je za porast rizika od povrede LCA [13]. U našoj studiji, samo jedan ispitanik ženskog pola u ispitivanoj grupi imao je vrednost ICW manju od 17 mm. Direktnim merenjem na kadaverima, Herzog i sar.[3] dobili su nešto manje vrednosti od 20,3 mm. Rizzo i sar.[14] u svojoj studiji na 26 kadaverskih kolena navode ICW od 20,2 mm za kolena muškaraca i 20,50 mm za kolena žena. Nešto veće vrednosti dobili su Didia i sar. [15] (22,4 mm) za polno mešovitu populaciju. U dve studije sprovedene na rendgenskim snimcima nađena je ICW od 23,5 mm [7], odnosno 20,7 mm [2]. Ni Laprade i sar. [4] kao ni Treitz i sar. [8] slično nama, nisu pronašli statistički značajnu razliku u ICW između muškaraca i žena.

U našoj studiji ICH ispitivane grupe iznosila je 31,4 mm, a kontrolne 30,3 mm. Ova razlika je bila statistički značajna i izraženija unutar ispitivane grupe, ali ne i unutar kontrolne grupe. Možemo reći da žene, generalno, kao i muškarci bez rupture LCA, imaju manju ICH od muškaraca sa rupturom LCA. Statistički značajnu razliku u ICH između muškaraca i žena sa rupturom LCA dobili su i Murshed i sar. [16] na osnovu MR snimaka. Ispitanici muškog pola u njihovoj studiji imali su vrednosti od 33,2 mm, a ženski 29,0 mm.

Postoje ogromne razlike u ICH koju su utvrdili pojedini autori, pre svega zbog različitog načina merenja. Koukoubis i sar.[17] merili su od najposteriornijih tačaka kondila do vrha jame i dobili visinu od 24 mm. S druge strane Herzog i sar. [3] merili su od nivoa zatkolenog žleba do prednjeg izlaza iz jame i dobili visinu od 22,8 mm za muškarce i 20,5 mm za žene. Chandrashekar i sar. [18] merili su ICH do izlaza (u našoj studiji merena je visina od krova do najposteriornijih tačaka butnih kondila), pa su samim tim i vrednosti bile nešto manje (23,1 za muškarce i 25,7 za žene).

Vrednost EW dobijene u ovoj studiji u nivou zatkolenog žleba iznosila je 74,8 mm za ispitivanu i 74,2 mm za kontrolnu grupu. Nije utvrđena razlika između ove dve grupe, ali su rezultati pokazali da muškarci u obe grupe imaju statistički značajno više vrednosti ICW (78,68 mm).

Slične vrednosti EW navode Chandrashekar i sar. [18]. Oni su, u studiji na 20 kadaverskih kolena, nekontaktnom metodom uz pomoć fotografskog 3D skenera, u nivou zatkolenog žleba dobili sledeće dimenzije: 76,06 mm kod muškaraca i 68,97 mm kod žena. Anderson i sar. [12] navode EW slične prethodnim (76 mm kod muškaraca i 67,3 mm kod žena).

U našoj studiji, vrednost NWI ispitivane grupe merene u nivou zatkolenog žleba iznosila je 0,285, a kontrolne 0,292. Za NWI nije utvrđena statistički značajna razlika ni unutar grupa, niti podgrupa formiranih prema polu. Stijak i sar. [19] u svojoj studiji sa 33 uparena bolesnika dobili su statistički značajno niže vrednosti NWI kod bolesnika sa rupturom LCA, nego u kontrolnoj grupi (0,280 : 0,301). Za razliku od naše, bolesnici iz te studije bili su upareni na osnovu godina, pola, strane tela i vrste fizičke aktivnosti, što je verovatno razlog postojanja statističke značajnosti. Muneta i sar. [20] dobili su vrednosti NWI za muškarce 0,25 a za žene 0,28. Studija izvedena na 50 kolena kadavera pokazuje da NWI muškaraca iznosi 0,28 a žena 0,27 [21]. U prethodnim studijama, kao i u našoj nije nađena statistički značajna razlika između muškaraca i žena ($p > 0,05$).

Souryal i sar. [6] prikazali su da su atletičari sa užom međukondilarnom jamom podložniji povredi LCA. Ispitanici muškog pola u njihovoj studiji imali su vrednost od 0,239, a ženskog 0,217. Verovatni razlog nešto manjih vrednosti treba tražiti u metodologiji njihove studije u kojoj su korišćeni rendgenski snimci.

Vrednosti dobijene u našoj studiji nešto su niže nego vrednosti koje su dobili Anderson i sar. [12] (muškarci 0,311, žene 0,305). Takođe, Tillman i sar. [9] merili su po 100 butnih kosti muškaraca i žena i nisu pronašli značajnu razliku između muškaraca (0,255) i žena (0,247), ali su pronašli značajnu razliku između Afrikanaca (0,257) i Evropljana (0,247).

LaPrade i sar. [4] u svojoj studiji sa 213 atletičara zaključili su da je suženje interkondilarne jame udruženo sa povređivanjem LCA. Ireland i sar. [2] u svojoj studiji su potvrdili da bolesnici sa insuficijentnom LCA imaju statistički značajno niži NWI nego bolesnici sa intaktnim LCA.

Treitz i sar. [8] nisu pronašli razliku u vrednosti NWI zdravih osoba i osoba sa povredom LCA. Lombardo i sar. [7] u svojoj jedanaestogodišnjoj prospektivnoj slučajno kontrolisanoj studiji izvedenoj na 615 atletičara muškaraca, nisu pronašli statistički značajnu razliku između NWI vrednosti atletičara sa intaktnom (0,235) i insuficijentnom (0,242) LCA. Merenja su vršena na radiografskim snimcima. Takođe, ni Harner i sar. [22] nisu pronašli statistički značajnu razliku u vrednosti NWI između grupe bolesnika sa obostranom povredom LCA i kontrolne grupe. Souryal i sar. [23] upoređivali su NWI tri grupe bolesnika: sa bilateralnom povredom, sa unilateralnom povredom i bez povrede LCA. Oni navode da postoji statistički značajna razlika u vrednosti NWI između bilateralne i obe druge grupe – unilateralne i kontrolne. Međutim, nisu dobili statističku značajnost između unilateralne i kontrolne grupe.

Oblik međukondilarne jame, takođe, igra ulogu u povređivanju LCA [9]. Kolena sa malom vrednošću NSI ne mogu imati normalnu funkciju LCA, jer se prilikom pune ekstenzije LCA oslanja na prednji deo međukondilarne jame, koji, ako je isuviše sužen, može da tare i konačno preseče LCA. Jame koje su šire u svom prednjem delu obezbeđuju više prostora za LCA prilikom pune ekstenzije. U našoj studiji NSI dobijen na osnovu vrednosti izmerenih u nivou zatkolenog žleba ispitivane grupe iznosi 0,685 i statistički značajno je niži od NSI kontrolne grupe (0,720). Ova razlika se pojačava u muškoj, a nestaje u ženskoj podgrupi. U slučaju NSI samo muškarci kontrolne grupe imaju značajno višu vrednost (0,749), dok muškarci ispitivane grupe i žene ispitivane i kontrolne grupe imaju niže vrednosti (0,714; 0,675; 0,662, respektivno).

Murshed i sar. [16] u svojoj studiji na MR snimcima, kao i Anderson i sar. [12], nisu pronašli statistički značajnu razliku ($p > 0,05$) u vrednosti NSI između muškaraca i žena. Ovi rezultati podudaraju se sa našim jer su navedeni autori posmatrali bolesnike sa rupturom LCA (naša ispitivana grupa).

Tillman i sar. [9] u studiji na 200 butnih kosti, merili su dimenzije međukondilarne jame u nivou *sulcus popliteus*-a i

dobili statistički značajnu razliku ($p > 0,05$) između NSI, vrednosti muškaraca (0,638) i žena (0,599), kao i Afrikanaca (0,606) i Evropljana (0,631).

Zaključak

Muškarci poseduju veće apsolutne vrednosti anatomskih parametara distalnog okrajka butne kosti nego žene. Međutim, vrednosti relativnih parametara međukondilarne jame (NWI i NSI) ne pokazuju razliku između pola. Samim tim, ne može se tvrditi da žene poseduju užu međukondilarnu jamu, već samo srazmerno manji distalni okrajak butne kosti.

Povećana ICH kao i manja vrednost NSI udružene su sa rupturom LCA, ali samo kod muškaraca. Kod žena verovatno postoje i drugi faktori, hormonske ili fiziološke prirode, koji imaju veći uticaj na povređivanje LCA. Ti faktori treba da budu predmet istraživanja narednih studija.

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Histochemical and immunohistochemical analyses of the myocardial scar fallowing acute myocardial infarction

Histohemijska i imunohistohemijska analiza ožiljka u miokardu posle akutnog infarkta miokarda

Vujadin Tatić*, Sašo Rafajlovski†‡, Vladimir Kanjuh§, Radoslav Gajanin‖, Dušan Suščević¶, Bela Balint¶‡, Slobodan Obradović†‡

***Center for Pathology and Forensic Medicine, †Clinic of Internal Emergency Medicine, ¶Institute of Transfusiology, Military Medical Academy, Belgrade, Serbia; §Serbian Academy of Science and Art, Belgrade, Serbia; ‡University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; ‖Faculty of Medicine, Banjaluka, Bosnia and Herzegovina**

Abstract

Background/Aim. The heart has traditionally been considered as a static organ without capacity of regeneration after trauma. Currently, the more and more often asked question is whether the heart has any intrinsic capacities to regenerate myocytes after myocardial infarction. The aim of this study was to present the existence of the preserved muscle fibers in the myocardial scar following myocardial infarction as well as the presence of numerous cells of various size and form that differently reacted to the used immunohistochemical antibodies. **Methods.** Histological, histochemical and immunohistochemical analyses of myocardial sections taken from 177 patients who had died of acute myocardial infarction and had the myocardial scar following myocardial infarction, were carried out. More sections taken both from the site of acute infarction and scar were examined by the following methods: hematoxylin-eosin (HE), periodic acid schiff (PAS), PAS-diastasis, Masson trichrom, Malory, van Gieson, vimentin, desmin, myosin, myoglobin, alpha actin, smoth muscle actin (SMA), p53, leukocyte common antigen (LCA), proliferating cell nuclear antigen (PCNA), Ki-67, actin HHF35, CD34, CD31, CD45, CD45Ro, CD8, CD20. **Results.** In all sections taken from the scar region, larger or smaller islets of the preserved muscle fibers with the signs of hypertrophy were found. In the scar, a large number of cells of various size and form: spindle, oval, elongated with abundant cytoplasm, small with one nucleus and cells with scanty cytoplasm, were found. The present cells differently reacted to histochemical and immunohistochemical methods. Large oval cells showed negative reaction to lymphocytic and leukocytic markers, and positive to alpha actin, actin HHF35, Ki-67, myosin, myoglobin and desmin. Elongated cells were also positive to those markers. Small mononuclear cells showed positive reaction to lymphocytic markers. Endothelial and smooth muscle cells in the blood vessel walls were positive to CD34 and CD31, and smooth muscle cells to SMA. Oval and elongated cells were positive to PCNA and Ki-67. The preserved muscle fibers in the scar were positive to myosin, myoglobin and desmin as well as elongated and oval cells. Other cells were negative to these markers. **Conclusion.** Our findings speak that myocardial regeneration is maybe possible and develops in human ischemic heart damages and that the myocardium is not a static organ without capacity of cell regeneration.

Key words:
myocardial infarction; cicatrix; myocardium; regeneration; myocytes, cardiac; immunohistochemistry; histological techniques.

Apstrakt

Uvod/Cilj. Tradicionalno, smatrano je da je srce statički organ i da je nesposobno da se regeneriše posle povrede. Danas, sve češće se postavlja pitanje da li srce ima unutrašnju sposobnost da regeneriše miocite posle infarkta miokarda. Cilj ove studije bio je da se prikaže postojanje očuvanih mišićnih vlakana u ožiljku srčanog mišića posle preležanog akutnog infarkta miokarda, kao i prisustvo mnogobrojnih ćelija različite veličine i oblika, koje su različito reagovale na primenu imunohistohemijskih antitela. **Metode.** Histološki, histohemijski i imunohistohemijski analizirani su isečci miokarda uzeti od 177 bolesnika umrlih od akutnog infarkta miokarda, koji su ranije već jednom preležali infarkt miokarda, i imali, kao posledicu, ožiljak u srčanom mišiću. Iz mesta akutnog infarkta, kao i iz ožiljka, uzimano je više isečaka miokarda, koji su tretirani sledećim metodama: HE, PAS, PAS-dijastaza, Masson trichrom, Malory, van Gieson,

Correspondence to: Vujadin Tatić, Center for Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Crnotravska 17, Belgrade, Serbia.

vimentin, dezmin, miozin, mioglobin, α-aktin, SMA, p53, LCA, PCNA, Ki-67, aktin HHF35, CD34, CD31, CD45, CD45Ro, CD8, CD20. **Rezultati.** U svim isečcima uzetim iz predela ožiljka nađena su veća ili manja ostrvca očuvanih mišićnih vlakana srca sa znacima hipertrofije. U ožiljku je nađen veliki broj ćelija različite veličine i oblika: vretenaste, ovalnog oblika, izdužene sa dosta citoplazme, sitne sa jednim jedrom i ćelije sa oskudnom citoplazmom. Prisutne ćelije su različito reagovale na primenu histohemijskih i imunohistohemijskih metoda. Velike, ovalne ćelije davale su negativnu reakciju na limfocitne i leukocitne markere, a pozitivne na alfa aktin, aktin HHF35, Ki-67, miozin, mioglobin i dezmin. Na ove markere bile su pozitivne i izdužene ćelije. Sitne monojedarne ćelije davale su pozitivnu reakciju na limfocitne markere. Endotelne ćelije i glatke mišićne ćelije u zidu krvnih sudova bile su pozitivne na CD34 i CD31, a glatke mišićne ćelije i na SMA. Ovalne i izdužene ćelije bile su pozitivne i na PCNA i Ki-67. Očuvana mišićna vlaka u ožiljku bila su pozitivna na miozin, mioglobin i dezmin, kao i izdužene i ovalne ćelije. Ostale ćelije bile su negativne na ove markere. **Zaključak**. Naš nalaz ide u prilog mišljenju da se miokardna regeneracija dešava u humanim ishemijskim povredama srca i da miokard nije statički organ bez ćelijske obnove.

Ključne reči:
infarkt miokarda; ožiljak; miokard; regeneracija; miocit srca; imunohistohemija; histološke tehnike.

Introduction

The heart has traditionally been considered as a static organ without capacity of regeneration after trauma [1, 2]. Currently, the more and more often asked question is whether the heart has any endogenous capacities to regenerate myocytes after myocardial infarction because the need for regeneration of damaged myocardium has been imposed [1, 3, 4]. There are numerous opinions that postnatal and adult hearts cannot regenerate and that the myocyte number present at birth dictates the lifetime heart function [1, 4–6]. These opinions confirm that the postnatal hearts are composed of a fixed myocyte number and if they die, they are permanently lost, so that the myocardium has to perform its vital function with a reduced number of cells, which will result in their hypertrophy and finally to their death. Still, some authors [1, 3, 4, 7–10] believe that there is some possibility of myocyte division in the pathologic heart. In the course of the previous years many authors [5, 8, 11–14] have documented the presence of mytotic forms in the human cardiomyocytes in acute and chronic ischemic cardiomyopathy, idiopathic dilatational cardiomyopathy, chronic aortic stenosis and ventricular dysfunction.

The aim of this study was to show the presence of the preserved muscle fibers in the myocardial scar after experienced acute myocardial infarction as well as the presence of numerous cells of various size and form that differently reacted to the used immunohistochemical antibodies.

Methods

Retrospective histological, histochemical and immunohistochemical analyses of sections from the myocardium of 177 deceased patients with acute myocardial infarction were carried out. Before death, all of them already had myocardial infarction and the cardiac muscle scar as its consequence.

From 1975 to 2000, at the Institute of Pathology and Forensic Medicine, Military Medical Academy, Belgrade, autopsies of 308 deceased patients due to acute myocardial infarction were performed. It was shown that 177 of them had already acute myocardial infarction. Among them there were 123 males and 54 females, aged 45–79 years, and most of them were aged 55–68 years.

The time period from the first infarction to death was 6 months to 2 years, and a period from death to autopsy was 7–12 hours. On the basis of data from the disease history, 163 of the autopsies showed systemic hypertension higher than 160 mmHg and 14 of them diabetes mellitus. Neither presence of some neoplasm nor chronic infection were found at any of 177 autopsies. Immediate cause of death in all patients was acute myocardial reinfarction.

At all autopsies, the mass of the heart was measured, localization, size of acute infarction and also the size of the scar as a consequence of previous infarction were precisely determined and measured. Several sections from the acute infarction site as well as from the scar and a borderline between the scar and the normal myocardial tissue were taken for analysis. Sections were fixed in 10% buffered neutral formalin, embedded into paraffin beds and cut by a microtome to 5–7 micrometers. The obtained sections were analysed by the following histologic, histochemical and immunohistochemical methods: hematoxylin-eosin (HE), periodic acid schiff (PAS), PAS diastasis, Masson trichrom, Malory, van Gieson, vimentin, desmin, myosin, myoglobin, alpha actin, smooth muscle actin (SMA), p53, leukocyte common antigen (LCA), proliferating cell nuclear antigen (PCNA), Ki-67, actin HHF35, CD34, CD31, CD45, CD8, CD20 and CD45-Ro.

Results

The mass of the deceased patients' hearts at autopsies was 350–1050 g, in most of them (n = 120) it was 350–650 g. Localization of the scar after the first cured infarction at 39 autopsies was in the region of the anterior left ventricular wall, at 50 of them in the region of the posterior left ventricular wall, at 55 in the region of the anterior left ventricular wall and interventricular septum, and at 33 autopsies in the region of the anterior and posterior left ventricular wall and interventricular septum. Serious atherosclerotic changes in the coronary blood vessels walls as well as obturation of their lumen were found at all autopsies. Obturations of the anterior descendent branch of the left coronary artery, then of the right coronary artery and of both the first and second marginal branches of the left coronary artery were the most frequent finding.

The reaction of different cells found in myocardial scar tissue to used markers is summarized in Table 1. Histochemical staining of various tissue is shown in Table 2.

The preserved muscle fibers in the scar were hypertrophic with large hypertrophic and hyperchromatic nucleus and with the preserved transversal stria (Figure 2).

Table 1

Reaction of cells present in the myocardial scar to used markers

Markers	Type of cells in the myocardial scar					
	Lympho-cytes	Leuko-cytes	Large oval cells abundant with cytoplasm	Elongated cells	Endothelial cells	Smooth muscle cells in the blood vessels wall
CD_8	+	–	–	–	–	–
CD_{20}	+	–	–	–	–	–
CD_{31}	–	–	+	+	+	–
CD_{34}	+	–	–	–	+	–
CD_{45}	+	+	–	–	–	–
CD_{45}-Ro	+	–	–	–	–	–
Alpha ACTIN	–	–	+	+	–	+
Ki-67	–	–	+	+	–	–
PCNA	–	–	+	+	–	–
ACTIN HHF_{35}	–	–	+	+	–	+
DESMIN	–	–	+	+	–	+
MYOGLOBIN	–	–	+	+	–	–
MYOSIN	–	–	+	+	–	–
LCA	+	+	–	–	–	–
SMA	–	–	–	–	–	+

PCNA – proliferating cell nuclear antigen; LCA – leukocyte common antigen; SMA – smooth muscle actin

Table 2

Tissue reactions to histochemical dyeing

Dyeing	Type of tissues		
	Heart muscle fibers	Collagen fibers	Elastic fibers
PAS	+	–	–
Masson trichrom	+ (red)	+ (green)	+ (green)
van Gieson	+ (yellow)	+ (red)	+ (red)
Malory	+ (red)	+ (green)	+ (green)

PAS – periodic acid schiff

Microscopic analysis was carried out for all sections from the myocardial scar of the deceased patients who already had bad myocardial infarction before the fatal one, revealed the preserved myocardial muscle fibers in the form of larger or smaller islets completely isolated from the surrounding preserved cardiac muscle, but surrounded by the connective tissue and without any contact with the normal muscle fibers (Figure 1).

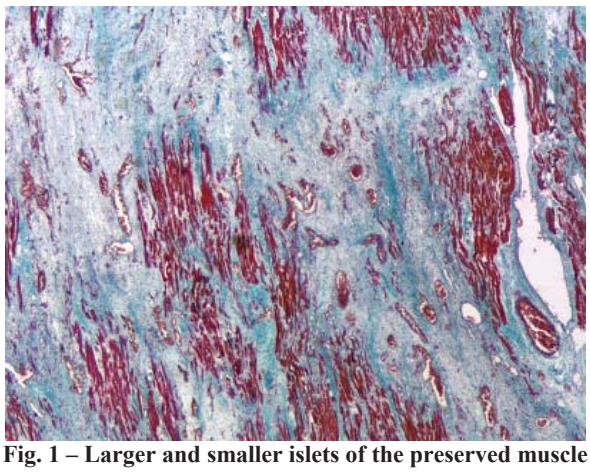

Fig. 1 – Larger and smaller islets of the preserved muscle fibers in the myocardial scar (Malory, x200)

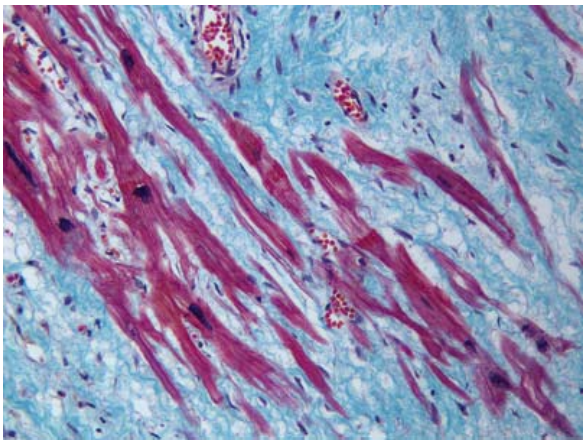

Fig. 2 – The preserved muscle fibers are hypertrophic with large hypertrophic and hyperchromatic nucleus (Masson trichrom, x400)

Around the preserved muscle fibers there was the enlarged newly formed connective tissue, in some sites very dense and in the others loose. The newly formed connective tissue was well vascularized by the numerous newly formed blood vessels with thin walls, coated with the monolayer endothelium. The lumens of newly formed blood vessels were

of various size and form and overfilled with blood. In the newly formed connective tissue (scar) there was a large number of both single cells and groups of cells of various sizes and forms (Figure 3).

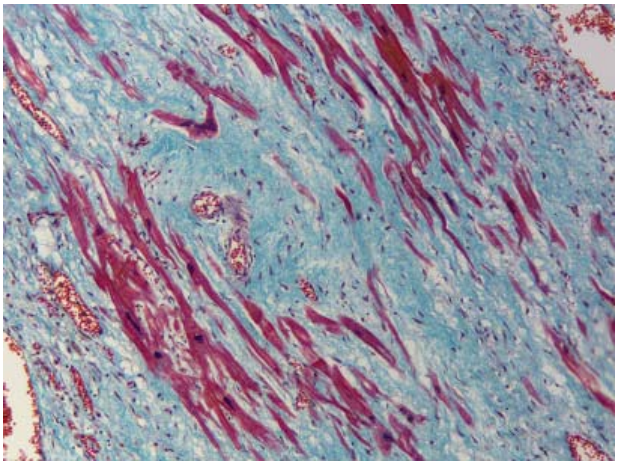

Fig. 3 – A large number of cells of various sizes and forms can be seen in the newly formed connective tissue (Masson trichrom, x200)

Some of the present cells were of the spindle form with a large hyperchromatic nucleus, the others were small with a little cytoplasm and one central nucleus. Some of these cells were oval with abundant cytoplasm and large circular nucleus. There were also elongated cells with abundant fine-grained cytoplasm and large circular nucleus. There were also cells with scanty cytoplasm so that only the nucleus was dominant. The present cells were mostly mononuclear and rarely with two or more nuclei. Only scattered blood vessels with a thick damaged wall could be seen in the scar. In more expressed vascularisation there was a larger number of cells. Myogenic, large oval cells with a large nucleus and abundant cytoplasm showed negative reaction to the lymphocytic and leukocytic markers CD34, CD45, CD20, CD8, CD45-Ro and LCA, but they were positive to alpha actin (Figure 4), actin HHF35 (Figure 5), Ki-67 (Figure 6), myosin, myoglobin (Figure 7) and desmin. Elongated myogenic cells were also positive to these markers (which would speak for cardiomyocytes). Other cells found in the scar were negative to these markers. Small mononuclear cells that would correspond to the lymphocytes as well as leukocytes presented in the scar, showed reaction both to the lymphocytic and leukocytic markers (Figure 8).

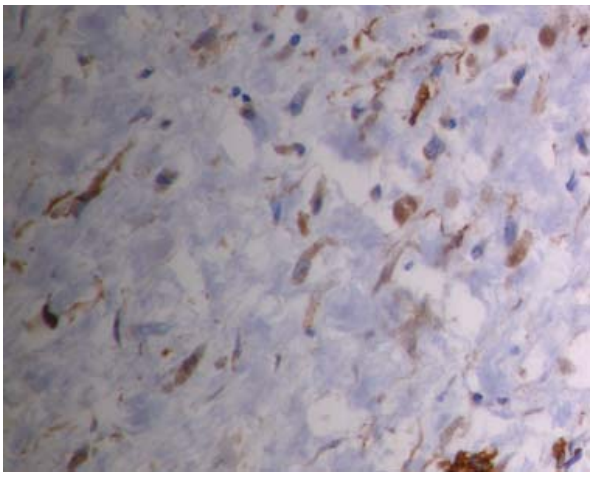

Fig. 4 – Large oval cells and elongated cells positive to alpha actin (x400)

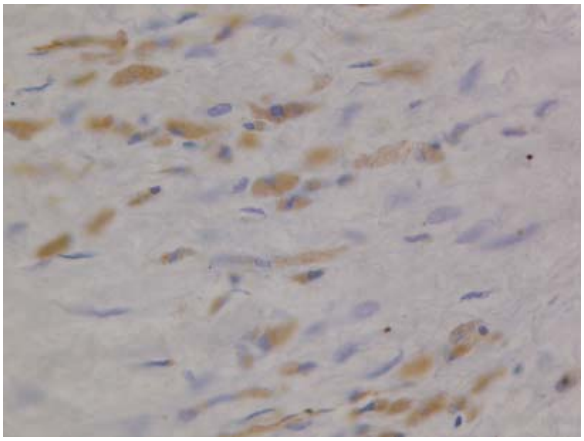

Fig. 5 – Oval and elongated cells in the scar positive to actin HHF35 (x400)

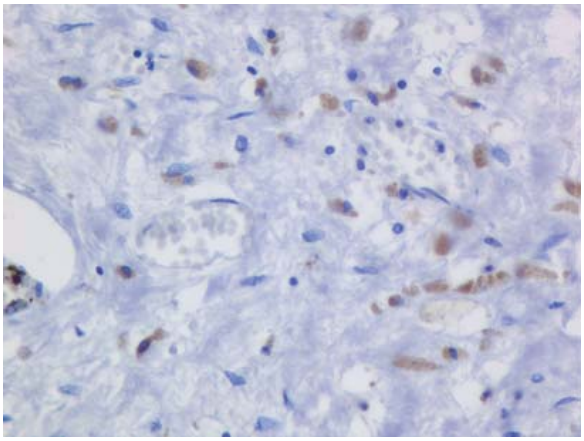

Fig. 6 – Large oval cells in the scar positive to Ki-67; other cells are negative (x400)

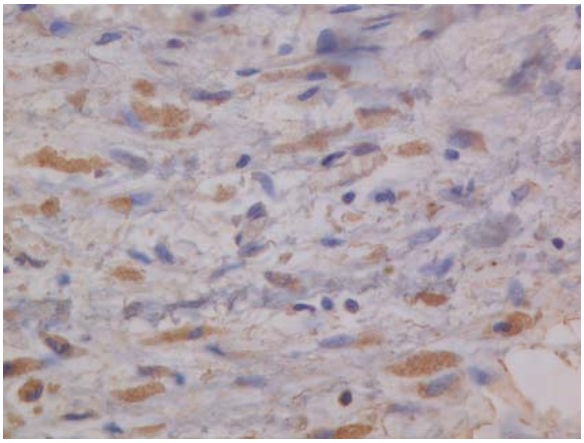

Fig. 7 – Large oval and elongated cells in the scar positive to myoglobin (x400)

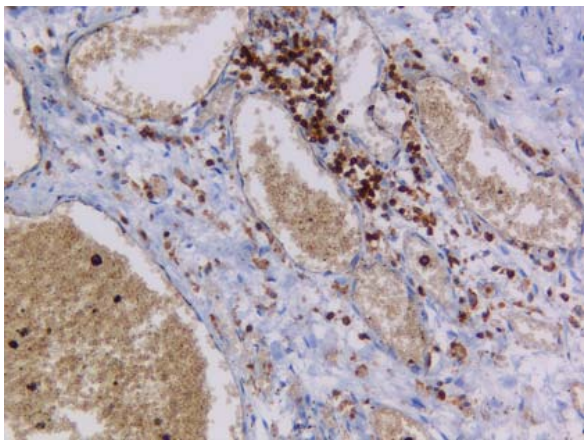

Fig. 8 – Lympocytes and leukocytes in the scar positive to LCA (x400)

cells showed positive reaction to PCNA markers (Figure 9), while spindle cells as well as other present cells were negative to PCNA marker. Expression to Ki-67 nuclear antigen was positive in all nuclei of large, oval and elongated myogenic cells (Figure 10).

Mitotic figures were noted in some nuclei of these cells suggesting cells division. These cells were also positive to PCNA marker for myocytic protein confirmation (Figures 9). The usage of myoglobulin, myosin and desmin markers showed positive reaction to the preserved muscle fibers in the scar (Figure 11), as well as to the elongated mononuclear cells and large, oval cells abundant with cytoplasm and with the large nucleus suggesting the presence of cardiac muscle fibers and most probably cardiomyocytes. Other cells were negative to these markers (Figures 1 and 2).

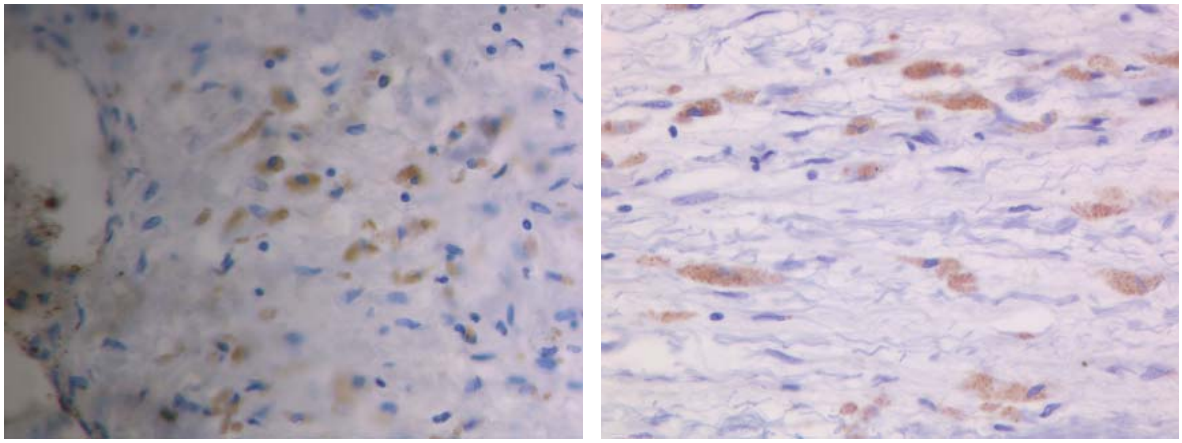

Fig. 9 – Oval and elongated cells in the scar positive to PCNA; other cells were negative (x400)

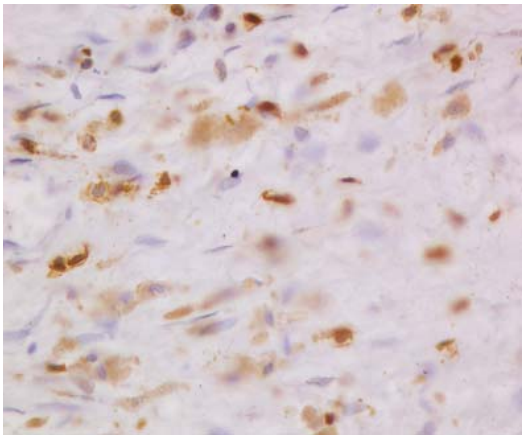

Fig. 10 – Oval and elongated cells in the scar positive to Ki-67 (x400)

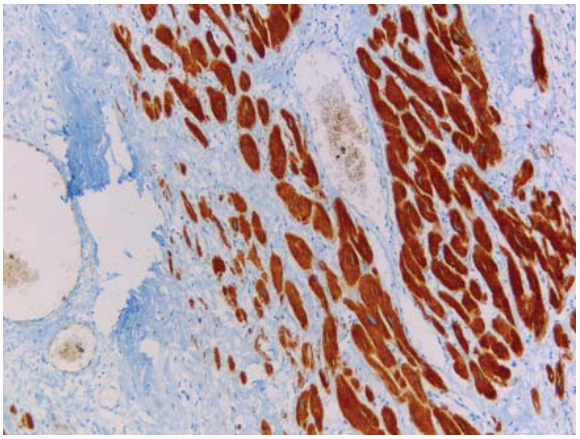

Fig. 11 – Preserved muscle fibers in the scar positive to desmin (x400)

CD34 and CD31 markers showed positive reactions to endothelial cells and smooth muscle cells in walls of the newly formed blood vessels in the scar. The usage of SMA markers resulted in positive reaction for the presence of the smooth muscle cells in walls of the newly formed blood vessels. The present oval cells abundant with cytoplasm and with the large nucleus as well as elongated mononuclear

Discussion

Cardiac failure is the leading cause of both morbidity and mortality in developed countries [10]. Hearts of adult persons are well supplied with blood and are capable to maintain tissue integrity during physiologic cell function [1, 3, 4]. Soon after birth the cardiac function is maintained by in-

creasing both the number and volume of myocytes which together contribute to development of the adult heart [2]. The question is whether the heart possesses endogenous capacity to regenerate myocytes after myocardial infarction [1, 3, 4]. Most of human bodily organs contain divisible and indivisible cells. However, indivisible cells can be in the Go phase and reenter the cellular cycle or become terminally differentiated without possible further division [3]. But, these mechanisms of cell growth have not been accepted so far when the myocardium is concerned and it is believed that cardiomyocytes cannot be regenerated in cells by the division because in mammals their division was discontinued immediately after birth [1, 4–6, 15]. On this basis human myocytes can live for the lifetime even if it were 100 years. It seems exceptionally extravagant that cardiomyocytes contracting 70 times a minute do that continually for 100 years. During that period they would contract 3.7 billion times [1, 3]. If it is true, then cardiomyocytes are immortal cells [1, 3]. It has been accepted that myocytes can enlarge their volume but not the number (the cardiac mass of a 42-weeks-old infant is 2.9 ± 6.2 g).

Nevertheless, some authors [3, 16] accept the possibility of myocyte division. In their studies they have measured the volume and number of human cardiac myocytes of patients died of decompensated cardiac hypertension and congestive cardiac failure. Mass of all the examined hearts was 500 g and more and it was characterized by noticeably increased myocyte number, more than cellular hypertrophy [3, 16]. Some other authors [17] claim that methods used by these authors can only suggest, but not confirm the real increase in the cell number. It was believed that cardiac hypertrophy is a consequence of the present myocytes hypertrophy [4, 8, 18] and that the heart is a terminally differentiated postmitotic organ. After these studies had been published, generations of a great number of pathologists and cardiovascular experts accepted the fact that myocyte mitosis was not seen in the adult myocardium. However, in the course of the last 10–12 years a greater number of authors [1, 3–5, 7–11] have documented the presence of mitotic figures in human cardiomyocytes in cases of acute and chronic ischemic cardiomyopathy, idiopathic dilatational cardiomyopathy, chronic aortic stenosis and ventricular dysfunction. Other authors [11, 19–21] emphasize that the formed parenchymatous cells are permanent in the normal myocardium, but that myocyte regeneration is also present in pathologic hearts, which they have microscopically confirmed.

Recognition that stem cells are present in the myocardium raised a question of their role in the treatment of the affected human heart [9, 10, 17, 18, 22]. Question related to the presence and role of adult cardiac stem cells is based upon the fact that these stem cells regenerate *in vivo* in cases of the myocardial infarction [9]. Urbanek et al. [22] emphasizes that the number of cardiac stem cells was increased in chronic myocardial infarction, and Quaini et al. [4] prove that the ventricular myocytes are not terminally differentiated cells. Beltrami et al. [8] have analyzed sections taken from three patients died 4–12 days after myocardial infarction and compared findings of sections taken from the normal hearts of 9 control groups of patients. By using methods of immunohistochemistry in sections taken from the deceased after myocardial infarction, the following was found: cardiomyocytes with elements characteristic for the cell division such as mitotic spindle and contractile ring formations, karyokinesis and cytokinesis. Similar findings were also found out in our own research. These findings confirm that there is a mitotic proliferation after myocardial infarction, and myocyte regeneration can contribute to increase in myocardial mass. This suggests that a prolonged cardiac failure can progressively influence upon mitotic activity. Regeneration initiation time depends on the span survival period after infarction and it starts already on the 10th day after experienced infarction. It reduces infarction by 40%–50% after 20 days. Ten days after infarction develops myocyte and blood vessels regeneration being improved in time [2, 8, 9.]

The human heart, just like the brain, is mostly composed of terminally differentiated cells, but it is not a terminally differentiated organ because it contains stem cells that can develop its regeneration [2, 3, 13, 23–27]. By the usage of Ki-67 nuclear antigen, Beltrami et al. [8] has found out positive reaction associated with cell division in all nuclei of the large oval and elongated cells. Similar results were found in our research. These cells were negative to lymphocyte, leukocyte and endothelial markers. Ki-67 is a nuclear antigen and in our research it was positive in myocytes of an infarcted heart suggesting that cardimyocytes are divisional. By using alpha actin Beltrami et al. [8] have found in these cells its accumulation in the contractile ring what was also confirmed in our study. These results show that in the adult heart after experienced infarction, there is a myocyte subpopulation not terminally differentiated and capable to divide soon after infarcton. In our research cells that were positive to Ki-67 nuclear antigen were also positive to the usage of: PCNA, alpha actin, actin HHF35, myoglobin, myosin and desmin, but showed negative reaction to lymphocyte, leukocyte and endothelial markers. Other authors' [1, 5, 8] finding are the same suggesting possible myocyte regeneration after myocardial infarction [1, 2, 5, 8]. It has been proved that heart stem cells are capable to differentiate into three types of heart cells: cardiomyocytes, smooth muscle cells in the blood vessel wall and endothelial cells [12]. We have showed the presence of both smooth muscle and endothelial cells in the walls of the newly formed blood vessels in the scar after infarction. Stem cell factor can affect and activate all the three mentioned cells during myocardial ischemia and result in a significant increase in new myocyte formations [2, 12]. Myocardium regeneration requires myocyte and blood vessels formation because myocytes cannot live and grow without blood vessels. However, blood vessels formation alone will not regenerate the dead myocardium and its contractile activity after infarction [7, 28, 29]. The preserved muscle fibers that we have found isolated in the myocardial scar after infarction were hypertrophic with the large nucleus suggesting their participation in synchronous contractions of heart muscle and possibly in prevention of the heart aneurysm development.

A finding that the mammalian heart contains stem cells that regenerate the myocytes and blood vessels represents a unique potential of the dead myocardium reconstruction after

infarction [6, 18, 30]. Myocardium regeneration occurs in human ischemic and nonischemic heart damages. Heart stem cells localized within infarction or close to it can be divided and differentiated reconstructing consequently the myocardium. This response can increase the number of myocyte and blood vessels reducing in that way infarction size, improving its function and reducing mortality rate [6, 18, 30]. The fact that myocardium is not a static organ and that cell reconstruction is not limited as well as both endothelial and vascular smooth muscle cells, requires reinterpretation of the heart biology and mechanism of its life.

Conclusion

The islets of the preserved cardiomyocytes (together with some other cells) surrounded by the connective tissue in the myocardial scar following myocardial infarction were found in our investigations. That it is about cardiomyocytes (and also about other cells) we have confirmed not only by clasical histopathologic dyeing but also by immunohistochemical methods and by broad battery of tests to corresponding markers. On the other hand, the mentioned islets of the preserved cardiomyocytes were not found in sections taken from necrotic tissue in the repeated acute myocardial infarction resulting in the fatal outcome. The question is what, in fact, the found islets of the preserved cardiomyocytes in the scar of the preceded infarction represent? Are they the remains of the preserved myocardium in the infarcted region supplied by some arterial collateral? Is it correlated with the regenerated myocardium due to progenitory cells delivered by blood and differentiated into cardiomyocytetes, or with proliferated cardiac stem sells themselves? Also, what is the significance of these preserved islets of cardiomyocytes? Do they take part in myocardial contractions? Are they the cause of cardiac arrhythmias in pathologic cases? The findings obtained and confirmed by this study are clear and therefore important and interesting, but further studies are necessary to answer the above raised questions.

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Dystocia as a cause of untimely cesarean section

Distocija kao uzrok nepravovremenog carskog reza

Janko Djurić*, Slobodan Arsenijević*, Dragic Banković†, Zoran Protrka*, Marija Sorak*, Aleksandra Dimitrijević*, Irena Tanasković‡

***Clinic of Gynecology and Obstretrics, Clinical Centre Kragujevac, Kragujevac, Serbia; †Faculty for Natural Sciences and Mathematics, University of Kragujevac, Kragujevac, Serbia; ‡Faculty of Medicine, University of Krajevac, Kragujevac, Serbia**

Abstract

Background/Aim. One of the most frequent indications for cesarean section is dystocia. It is impossible to predict, difficult to identify and coincident with the rapid expiry of the expected time, so it is important to point out some mistakes in expecting vaginal delivery. The aim of this study was to examine the frequency and the length of dystocia-related cesarean delivery, as well as the vitality of the newborn immediately after birth. **Methods.** A prospective 3-year study was conducted including a total number of 6,470 deliveries regardless of whether they were completed using cesarean section after an unsuccessful attempt of spontaneous vaginal delivery or not. The Apgar score, a proved useful tool for the assessment of the vitality of newborn children in the first minute, was used. **Results.** On the basis of the established indications, 653 (10.10%) of deliveries were completed using cesarean section. Dystocia was the third most common indication for cesarean section (16.38%). Deliveries in which dystocia was established as a diagnosis lasted much longer ($p = 0.030$) which resulted in weaker vitality of newborn children ($p = 0.000$) compared to the deliveries ended by spontaneous vaginal delivery. **Conclusion.** This study shows that deliveries caused by dystocia last much longer and newborn children are of weaker vitality compared to other deliveries caused not by dystocia. Decisions concerning cesarean section must be made in a timely fashion.

Key words:
dystocia; cesarean section; risk assessment; infant newborn; apgar score.

Apstrakt

Uvod/Cilj. Distocija je jedna od najčešćih indikacija za carski rez. Distociju je nemoguće predvideti, teško se identifikuje, a istovremeno, očekivano vreme za porođaj brzo ističe, zbog čega je važno da se ukaže na neke propuste u očekivanom vaginalnom porođaju. Cilj ovog rada bio je da se utvrdi učestalost distocije kao indikacije za carski rez i trajanje takvog carskog reza, kao i vitalnost novorođene dece. **Metode.** Ispitivanjem, koje je sprovedeno kao prospektivna 3-godišnja studija, obuhvaćeno je ukupno 6 470 porođaja. Istraživanjem su obuhvaćeni svi porođaji, bez obzira na to da li su bili završeni carskim rezom posle neuspešnog pokušaja spontanog vaginalnog porođaja ili su prethodno bili planirani. Vitalnost novorođenčadi merena je Apgar skorom u prvom minutu. **Rezultati.** Na osnovu ustanovljenih indikacija, 653 porođaja (10,10%) bilo je završeno carskim rezom. Među svim porođajima završenim carskim rezom, distocija je bila treća najčešća indikacija (16,38%). Porođaji koji su bili završeni carskim rezom trajali su značajno duže od spontanih vaginalnih porođaja ($p = 0,030$). Utvrđena je značajno bolja vitalnost novorođenčadi posle spontanog vaginalnog porođaja u odnosu na carski rez ($p = 0,000$). **Zaključak.** Porođaji čiji uzrok je distocija traju duže, a novorođenčad iz takvih porođaja imaju slabiju vitalnost u poređenju sa ostalom novorođenčadi. Odluka o primeni carskog reza mora biti doneta pravovremeno.

Ključne reči:
distocija; carski rez; rizik, procena; novorođenče; apgar skala.

Introduction

Dystocia is a dysfunctional delivery which in clinical practice often means delivery that does not progress as well as cephalopelvic disproportion. In a broader sense, dystocia represents fetal position disturbances (oblique and transverse position), rotational anomalies (occipito-posterior position, fetal head high straight and fetal head down transverse position), primary uterine inertia and a series of other conditions. Dystocia is the second most common indication for cesarean section in the United States [1], United Kingdom (UK) [2], Sweden [3] and Slovenia [4]. Abnormal uterine contractility is the

Correspondence to: Janko Djurić, Clinic of Gynecology and Obstretrics, Clinical Centre Kragujevac, Kragujevac, Serbia.
Phone: +381 34 306 800, +381 64 877 66 65. E-mail: jnkdjuric@yahoo.com

cause of functional (dynamic) dystocia. Delivery success depends on the delivery object (neonate), birth canal and delivery forces. It is clear that conditions for a normal delivery are as follows: appropriate size and shape of the pelvis as well as proper size of the child. However, good contractions at a normal frequency are also important. Proper contractions can overcome mild or borderline fetopelvic disproportion while weak contractions often lead to a prolonged delivery or even to cessation of delivery even if there is an optimal ratio between the pelvis and the fetus.

The efficacy of delivery forces and delivery progress are estimated according to: the opening of the internal orifice of the uterus and the lowering of the fetal head.

There are three types of dysfunctional deliveries, which are as follows: delivery with a prolonged latent phase, i.e., the phase lasts longer than 20 h in primipara or more than 14 h in pluripara; prolonged active delivery when dilatation in the primipara is slower than 1.2 cm/h and slower than 1.5 cm/h in the pluripara, and secondary stoppage that occurs when cervical dilatation in the active phase does not progress for more than two hours.

Dystocia, in addition to therapy, represents one of the leading indications for cesarean section [5–9]. Controversial attitudes toward the timely diagnosis and administration of therapy, as a possible genetic reason for dystocia [10] are still a major problem for obstetricians, especially in the primipara. Overcoming this obstacle would require a safe means by which to decrease the number of Cesarean sections [11, 12].

The aim of this study was to examine the frequency and duration of dystocia-related cesarean delivery, as well as the vitality of the newborn immediately after birth.

Methods

This investigation was performed as a prospective study of a population of women that had delivered babies *via* cesarean section at the Maternity Hospital of Clinical Center Kragujevac during a 3-year period. There were 6,470 deliveries in the examined period, and on the basis of the established indications 653 deliveries were completed using surgery-cesarean sections.

By analyzing the indications that caused deliveries to be completed by cesarean sections, it was determined that the most common indications were as follows: fetal distress (asphyxia), previous cesarean section, dystocia, and pelvic presentation.

Two parameters were used, which were as follows: the first-minute Apgar score and the length of delivery. The obtained data were methodologically classified and statistically processed by Bonferroni and Dunet T_3.

Results

A total of 6,470 deliveries occured during a 3-year study period in the Clinic of Gynecology and Obstretics, Clinical Center Kragujevac. The total rate of operatively completed deliveries using cesarean section was 10.10%.

The most common indications for cesarean sections as well as cesareon delivery rates are shown in Table 1. Because the definition of dystocia also includes cephalopelvic disproportion, the most common indication for cesarean section is dysfunctional delivery.

Table 1

The most common indications and rates of cesarean section in the examined 3-year-period

Indication	The rate of cesarean section (%)
Total distress-birth asphyxia	19.44
Previous Cesarean section	18.52
Dystocia	16.38
Pelvic presentation	11.02
Placenta previa and placental abruption	9.80
Disproportion	9.80

The mean values of delivery length, as expressed in minutes, in deliveries completed by cesarean sections and in vaginal deliveries are shown in Figure 1.

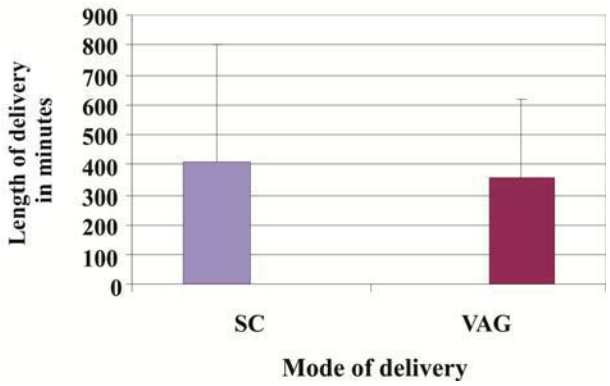

Fig. 1 – Delivery length based on the mode of delivery

CS – cesarean section; VAG – vaginal delivery

Deliveries completed by cesarean section lasted longer than spontaneous vaginal deliveries ($p = 0.030$). There was sufficient time for patients from the control group (vaginal delivery) to give birth from the beginning of a delivery to the decision to complete it operatively.

It is absurd that deliveries completed by cesarean section last longer than vaginal deliveries, which indicates the lack of timely decision-making to complete delivery operatively.

The mean values of the first-minute Apgar score in vaginal deliveries and in deliveries completed by cesarean section are shown in Figure 2.

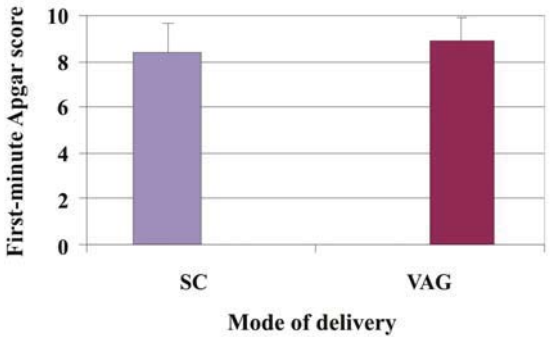

Fig. 2 – The Apgar score based on the mode of delivery

CS – cesarean section; VAG – vaginal delivery

The Apgar score as a proven useful tool for the assessment of the vitality of newborn children in the first-minute, was significantly better in vaginal deliveries ($p = 0.000$) than in newborn children from deliveries completed by cesarean section. The lack of a timely decision to complete the delivery by cesarean section may have resulted in the weaker vitality of the fetus.

The basic explanation for the results shown here, could be seen and understood best when we compare three most common indications for cesarean section: fetal distress (asphyxia), dystocia and pelvic presentation with vaginal delivery with head presentation, vaginal delivery with pelvic presentation and vaginal delivery after previous cesarean section.

The arithmetic means and standard deviations of delivery length expressed in minutes based on the delivery mode are shown in Table 2.

The analysis of variances showed a statistically significant difference in delivery length based on the delivery mode ($p = 0.000$) (Table 3).

Table 3 shows that delivery completed by cesarean section secondary to dystocia lasts significantly longer as compared to the other modes of delivery presented in this study. It is clear that the lack of timely recognition of dysfunctional delivery resulted in a statistically significant difference in the duration of delivery for each of the examined modes of delivery.

Table 4 shows the means and standard deviations of the Apgar scores of newborn children for the examined modes of delivery.

The analysis of variances showed that there was a statistically significant difference in the Apgar score of children based on the mode of delivery ($p = 0.003$).

Table 5 shows a highly significant difference in the Apgar score between vaginal delivery with head presentation and delivery by cesarean section due to dystocia ($p = 0.000$). The lack of timely recognition of dystocia and the significant prolongation of delivery resulted in the weaker vitality of a fetus and statistically significantly lower the Apgar score.

Table 2

Delivery length based on the mode of completion

Indications	Length of delivery – minutes ($\bar{x} \pm SD$)
Vaginal – head presentation	341 ± 251
Vaginal – pelvic presentation	386 ± 295
Vaginal, after cesarean section	407 ± 271
Cesarean section, pelvic	286 ± 268
Cesarean section, dystocia	617 ± 495
Cesarean section, asphyxia	298 ± 265

Table 3

Comparison of delivery length based on the delivery mode

Mode of delivery	Mode of delivery	(Bonferroni)
Vaginal – head presentation	CS dystocia	0.000
Vaginal – pelvic presentation	CS dystocia	0.001
Vaginal, after CS	CS dystocia	0.007
CS pelvic presentation	CS dystocia	0.000
CS asphyxia	CS dystocia	0.000

CS – cesarean section

Table 4

The Apgar score based on the mode of delivery

Mode of delivery	Apgar score ($\bar{x} \pm SD$)
Vaginal – head presentation	9.03 ± 0.79
Vaginal – pelvic presentation	8.41 ± 1.20
Vaginal after CS	8.75 ± 1.34
CS pelvic presentation	8.68 ± 1.06
CS dystocia	8.44 ± 1.14
CS section asphyxia	8.14 ± 1.34

CS – cesarean section

Table 5

Comparison of the Apgar score based on the mode of delivery

Mode of delivery	Mode of delivery	(Dunnet T3)
Vaginal – head presentation	Vaginal – pelvic presentation	0.001
Vaginal – head presentation	CS dystocia	0.000
Vaginal – head presentation	CS asphyxia	0.000
CS pelvic presentation	CS asphyxia	0.027

CS – cesarean section

Discussion

The experience and ability of obstetricians to recognize dysfunctional delivery in a timely fashion are a key to solving the problem with adequate therapy, and the decision to complete the delivery using cesarean section should not be postponed. It is very difficult to determine the moment at which this decision should be made, as it is not always clear how long one should wait. Because the definition of dystocia is broad, it is impossible to obtain uniformity in decision-making regarding this condition. It is relatively easy to make the decision to do cesarean section in clear cases of cephalopelvic disproportions or dysfunction in the fetal position. The biggest problem occurs in deliveries that do not progress, such deliveries can mislead the practitioner into believing that something will eventually happen. As a result, precious time is lost, the delivery is postponed, the vitality of the newborn is lost, and at the end, money is also lost. The experience of the obstetrician in the recognition of such situations is of immense importance.

Worldwide, dystocia is the second most common indication for cesarean section based on frequency [1–4], while it was the third most common indication in this study.

The four most common indications for cesarean section in the United States include the following: previous cesarean section, dystocia, fetal distress and pelvic presentation [1]. There have been certain changes in the indications for cesarean section during the last 30 years. Previous cesarean section, as an indication, is present in about 50% of pregnancies, where a previous pregnancy has also been completed using cesarean section. The number of cesarean sections due to intrapartal fetal distress has been doubled while those due to dystocia has been tripled. With respect to pelvic presentation, the number of cesarean sections has increased from 30% to 88%, and in twin pregnancies, it has increased from 13% to 47%. Cesarean section, at the mother's request, has increased to 23% [13]. Similar results exist in most countries with small variations. In 2001, 25.10% of cesarean sections were performed in Singapore, the most common indication was dystocia (5.41%), followed by previous cesarean section and placenta previa [14]. Of the total number in the United States, previous cesarean sections account for 8%, dystocia for 7%, pelvic presentation for 4%, and fetal distress for 2%–3% [15].

The most common indications for cesarean section in Serbia are as follows: complications during the delivery, previous cesarean section, risky pregnancy, fetopelvic disproportion and pathological fetal presentation [16]. At our clinic, the three most common indications are fetal distress, previous cesarean section and dystocia. The decision concerning operative completion of delivery is restrictive, thus the rate is slightly above 10% which is far from the world average.

Deliveries completed by cesarean section last longer than deliveries completed *via* spontaneous vaginal delivery, resulting in the weaker vitality of newborn children, which is known to result in the lower Apgar scores. In our study, we have similar results when we compare individual indications for cesarean section.

The difference in the price of elective cesarean section and vaginal delivery is not larger than 10% [17]. The most expensive delivery is the delivery that is completed by cesarean section after an unsuccessful, lengthy vaginal delivery. Unnecessary delays in decision-making regarding operative completion of delivery in deliveries that are already recognized to be pathological based on their prolonged times, make postoperative care significantly more expensive.

Conclusion

This study shows that deliveries in which dystocia has been established as a diagnosis last longer and that newborn children are of the weaker vitality when compared to children from deliveries in which there is no dystocia.

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Collateral branches of the brachial plexus as donors in nerve transfers

Bočne grane brahijalnog pleksusa – donori u transferima nerava

Miroslav Samardžić*, Lukas Rasulić*, Novak Lakićević†, Vladimir Baščarević*, Irena Cvrkota*, Mirko Mićović*, Andrija Savić*

***Neurosurgical Clinic, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, †Neurosurgical Clinic, Clinical Center of Montenegro, Podgorica, Montenegro**

Abstract

Background/Aim. Nerve transfers in cases of directly irreparable, or high level extensive brachial plexus traction injuries are performed using a variety of donor nerves with various success but an ideal method has not been established. The purpose of this study was to analyze the results of nerve transfers in patients with traction injuries to the brachial plexus using the thoracodorsal and medial pectoral nerves as donors. **Methods**. This study included 40 patients with 25 procedures using the thoracodorsal nerve and 33 procedures using the medial pectoral nerve as donors for reinnervation of the musculocutaneous or axillary nerve. The results were analyzed according to the donor nerve, the age of the patient and the timing of surgery. **Results**. The total rate of recovery for elbow flexion was 94.1%, for shoulder abduction 89.3%, and for shoulder external rotation 64.3%. The corresponding rates of recovery using the thoracodorsal nerve were 100%, 93.7% and 68.7%, respectively. The rates of recovery with medial pectoral nerve transfers were 90.5%, 83.3% and 58.3%, respectively. Despite the obvious differences in the rates of recovery, statistical significance was found only between the rates and quality of recovery for the musculocutaneous and axillary nerve using the thoracodorsal nerve as donor. **Conclusion**. According to our findings, nerve transfers using collateral branches of the brachial plexus in cases with upper palsy offer several advantages and yield high rate and good quality of recovery.

Key words:
brachial plexus; wounds and injuries; nerve transfer; thoracic nerves; neurosurgical procedures; treatment outcome.

Apstrakt

Uvod/Cilj. Za nervne transfere u slučajevima nemogućnosti direktne rekonstrukcije visokih ekstenzivnih povreda brahijalnog pleksusa koje ne podležu direktnoj reparaciji koriste se različiti donorni nervi. Ovo istraživanje imalo je za cilj da analizira rezultate nervnih transfera kod bolesnika sa trakcionom povredom brahijalnog pleksusa u kojima se kao donori koriste torakodorzalni i medijalni pektoralni nervi. **Metode.** Istraživanjem je bilo obuhvaćeno 40 bolesnika kod kojih je kao donor za reinervaciju muskulokutaneusa ili aksilarisa u 25 postupaka korišćen torakodorzalni nerv i u 33 postupka medijalni pektoralni nerv. Rezultati su analizirani prema donornom nervu, uzrastu bolesnika i vremenu kada je operacija izvršena. **Rezultati.** Ukupna stopa oporavka iznosila je 94,1% za fleksiju podlaktice, 89,3% za abdukciju ramena i 64,3% za spoljnu rotaciju ramena. Odgovarajuće stope oporavka pri korišćenju torakodorzalnog nerva bile su 100%, 93,7% i 68,7%, a pri korišćenju medijalnog pektoralnog nerva 90,5%, 83,3% i 58,3%, respektivno. Uprkos očiglednim razlikama u stopama oporavka, statistički značajne korelacije ustanovljene su samo za stope i kvalitet oporavka muskulokutaneusa i aksilarisa u slučajevima kada je kao donor korišćen torakodorzalni nerv. **Zaključak.** Prema našim nalazima, nervni transferi u slučajevima gornje paralize u kojima se kao donori koriste bočne grane brahijalnog pleksusa imaju nekoliko prednosti i daju visoku stopu i dobar kvalitet oporavka.

Ključne reči:
plexus brachialis; rane i povrede; transfer živca; nn. thoracici; neurohirurške procedure; lečenje, ishod.

Introduction

In the past, nerve transfers were the treatment of choice in cases with spinal nerve root avulsion, or those with directly irreparable proximal lesions, *ie* very proximal or injuries without a nerve available for grafting. Recently, indications for nerve transfers have been extended to high level nerve injuries with extensive gap for grafting and delayed nerve repairs [1], significant bony or vascular injuries in the region of direct repair and previously failed proximal nerve

Correspondence to: Miroslav Samardžić. Neurosurgical Clinic, Clinical Center of Serbia, Koste Todorovića 4, 11 000 Belgrade, Serbia. Phone: +38111 3615 582; Fax: +38111 3615 577, Mob.: +381 63 205 591. E-mail: lukas.rasulic@kcs.ac.rs

repair [2]. The main advantage of this procedure over nerve grafting is a conversion of proximal high-level injury to a low-level one [1].

Nerve transfers have been attempted using a variety of donor nerves, but an ideal method has not been estabilshed. In general, there are two types of donors: extraplexal, including intercostal, spinal accessory, phrenic, motor branches of the cervical plexus, or collateral C7 spinal nerve, and intraplexal, including proximal spinal nerve stumps or collateral motor branches of the brachial plexus. In fact, the latter presents a distal form of the classic intraplexal nerve transfer.

Nerve transfers using these nerves were performed for the first time in 1920 by Vulipus and Stoffel (according to ref. [3]), who transferred some of the branches to the pectoral muscles onto the musculocutaneous or axillary nerves. In 1929 Foerster performed transfer of nerves to the *latissimus dorsi* and subscapular muscles onto the axillary nerve, as reported by Narakas [4, 5]. Thereafter, in 1948 Lurja (according to ref. [3]) reported transfer of the pectoral and thoracodorsal nerves, particularly onto the musculocutaneous nerve in patients with upper trunk injuries.

We used these two nerves in nerve transfer for the first time in 1980. Thoracodorsal to musculocutaneous and medial pectoral to the axillary nerve transfers were performed in a 24-year-old man four months after a motorcycle accident. Good recovery of both functions was obtained one year after the surgery. The aim of this study was to analyze the results of nerve transfers in patients with traction injuries to the brachial plexus using the thoracodorsal and medial pectoral nerves as donors.

Methods

During the past 30 years, since January 1980, we performed nerve transfer using collateral branches of the brachial plexus as donors in 44 patients with upper palsy due to traction injury. The number of followed up patients was 40, or more precisely 33 with nerve transfers using the medial pectoral nerve, and 29 using the thoracodorsal nerve as donor. Both nerves were used simultaneoulsy in 22 of the followed up patients. The age of the followed up patients ranged from 9 do 55 years, with 27 (67.5%) being less than 30 years of age.

The preoperative diagnosis was made on the basis of standard clinical, electrodiagnostic and radiologic tests. Using these methods we diagnosed a variety of injury patterns to the C5, C6, and sometimes C7 spinal nerve roots or spinal nerves. Extended upper brachial plexus palsy was present in 11 patients.

Indications for nerve transfer included preoperatively documented avulsion of the C5 and C6 spinal nerve roots, or intraoperatively demonstrated directly irreparable very proximal lesion of the corresponding spinal nerves, and high lesions with a long nerve gap. Surgical procedures were performed 3 do 16 months (mean 5 months) after injuries, and 33 patients (82.5%) were treated within 6 months after injury. Moreover, 17 patients (42.5%) were treated within 3 months after the injury.

The extent of surgical exploration was adopted to the reliability of the preoperative diagnosis. In the majority of cases the brachial plexus was explored only infraclavicularly. In diagnostically unclear cases, we performed an additional supraclavicular exploration limited to the C5 and C6 spinal nerves and upper trunk.

In these 44 patients we performed 38 reinnervations of the musculocutaneous nerve, 13 using the thoracodorsal nerve and 25 using the medial pectoral nerve as donors, and 33 reinnervations of the axillary nerve, 20 using the thoracodorsal nerve and 13 using the medial pectoral nerve as donors (Table 1). Both nerves were used simultaneously in 24 patients, and in the remaining cases nerve transfers using these collateral branches were combined with the spinal accessory or intercostal nerve transfers. The choice of donor and recipient nerve was based predominantly on the possibility for a direct nerve anastomosis. In seven nerve transfers we combined the thoracodorsal nerve with the subscapular or long thoracic nerves, and in another four transfers with the intercostal nerves. In eight nerve transfers the medial pectoral nerve was combined with the spinal accessory or intercostal nerves. The main reason for these combinations was completion of the suture line in cases with recipient nerves of considerably larger diameter.

Table 1
Summary of nerve transfers using collateral branches of the brachial plexus as donors

Donor nerve	Recipient nerve		
	Musculocutaneous	Axillary	Total
Thoracodorsal	9	13	22
Thoracodorsal and intercostal	2	2	4
Thoracodorsal and subsapular or long thoracic	2	5[a]	7
Medial pectoral	21	9	30
Medial pectoral and spinal accessory or intercostal	4[b]	4[c]	8
Total	38	33	71

a – one case combined with the long thoracic nerve
b – all combined with the spinal accessory nerve
c – all combined with one intercostal nerve

The medial pectoral nerve, either by itself or in combination with a branch of pectoral ansa, or its two terminal branches joined in a common trunk by fibrin glue, and the thoracodorsal nerve were anastomosed to the recipient nerves either directly or using short nerve grafts. Grafts 2 do

5 cm in length were used in five cases of medial pectoral nerve transfer. In one case with an extensive peripheral lesion to the musculocutaneous nerve, we used an 8 cm long nerve graft in thoracodorsal nerve transfer. The epifascicular epineurium of the recipient nerves was removed in order to reduce fibrosis on the suture line. The anastomoses were completed with two epiperineural sutures on the upper side of the nerve, or with a circumferential suture using four to five stithces around the nerve. In the majority of cases, the suturing was combined with fibrin gluing.

The results of the surgery were related to the donor and recipient nerves according to the modification of grading system which we used in our previous reports [6], as follows: 1) "bad" denotes no movement or weightless movement; 2) "fair" denotes movement against gravity with the ability to hold position, active abduction up to 45 degrees, elbow flexion up to 90 degrees, the range of external rotation from full internal rotation up to 45 degrees; 3) "good" denotes movement against resistance with the ability to repeat movements in succession, active abduction of more than 45 degrees, full range elbow flexion, external rotation up to 90 degrees. 4) "excellent" denotes near normal function with external rotation over 90 degrees.

Fair, good, and excellent results were considered to represent recovery. According to our grading system, recovery roughly corresponds to M2 or more grade of recovery according to the Louisiana State University Medical Center grading system, and to M3 or more grade of recovery according to the British Medical Research Council system. The quality of recovery was estimated and the basis of proportions of excellent and good versus fair results. The follow-up period was at least two years.

Statistical analyses were performed using commercially available software (SPSS version 15.0, Inc., Chicago IL). The following tests were performed: analysis of descriptive values (number and percentage of cases, mean, minimal and maximal values), Pearson's $\chi 2$-test, Fisher exact test, and Mann Whitney *U*-test. The dependent variables were elbow flexion, arm abduction and external rotation. The significance of the association of independent variables including the type of donor nerve, the age of the patient and the timing of surgery were tested. A p-value of ≤ 0.05 was considered significant.

Results

Functional recovery of elbow flexion was obtained in 32 (94.1%) out of 34 nerve transfers in total, with good quality in 25 (78.1%) of 32 functionally useful transfers. Using the thoracodorsal nerve as donor we obtained recovery in all 13 cases, with good quality of recovery in 12 (92.3%) of them (Table 2). Using the medial pectoral nerve as donor the rate of recovery was somewhat lower, *ie* 19 (90.5%) of 21 cases, and the quality of recovery was significantly lower, 13 (68.4%) excellent and good results among recoveries (Table 3, Fig. 1).

Shoulder abduction recovery was obtained in 25 (89.3%) out of 28 nerve transfers in total. The quality of recovery was also lower compared to that for elbow flexion. Excellent and good results were obtained in 16 (64%) of 25 recovered cases. Using the thoracodorsal nerve as donor we achieved functional recovery in 15 (93.7%) of 16 cases with good quality of recovery in only 9 (60%) of 15 recoveries (Table 2, Fig. 2). The rate of medial pectoral nerve recovery was somewhat lower, 10 (83.3%) of 12 transfers, but the quality of recovery was better, 7 (70%) excellent and good results among recoveries (Table 3).

Table 2

The results of 29 nerve transfers using the thoracodarsal nerve as donor

Donor nerve	Outcomes (number of cases)							
	Musculocutaneous				Axillary			
	Bad	Fair	Good	Excellent	Bad	Fair	Good	Excellent
Thoracodorsal		1	6	2		5	4	1
Thoracodorsal and intercostal			1	1	1		1	
Thoracodorsal and subscapular or long thoracic			2			1	2*	1
Total		1	9	3	1	6	7	2

***one case combined with the long thoracic nerve**

Table 3

The results of 33 nerve transfers using the medial pectoral nerve as donor

Donor nerve	Outcomes (number of cases)							
	Musculocutaneous				Axillary			
	Bad	Fair	Good	Excellent	Bad	Fair	Good	Excellent
Medial pectoral	1	6	7	3	2	3	2	1
Medial pectoral and spinal accessory or intercostal	1		1	2			3	1
Total	2	6	8	5	2	3	5	2

Fig. 1 – Excellent recovery of elbow flexion (A) with preserved brachio-thoracic pinch (B) for a 19-year-old male patient. Reinnervation of the left musculocutaneous nerve using the medial pectoral nerve as donor was done 3 months after injury

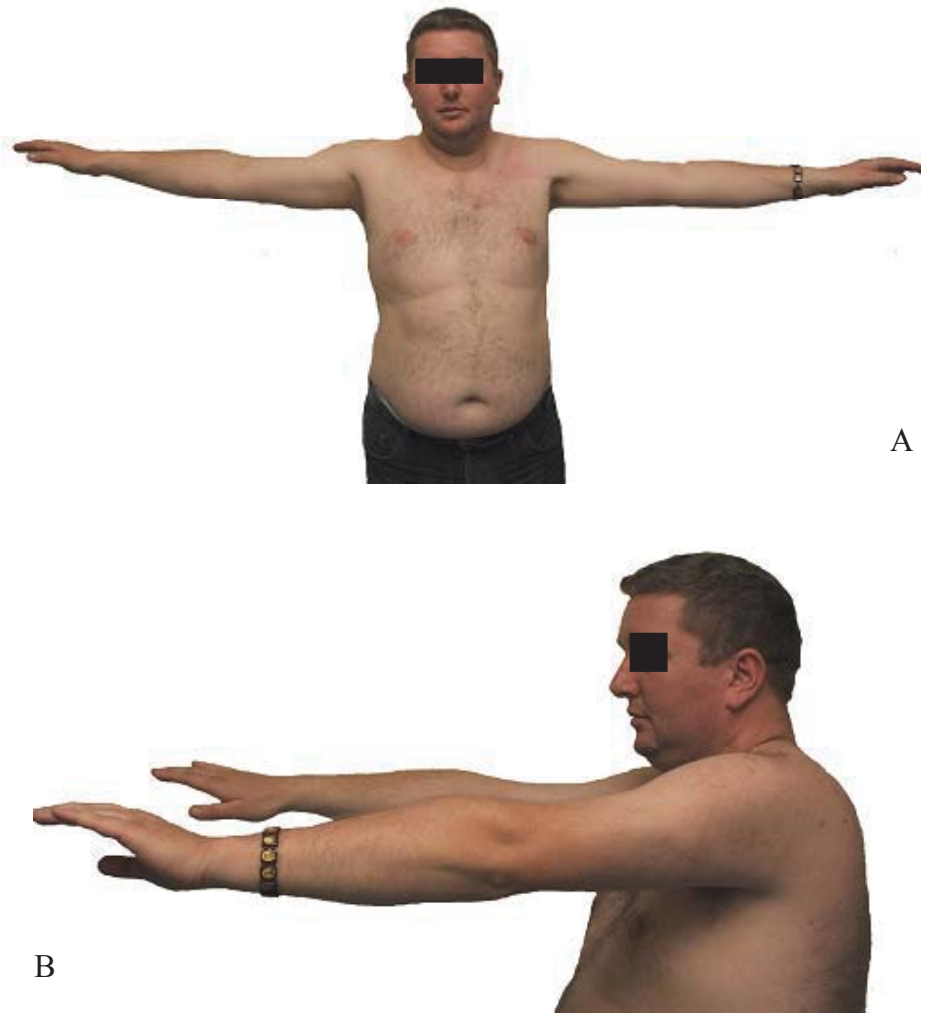

Fig. 2 – Nearly a complete recovery of arm abduction (A) and anteflexion (B) following reinnervation of the left axillary nerve using the thoracodorsal nerve as donor

Some shoulder external rotation recovery was obtained in 18 (64.3%) of 28 nerve transfers to the axillary nerve. Excellent and good results were obtained in only 6 (33.3%) of 18 recoveries and were related to the good quality of recovery of the elbow flexion and shoulder abuction. The rates of recovery were similar for both nerves, 11 (68.7%) of 16 transfers using the thoracodorsal nerve, and 7 (58.3%) of 12 transfers using the medial pectoral nerve. The quality of recovery was also similar, 4 (36.3%) excellent and good results for the thoracodorsal nerve and 2 (28.6%) for the medial pectoral nerve among recoveries (Table 4, Fig. 3).

surgical procedures performed within 6 months after the injuries.

There was no significant difference in the results obtained using the thoracodorsal or medial pectoral nerves as donors, either for the musculocutaneous nerve or for the axillary nerve (Pearson's $\chi 2$ test, $p = 0.213$ and $p = 0.858$, respectively). The same was true for the various techniques of nerve transfer because there was no significant difference between solitary thoracodorsal or pectoral medial nerve transfer and transfer of these nerves in combination with other donors. However, on the basis of the recovery percent-

Table 4

The results of thoracodorsal and medial pectoral nerve transfers regarding shoulder external rotation

Donor nerve	Result			
	Bad	Fair	Good	Excellent
Thoracodorsal	2	4	2	2
Thoracodorsal and intercostal	1	1		
Thoracodorsal and subsapular or long thoracic	2	2		
Medial pectoral	3	3	2	
Medial pectoral and intercostal or spinal accessory	2	2		
Total	10	12	4	2

Fig. 3 – Shoulder external rotation recovery over 90 degrees

The first signs of recovery appeared after 4 to 12 months (mean 7 months) for elbow flexion, and 4 to 13 months (mean 8 months) for shoulder abduction and external rotation using the thoracodorsal nerve as donor, or after 5 do 15 months (mean 9 months) and 4 do 12 monthas (mean 6 months) using the medial pectoral nerve as donor.

Recovery, *ie* maximal strength, was completed after 11 do 21 months (mean 13 months) for elbow flexion and after 9 to 24 months (mean 17 months) for shoulder abduction and external rotation when the thoracodorsal nerve was used as donor. In procedures using the medial pectoral nerve, complete recovery was achieved within 12 to 24 months (mean 17 months), and within 8 to 24 months (mean 15 months), respectively.

In general, statistical analyses showed no significant correlations among the age of the patient, the timing of surgery and the final outcome, probably because of the predominance of the patients of less than 30 years of age and ages, there could be a slight trend toward better results for thoracodorsal nerve transfer. Similarly, there was no significant difference in the quality of recovery within these two nerves and various techniques used (Fisher test, $p = 0.195$, and $p = 0.683$ respectively). On the basis of the recovery percentages, there was a trend toward better quality of recovery for the musculocutanoeus nerve using the thoracodorsal nerve as donor, and for the axillary nerve using the medial pectoral nerve as donor.

In procedures using the thoracodorsal nerve as donor, the rate of recovery for the musculocutaneous nerve was significantly better than for the axillary nerve (Mann Whitney test, $p = 0.038$), and the quality of recovery was also significantly better (Fisher test, $p = 0.04$). There was no statistically significant difference between rates and quality of recovery for the musculocutaneous and axillary nerve in procedures using the medial pectoral nerve as donor (Mann Whitney test, $p = 0.0671$).

Regarding the rate and quality of recovery for the shoulder external rotation following reinnervation of the axillary nerve, there was no significant difference regarding the donor nerve used.

Comparing the average times of appearance of the initial signs of recovery and maximal recovery, we observed no significant differences between the types of donor and recipient nerves.

Comparative reviews of thoracodorsal and medial pectoral nerve transfer results are given in Table 5 and Table 6, respectively.

Table 5

The results of thoracordorsal nerve transfer

Series (reference number)	Rate of useful recovery n/total (%)
Axillary nerve as recipient	
Borrero, 2007 [7] (a)	8/8 (100)
Dai, 1990 [8]	2/2 (100)
Haninec et al, 2007 [9]	6/7 (86)
Samardzic et al, 2005 [10]	14/15(93.3)
Sulaiman et al, 2009 [11]	4/1 (36)
Musculocutaneous nerve as recipient	
Dai, 1990 [8]	1/1 (100)
Haninec et al, 2007 [9]	3/3 (100)
Novak et al, 2002 [12] (b)	5/6 (83/3)
Richardson, 1997 [13]	4/4 (100)
Samardzic et al, 2005 [10]	12/12 (100)
Tung et al, 2003 [14] (c)	1/1 (100)

(a) – nerve transfer of the thoracodorsal or lower subascapular nerve – not specified
(b) – a modified technique using two branches of the thoracodorsal nerve
(c) – nerve transfer to the brachial muscle branch combined with the Oberlin procedure to the biceps muscle branch

Table 6

The results of medial pectoral nerve transfer

Series (reference number)	Rate of useful recovery n/total n (%)
Axillary nerve as recipient	
Ranalli et al, 2008 [15] (a)	1/1 (100)
Samardzic et al, 2002 [16]	9/11 (81.8)
Musculocutaneous nerve as recipient	
Blauw and Sloff, 2003 [3] (b)	22/25 (88.8)
Brandt and Mackinnon, 1993 [17]	4/5 (80)
Haninec et al, 2007 [9]	10/11 (91)
Samardzic et al, 2002 [16]	12/14 (85.7)
Sulaiman et al, 2009 [11]	36/41 (87)
Sulaiman et al, 2009 [11] (c)	14/14 (100)
Tung et al, 2003 [14] (d)	6/6 (100)
Wellons et al, 2009 [18]	16/20 (80)

(a) – nerve transfer supplemented by additional spinal accessory to subascapular nerve transfer
(b) – patients with obstetric brachial plexus palsy
(c) – nerve transfer to the brachial muscle branch supplemented by the Oberlin procedure to the biceps muscle branch
(d) – nerve transfer combined with direct repair from the C5 and C6 spinal nerve

Discussion

Nerve transfers using collateral branches of the brachial plexus present a distal form of the intraplexal nerve transfer that generally yield better results because of the higher number of motor fibers and more physiologic reconstruction. However, these offer some advantages to the classical intraplexal transfer, such as insignificant axonal mixing, the absence of mass or cross innervation, anastomosis close to the target muscle and more precise evaluation of donor nerve functional validity compared to that of the proximal nerve stumps.

Collateral branches of the brachial plexus, particularly the thoracodorsal and medial pectoral nerves, are voluntary motor nerves with a significant number of motor fibers, close functional relationship with upper arm nerves, better cortical reintegration owing to central plasticity based on preexisting central and medullary synaptic connections [7, 19], anatomic proximity to the recipient nerves that enables tension free direct anastomosis or rarely anastomosis using short nerve grafts close to motor end plate of the target muscle [1, 2, 10, 16]. These nerves do not fulfill some other criteria, including the criterion that a motor donor nerve should be expendable or redundant, without significant diameter mismatching with the recipient nerve and preferrably innervating synergistic

muscles with the target muscle [1, 2]. These problems are especially important for the use of the medial pectoral nerve, but they may be overcome, at least partially, as we shall see later.

The first priorities in brachial plexus repair are restoration of full range and strong elbow flexion, shoulder stability, active arm abduction and some external rotation [5]. Recovery of all functions is equally important since these enable elbow movements through a more functional range [20]. The recovery of elbow flexion may be achieved through reinnervation of the musculocutaneous nerve using different technical methods. Since the biceps muscle acts as a primary forearm supinator and secondarily provides elbow flexion, and the brachialis muscle is the primary muscle providing elbow flexion, Tung et al. [14] proposed separate neurotization of both muscles in order to maximize the potential for recovery of strong function. On the other hand restoration of shoulder function is somewhat controversial. Several authors recommended reinnervation of the suprascapular nerve since the supra- and infrascapular muscles are important for initiation of the arm abduction and some external rotation. In a metaanalysis Merrel et al. [21] concluded that significantly better results were achieved an by the spinal accessory to suprascapular nerve transfer than with nerve transfer to the axillary nerve, with 92% *vs.* 69% recoveries. Using this procedure, Terzis et al. [22, 23] reported good or excellent recovery of shoulder abduction (grade 3 or more) in 79% of the patients and in 55% of the patients for external rotation. Bertelli and Ghizoni [24] achieved average an range of arm abduction up to 122 degrees, and external rotation up to 118 degrees in patients with upper palsy. Venkatramani et al. [25] obtained somewhat lower average ranges, 66 degrees for arm abduction and 44 degrees for external rotation. Suzuki et al. [26] obtained similar average shoulder abduction of 77.1 degrees but shoulder external rotation was only 16.7 degrees. However, Malessy et al. [27] achieved grade M3 or M4 reinnervation of the supraspinatus and infraspinatus muscles in 17% and only 8%, respectively. He concluded that reinnervation of the shoulder in patients with upper brachial plexus palsy following suprascapular nerve neurotization is dissapointly low. In a significant number of our cases we obtained good arm abduction and some external rotation reinnervating only the axillary nerve. This could be explained by reinnervation of the teres minor and posterior fibers of the deltoid muscle that act as shoulder external rotators. Furthermore, the reinnervated biceps contributes to shoulder stability through its long head and produces some active external rotation [28]. Probably the best solution is dual nerve transfer to both the suprascapular and axillary nerves [29]. However, the first muscle to be reinnervated attracts a majority of axons and in this case the supraspinatus reduces the potential for reinnervation of the external rotator, the infraspinatus muscle [30].

The thoracodorsal nerve

The thoracodorsal nerve is a motor nerve that originates from the posterior cord and receives nerve fibers from the seventh, eight, and sometimes sixth cervical nerves. More than 52% of motor fibers originate from the C7 nerve root [31]. This nerve has cerebral centers integrated into the function of the upper extremity and innervates the latissimus dorsi muscle. The mean surgically useable length of the nerve is 12.3 cm with a range of 8.5 to 19.0 cm [32]. The diameter of the nerve ranges from 2.1 to 3 mm [10, 33]. The number of myelinated fibers ranges from 1,530 to 2,479 [10]. According to these characteristics, the thoracodorsal nerve may be considered as an excellent donor in motor nerve transfers.

The number of motor axons in the thoracodorsal nerve is sufficient for reinnervation of the biceps and brachialis muscles without a need for neurolysis and exclusion [12, 14] or redirection of the lateral antebrachial cutaneous sensory nerve fibers. Similarly, we think that there is no need for augmentation by additional nerve transfer to the brachialis muscle as proposed by Tung et al. [14]. However, nerve anastomosis should be done distally to the branches to the coracobrachialis muscle since this is not important for elbow flexion and shoud not be reinnervated [17]. It should be emphasized that in the majority of cases with extended upper brachial plexus palsy involving the C7 spinal nerve, or injuries to the middle trunk and posterior cord, the thoracodorsal nerve is not functional.

Regarding functional deficit after thoracodorsal nerve section, we believe that additional palsy of arm adduction and internal rotation due to the loss of the latissimus dorsi in severely disabled shoulder and arm movements presents an acceptable sacrifice [6, 10, 12]. Similarly, Borrero [7], Novak et al. [12] and Tung et al. [11] did not register ill effects from the denervation of the latissimus dorsi muscle. Narakas [5] recommended the thoracodorsal nerve transfer exclusively for the axillary nerve, similarly to the first report by Foerster according to Narakas [4, 5], and Kline [15], but the results were not so encouraging [11]. We obtained functional recovery in all 13 cases for the musculocutaneous nerve, and in 15 (93.7%) of 16 cases for the axillary nerve. Our results are supported by those published by Richardson [13], who obtained functional recovery of the biceps muscle in all four cases with nerve repair delayed for two years, as well as by Novak et al. [12], who reported successful reinnervation of the biceps muscle in all six cases using a modified technique, *ie* separate transfer of the thoracodorsal divisions to the biceps and brachialis branches of the musculocutaneous nerve. They obtained M4 or M5 grades in five of their cases. Dai et al. [8] obtained recovery in one case of nerve transfer to the musculocutaneous nerve and in two cases for the axillary nerve. Finally, Tung et al. [14] used this nerve in one case, for reinnervation of the brachialis branch of the musculocutaneous nerve in combination with Oberiln procedure and obtained good reinnervation (Table 5). By contrast, Narakas [5] used the thoracodorsal nerve for reinnervation of the axillary nerve without any significant functional improvement: he obtained proper reinnervation of the deltoid muscle, but not with muscle contractions.

Our results concur with those published by Borrero [7], and Haninec et al. [9]. However, Borrero used the subscapular or thoracodorsal nerve without precise specification for his 8 cases (Table 5). The results of thoracodorsal nerve

transfer to the axillary nerve are less impressive, especially regarding the quality of recovery, probably due to the functional complexity of the shoulder abduction, the role of the supraspinatus muscle that is not reinnervated in these cases, and essentially antagonistic function of the latissimus dorsi muscle, although this could be successfully retrained [12].

Finally, the use of the thoracodorsal nerve will preclude the use of the latissimus dorsi muscle for secondary procedures.

The medial pectoral nerve

The medial pectoral nerve is a motor nerve that derives from the anterior division of the inferior trunk and receives nerve fibers from the 8th cervical and the 1st thoracic nerves. This nerve has also cerebral centers that are integrated into the function of the upper extremity and innervates with several branches the sternal part of the pectoralis major muscle [34].

The anatomic relationship of the lateral and medial pectoral nerves is variable and somewhat unclear. Classically, they have been described as two distinct nerves linked with ansa that develops at the expense of the lateral nerve [3, 16, 35]. Some authors, however, have described three distinct nerves: the superior, medial and inferior [36]. The medial nerve derives from the anterior division of the middle trunk and terminates with two constant branches, superficial and deep. The deep branch forms plexus with inferior branch (medial pectoral nerve) in all cases. An additional branch originates from this anastomosis [36]. The medial pectoral nerve ends in the pectoralis major muscle with two or three branches [18]. Sometimes, we found four branches in our operative cases [16]. Similarly, in our patients, we observed one or two branches from the pectoral ansa.

Surgically useable length of the medial pectoral nerve ranged from 30 do 78 mm [35]. However, this length may be increased by dissecting terminal branches and their section close to the pectoral muscle. The mean diameter of the nerve ranges from 1.5 to 2.5 or 2.7 mm [33, 35]. The number of motor fibers ranges from 1, 170 to 2,140 in the main trunk [34] and may reach 400 to 600 fibers in a muscular branch [4]. The above mentioned branch of the pectoral ansa contains 330 to 440 nerve fibers [37]. These characteristics make the medial pectoral nerve a valuable donor for motor nerve transfer, especially with regard to the number of motor fibers.

There are three main surgical problems in performing anastomosis with the axillary and especially the musculocutaneous nerve. These are the large discrepancy in the diameter of the nerves, the insufficient length of the former for direct anastomosis, and its functional preservation.

In case of diameter mismatch, some authors have sutured the medial pectoral nerve to the fascicle of the musculocutaneous nerve, or have used an epineural suture over the part of the musculocutaneous nerve cross-sectional area [35]. In the majority of cases, we removed the fascicular epineurium of the recipient nerve and bundled the medial pectoral nerve with the branch of the pectoral ansa, in order to overcome this problem. More recently, we also bundled several branches of the medial pectoral nerve in a common trunk using fibrin glue [33]. In cases in which these procedures were insufficient, we used an additional donor nerve, usually one intercostal or spinal accessory nerve [6, 16]. Sulaiman et al. [11], as well as Kline and Tiell [43], used a combination of the medial pectoral nerve to the medial half of the musculocutaneous nerve transfer with grafting from the anterior division of lateral cord to the musculocutaneous nerve. This technique maximized axonal regeneration from two outflows, proximally repaired plexus elements, and the medial pectoral nerve transfer, and additionally they solved the problem of diameter mismatch.

The technically ideal nerve transfer allows direct nerve anastomoses between the donor and recipient nerves. According to some investigations, the length of the medial pectoral nerve is insufficient for tension-free direct anastomosis with the musculocutaneous nerve in approximately one third of cases. The average length of this gap is approximately 15 to 20 mm [6, 36, 37]. This problem may be overcome in several ways, such as retrograde split of the musculocutaneous nerve into the lateral cord, distal section of the medial pectoral nerve branches [35], dissection of the nerve trunk from its branch to the pectoral ansa [39], and sectioning the arcade between the pectoral nerves [6, 16, 18, 26, 35, 36]. We used nerve grafts in our earliest cases and in cases with double level lesion that included peripheral injury to the musculocutaneous nerve. In these cases the length of nerve graft was up to 5.0 cm [6, 16]. In reinnervation of the axillary nerve, we were able to perform direct anastomosis in all cases.

Similarly to transfer of the thoracodorsal nerve, we think that additional palsy of arm adduction and internal rotation is not as significant in patients with severely disabled shoulder function [6, 16]. Furthermore, in cases of predominant innervation from the C7 spinal nerve root, the function of synergic muscles such as teres major may sometimes be partially preserved. In addition, some function of the pectoral muscles may be retained because of multiple innervation patterns of the pectoralis major muscle since the usual origin of the lateral pectoral nerve is from the C5 to C7 spinal nerves with the mean percentage of supply for pectoral muscles 50% from the C7 spinal nerve. Functional preservation is also possible by distal sectioning and sparing some of the branches [37, 38]. According to our results and the results of some other published series, the remaining branch or branches usually produce strong contractions of the pectoralis major mucle [35]. End-to-side neurorrhaphy is another possibility for functional preservation of the donor nerves [39], but only Wellons et al. [18] used this technique in one case of medial pectoral to the musculocutaneous nerve transfer.

Brandt and Mackinnon [17] used a modified technique of anastomosis distal to the branches to the coracobrachialis muscle in which they divided and redirected the lateral antebrachial cutaneous nerve to the biceps muscle. Using this technique they avoided wasting of motor nerve fibers for reinnervation of the functionally unimportant coracobrachialis muscle and their ingrowth into sensory endoneurial tubules, thus achieving anastomosis as close as possible to the biceps muscle branch [20]. Tung et al. [14] used this nerve for reinnervation of the bracialis branch of the musculocutaneous nerve

in combination with Oberlin procedure and achieved reinnervation that was comparable to that of the biceps muscle in all six cases. They stated that neurolysis and exculsion of the sensory component is not necessary with this method.

Although the homolateral use of the medial pectoral nerve is controversial because the potential absence of arm adduction may be very disabling, we used this nerve due to the reasons mentioned above and achieved recovery in 19 (90.5%) of 21 cases who underwent nerve transfer to the musculocutaneous nerve, and in 10 (83.3%) of 12 patients with transfer to the axillary nerve. Ranalli et al. [15] recommended this nerve transfer in both situations. Our results are in accordance with those published by others (Table 5). However, Blaauw and Sloff [3], and Wellons et al. [18] published results of the medial pectoral to the musculocutaneous nerve transfer in obstetric upper brachial plexus palsy.

Long thoracic nerve

The long thoracic nerve arises from the ventral rami of the 5th, 6th and 7th spinal nerve. The 8th cervical spinal nerve may contribute in 8% of cases. The mean surgically useable length is 22.0 cm, ranging from 18.0 to 27.0 cm. The overall mean diameter of the nerve is 3.0 mm, ranging from 2.2 to 3.5 mm [40]. The number of motor fibers ranges from 1,600 to 1,800, but only half of them can be used in patients with upper brachial plexus palsy [17].

Lurje used this nerve distal to its innervation for the superior two digitations of the serratus anterior muscle for reinnervation of transected suprascapular nerve in 1948 (according to ref. [40]). Narakas and Hentz [28] used the long thoracic nerve in reinnervation of the different parts of the brachial plexus in seven patients with good recovery in only two of them. More recently, Haninec et al. [9] obtained useful functional recovery in all three cases for the musculocutaneous nerve and in 6 (55%) of 11 cases for the axillary nerve. We used the long thoracic nerve in only one case as supplement in nerve transfer of the thoracodorsal to the axillary nerve.

Lower subscapular nerve

The lower subscapular nerve usually originates from the posterior cord but this is very variable. Ballestros and Ramirez [41] found its origin from the axillary nerve in 54.4% of cases, and even from the thoracodorsal nerve in 12.3% of cases. The nerve fibers supply is from the 5th, 6th and sometimes 7th cervical spinal nerves. Therefore, this nerve may be of little value for reinnervation in cases with upper brachial plexus palsy. The mean length of lower subscapular nerve from its origin to the site at which it branches to the subscapularis muscle is 3.5 cm, ranging from 1.5 to 6.2 cm. The mean distance from this branch to its termination at the distal teres major muscle is 6.0 cm, ranging from 3.3 to 8.9 cm. Therefore, the mean length of the entire nerve is 9.5 cm, ranging from 7.1 to 11.4 cm [42]. The mean distance from the musculocutaneous nerve is 1.5 to 2.0 cm and from the axillary nerve 2.5 cm [42]. The mean diameter of the lower subscapular nerve is 2.3 mm, ranging from 1.9 to 2.5 mm [43]. The lower subscapular nerve has approximately 2,100 motor fibers [33].

The lower subscapular nerve has been rarely used in nerve transfers. Borrero [7] used this nerve or the thoracodorsal nerve (not specified) for reinnervation of the deltoid muscle with success in all eight cases. He stated that denervating the subscapular muscle was not detrimental, and in some cases it was beneficial because it lessened excessive internal rotation tendency. We used the lower subscapular nerve as supplement for reinnervation in transfer of the thoracodorsal nerve to the musculocutaneous nerve in two cases, and to the axillary nerve in four cases (Table 1). The recovery was obtained in all five cases that we followed up with good quality of recovery in five of them (Table 2).

Including experience published by other authors, surgical results of this type of nerve transfer could be improved using double nerve transfers, i.e. an additional spinal accessory to suprascapular nerve transfer for shoulder abduction, and fascicular nerve transfer to the brachialis muscle branch for elbow flexion. The latter may be especially important in cases with diameter mismatch between the medial pectoral and the musculocutaneous nerve. Furthermore, the medial pectoral and thoracodorsal nerve transfers may be very promising for older patients and those with delayed surgery.

Conclusion

According to our experience and the results we obtained, nerve transfers using collateral branches of the brachial plexus in patients with upper palsy have several advantages: simplicity of the surgical procedure, significant gain in operative time, high rate of recovery, good quality of recovery in a significant number of cases, early signs of recovery, relatively short period for recovery completion, low rate of significant functional impairment due to loss in donor nerve innervation zone, generally, a slight trend toward better results using the thoracodorsal nerve as donor, and this nerve is a significantly better donor for reinnervation of the musculocutaneous than for the axillary nerve, the medial pectoral nerve, however, offers somewhat better quality of recovery in reinnervation of the axillary nerve, and, finally, any combination of donor and recipient nerves does not preclude good result.

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Različita težina kliničke slike hemoragijske groznice sa bubrežnim sindromom: kako je prepoznati

Clinical presentation of different severities of hemorrhagic fever with renal syndrome: How to recognise it

Mirjana Laušević*†, Željko Laušević†‡, Biljana Stojimirović*†

***Klinika za nefrologiju, ‡Centar za urgentnu hirurgiju, Klinički centar Srbije, Beograd, Srbija; †Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija**

Apstrakt

Uvod/Cilj. Faktori koji određuju težinu kliničke slike hemoragijske groznice sa bubrežnim sindromom, osim serotipa virusa, jesu HLA haplotip i polimorfizam citokinskih gena. Kako su ovi podaci još uvek nedostupni u svakodnevnoj kliničkoj praksi, cilj rada bio je da se utvrdi povezanost težine kliničke slike sa simptomima, fizikalnim, laboratorijskim i radiografskim nalazom kod bolesnika. **Metode.** Ispitano je 30 bolesnika (27 muškaraca i 3 žene), prosečne starosti 40 ± 14,9 godina koji su lečeni od hemoragijske groznice sa bubrežnim sindromom od 01.01.1999. do 31.12.2009. u Kliničkom centru Srbije. Od ukupnog broja bolesnika, 9(30%) bolesnika imalo je blagu, 14(46,7%) umereno tešku i 7(23,3%) tešku kliničku sliku; 24(80%) bolesnika se oporavilo, 6(20%) je umrlo u akutnoj fazi oboljenja, dok je 19(63,3%) lečeno hemodijalizama. **Rezultati.** Kod bolesnika sa teškom kliničkom slikom registrovan je statistički značajno viši titar antitela na serotip virusa Beograd. Kod njih su češće bili prisutni hipotenzija, anurija, makrohematurija, plućna infiltracija, pleuralni izliv, hepatomegalija i pozitivni meningealni znaci. Statistički značajna razlika između grupa sa blagom, srednje teškom i teškom kliničkom slikom nađena je u koncentraciji serumskih proteina, albumina, kalcijuma, transaminaza na prijemu, serumskog natrijuma i kalcijuma 14. dana hospitalizacije, koncentraciji hemoglobina 21. dana hospitalizacije i koncentraciji kreatinina i fosfora 14. i 21. dana. Potvrđena je statistički značajna korelacija između težine kliničke slike i broja trombocita, broja leukocita, koncentracije hemoglobina, serumskog kalcijuma i transaminaza na prijemu, dok je multivarijantnom analizom ustanovljen statistički značajan uticaj kombinacija faktora (trombociti i leukociti na prijemu; trombociti i koncentracija hemoglobina na prijemu). **Zaključak.** Na osnovu laboratorijskog i kliničkog nalaza na prijemu možemo prepoznati bolesnike kod kojih će se ispoljiti različita težina kliničke slike, sa različitom dinamikom kasnijih promena i ishodom.

Ključne reči:
hemoragijska groznica sa bubrežnim sindromom; znaci i simptomi; fizikalni pregled; radiografija; prognoza; lečenje, ishod.

Abstract

Background/Aim. Besides viral serotype, HLA haplotype and cytokine genes polymorphism are associated with clinical presentation of hemorrhagic fever with renal syndrome. Since these analyses are unavailable in routine clinical practice, the aim of this study was to assess clinical, laboratory and radiographic findings associated with clinical presentation of disease severity. **Methods.** A total of 30 patients (27 men and 3 women), average age 40 ± 14.9 years, treated for hemorrhagic fever with renal syndrome from January 1, 1999 to December 31, 2009 in Clinical Center of Serbia, were included in the study. Nine patients (30%) had mild, 14 (46.7%) moderate and 7 (23.3%) severe form of the disease; 24 (80%) recovered, 6 (20%) died in the acute phase of the illness, and 19 patients (63.3%) required hemodialysis. **Results.** The average titer of antiviral antibodies in patients infected with Belgrade serotype virus were significantly higher in those with severe clinical presentation. Hypotension, anuria, macrohaematuria, pulmonary infiltration, pleural effusion, hepatomegalia and positive meningeal signs were more frequent in the patients with severe form of the disease. Statistically significant differences between groups with mild, moderate and severe clinical picture were found in serum total protein, albumin, calcium, glutamate pyruvate and glutamate oxaloacetate transaminase on admittance; serum creatinine and phosphorus concentration on day 14 and day 21; serum sodium and calciums on day 14; hemoglobine concentration on day 21. A statistically significant correlation was found between clinical presentation of the disease severity and platelet count, white blood cell count, hemoglobine concentration, serum calcium and serum transaminases on admittance. Multivariate analysis identified variables` combinations associated with clinical presentation of the disease. **Conclusion.** Our study confirmed that we can distinguish patients who will manifest different severities of the disease on the basis of careful consideration of laboratory and clinical findings on admission.

Key words:
hemorrhagic fever with renal syndrome; sign and symptoms; physical examination; radiography; prognosis; treatment outcome.

Correspondence to: Mirjana Laušević, Klinika za nefrologiju, Klinički Centar Srbije, Pasterova 2, 11 000 Beograd, Srbija. Tel.: +381 11 2422 998, Mob: +381 64 165 88 77. E-mail: mlausevic@gmail.com

Uvod

Hantavirusi su široko rasprostranjeni u svetu. Kliničku sliku hemoragijske groznice sa bubrežnim sindromom (*hemorhagic fever with renal syndrome* – HFRS) koju izazivaju hantavirusi delimo na blagu, umereno tešku i tešku. Kod teških oblika bolesti obično razlikujemo pet faza: febrilnu, hipotenzivnu, oliguričnu, poliuričnu i fazu oporavka. Kod mnogih bolesnika pojedine faze oboljenja međusobno se preklapaju ili neke od njih izostaju.

U zemljama Dalekog istoka uzročnici HFRS najčešće su serotipovi virusa Hantan i Seoul. Pumala virus je najčešći uzročnik oboljenja u Centralnoj Evropi i Skandinavskim zemljama [1]. Ranije se smatralo da infekcija Pumala serotipom virusa izaziva blaže kliničke forme oboljenja, a danas je poznato da težina kliničke slike zavisi i od individualne predispozicije domaćina [2–4]. Smatra se da osim serotipa virusa i polimorfizam gena za citokine ima važnu ulogu u određivanju težine kliničke slike i ishoda oboljenja [5]. Bolesnici sa blagom kliničkom slikom i seropozitivne osobe sa supkliničkom formom oboljenja razlikuju se u pogledu distribucije gena za faktor nekroze tumora alfa (TNFα) i interleukin-1 (IL-1) od bolesnika sa težom formom oboljenja. Težu kliničku sliku imaju TNF alel 2-pozitivni bolesnici u odnosu na TNF alel 2-negativne [6]. Homozigoti za isti alel imaju izraženije sniženje bubrežne funkcije i češću potrebu za hemodijalizama od heterozigota [7]. Polimorfizam gena za citokine nije nezavisan faktor koji utiče na kliničku sliku, već se u tom pogledu pridružuje drugim genetskim faktorima kao što je HLA haplotip [8]. Teže kliničke slike su učestalije kod bolesnika sa određenim HLA antigenima, kao što je HLA B8 i DRB1*0301, dok je prisustvo HLA B27 povezano sa blažom kliničkom slikom [9].

Za razliku u patogenom potencijalu različitih serotipova hantavirusa odgovorna je varijabilnost G1 i G2 glikoproteina virusa preko kojih se oni vezuju sa integrinima, posrednicima za ulazak u ćeliju domaćina [10]. Teža klinička slika i veći mortalitet u regionu Balkana sugerisali su postojanje novih serotipova virusa, što je potvrđeno 90-ih godina prošlog veka. Tada je u Srbiji iz krvi bolesnika prvi put izolovan virus genetski sličan Hantan virusu, koji izazva oboljenje sa visokim mortalitetom (20%) i nazvan je Beograd [3, 11].

S obzirom na to da u rutinskom kliničkom radu nisu dostupna genetska ispitivanja koja bi ukazala na moguć razvoj teške forme oboljenja, a serološkim tehnikama često registrujemo koreakcije među serotipovima, cilj rada bio je da se ispita koji klinički, biohemijski i radiografski parametri i njihove kombinacije prate teže kliničke forme oboljenja.

Metode

Istraživanjem je bilo obuhvaćeno 30 bolesnika (27 muškaraca i 3 žene) hospitalizovanih na Nefrološkoj i Infektivnoj klinici Kliničkog centra Srbije u periodu 01.01.1999. do 31.12.2009. godine. Bolest je dokazivana na osnovu porasta titra antihantavirusnih IgG antitela u dva uzastopna uzorka seruma uzetih u vremenskom periodu od 7 dana, reakcijom indirektne imunofluorescencije (IIF).

Za klasifikaciju težine kliničke slike korišćeni su sledeći kriterijumi: laka ili blaga klinička slika bila je prisutna ako visina telesne temperature nije prelazila 39°C, broj dana sa temperaturom iznad 38°C ≤ 4, maksimalni broj leukocita ≤ 14 $\times 10^9$/L, minimalni broj trombocita ≥ 90 $\times 10^9$/L, minimalna visina sistolnog krvnog pritiska 96 mmHg i maksimalni dnevni volumen urina ≤ 3400 mL. Teška klinička slika bila je prisutna ako je bio pozitivan bilo koji od navedenih kriterijuma: visina telesne temperature ≥ 41°C, broj dana sa temperaturom iznad 38°C ≥ 7, maksimalan broj leukocita ≥ 30 $\times 10^9$/L, minimalan broj trombocita ≤ 39 $\times 10^9$/L, visina sistolnog krvnog pritiska ≤ 80 mmHg i maksimalni dnevni volumen urina ≥ 5000 mL. Bolesnici sa srednje teškom kliničkom slikom nisu ispunjavali nijedan kriterijum za tešku kliničku sliku, a vrednost najmanje jednog parametra je prevazilazila kriterijume za laku kliničku sliku.

Prosečna starost bolesnika bila je 40 ± 14,9 godina. Od 30 bolesnika 9 (30%) je imalo blagu, 14 (46,7%) srednje tešku, a 7 (23,3%) tešku kliničku sliku. Bolesnici sa blagom i srednje teškom kliničkom slikom bili su u proseku mlađi (38,8 ± 15,0 i 38,3 ± 13,0 godina) u odnosu na bolesnike sa teškom kliničkom slikom (45 ± 19,2 godina). Prvi simptomi bolesti javili su se 8 ± 3,3 dana pre hospitalizacije, a dužina hospitalizacije bila je prosečno 21,3 ± 12,3 dana. Bolesnici sa teškom kliničkom slikom hospitalizovani su ranije, s obzirom na početak prvih simptoma bolesti (6,6 ± 2,9 dana) u odnosu na bolesnike sa blagom i srednje teškom kliničkom slikom (8,1 ± 2,98 i 8,6 ± 4,0 dana), a dužina hospitalizacije ovih bolesnika bila je u proseku veća (26,8 ± 23,4 dana *vs* 19,9 ± 5,8 i 19,9 ± 8,7 dana).

Neposredno nakon prijema bolesnicima su uzimani uzorci krvi za kompletnu krvnu sliku i biohemiju, a ponovljeni uzorci krvi za ispitivanja po danima hospitalizacije uzimani su pre doručka, hemodijalize i primene heparina. Kod 19 (63,3%) bolesnika lečenih hemodijalizama one su započete u prva 24 časa po prijemu u našu ustanovu, a primenjena je bikarbonatna hemodijaliza sa polisulfonskom dijaliznom membranom F6 HPS proizvođača Fresenius Medical Care.

Za testiranje značajnosti razlike obeležja korišćene su univarijantna i multivarijantna analiza varijanse i metode korelacije. Statistička obrada urađena je pomoću programa SPSS-u10.0.

Rezultati

Konzervativno je lečeno ukupno 11 (36,7%) bolesnika, od tog broja 9 (81,8%) bolesnika se oporavilo, a dva (18,2%) su umrla. Hemodijalizama je lečeno 19 (63,3%) bolesnika, od toga 15 (78,9%) se oporavilo, a 4 (21,1%) su umrla u akutnoj fazi bolesti. Serotip virusa i prosečne vrednosti titra IgG antitela na pojedine serotipove prema težini kliničke slike prikazane su u tabeli 1.

Kod bolesnika sa teškom kliničkom slikom u poređenju sa bolesnicima sa blagom kliničkom slikom bili su češće prisutni hipotenzija (71,4% *vs* 0%), anurija (57,1% *vs* 0%), makrohematurija (21,4% vs 11,1%), plućna infiltracija (71,4% *vs* 22,2%), pleuralni izliv (71,4% *vs* 0%), hepatomegalija (21,4% *vs* 11,1%) i pozitivni meningealni znaci (85,7% *vs* 0%). Statistički značajna razlika između grupa sa blagom, srednje teškom i teškom kliničkom slikom nađena je u kon-

Tabela 1

Zastupljenost Hantan (H), Seoul (S), Pumala (P) i Beograd (B) serotipa virusa i prosečna visina titra antivirusnih antitela prema težini kliničke slike

Serotip virusa	Klinička slika		
	blaga	umerena	teška
H, S, B + [n (%)]	4 (44,4)	9 (64,3)	3 (42,8)
P + [n (%)]	1 (11,1)	3 (21,4)	2 (28,6)
H, S, P, B + [n (%)]	4 (44,4)	2 (14,3)	2 (28,6)
H ($\bar{x}$ ± SD)	1198,22 ± 843,48*	1405,71 ± 1209,47*	1618,29 ± 1418,85*
P ($\bar{x}$ ± SD)	291,56 ± 660,171**	468,57 ± 756,385**	1618,29 ± 1418,85**
S ($\bar{x}$ ± SD)	1425,78 ± 1269,87	1442,29 ± 1187,92*	2349,71 ± 2745,90*
B ($\bar{x}$ ± SD)	1312 ± 765,99*	1442,29 ± 1187,92*	3227,43 ± 3509,24*

*** – $p < 0,05$**
**** – $p < 0,01$**

centraciji serumskih proteina, albumina, kalcijuma, transaminaza na prijemu, serumskog natrijuma i kalcijuma 14. dana hospitalizacije; koncentraciji hemoglobina 21. dana hospitalizacije i koncentraciji kreatinina i fosfora 14. i 21. dana hospitalizacije. Značajnost razlike promena prosečnih vrednosti biohemijskih parametara nultog, 7, 14. i 21. dana između bolesnika sa blagom, srednje teškom i teškom kliničkom slikom poređena je Studentovim *t*-testom i prikazana u tabeli 2.

Tabela 2

Prosečne vrednosti laboratorijskih parametara i diureze po danima hospitalizacije u odnosu na težinu kliničke slike

Biohemijski parametri	Klinička slika			
	blaga	umerena	teška	F
Hg 0	121,7	136,1	110,8	2,31
Hg 21	126,2	107,1	101,4	4,25*
Kr 0	863,6	823,7	997,9	1,25
Kr 7	381,3 ^{a1}	491,5 ^{a1}	795,4 ^{a1}	1,89
Kr 14	137,8	168,4	464,2 ^{b2}	6,17*
Kr 21	129,2	125,7	241,8 ^{c2}	3,84*
Ur 0	36,0	38,0	42,0	0,55
Ur 7	19,8 ^{a1}	21,3 ^{a2}	22,4 ^{a1}	0,05
Ur 14	9,6	11,3 ^{b2}	13,9	0,79
Ur 21	8,2	7,2 ^{c2}	9,5 ^{c1}	0,8
TP_0	60,4	55,2	52,7	2,97*
TP_14	59,1	63,4 ^{a1}	66,3 ^{a1}	0,36
Alb 0	38,0	30,8	24,3	2,97*
Alb 14	35,2	33,8	31,0 ^{a1}	0,99
AST 0	25,8	77,4	118,3	2,25*
AST 14	27,0	22,1 ^{a1}	40,0	1,09
ALT 0	24,7	134,8	173,0	2,51*
ALT 14	27,3	31,3	32,2	0,11
Na 0	133,0	127,9	130,3	1,47
Na 14	139,8 ^{a1}	135,7 ^{a2}	133,0 ^{a1}	3,26*
Na 21	141,0	139,2 ^{c2}	138,2	1,68
Ca 0	2,0	1,8	1,7	2,9*
Ca 14	2,3 ^{a2}	2,0 ^{a1}	2,1	2,92*
Ca 21	2,3	2,2 ^{c2}	2,4 ^{c2}	1,07
P 0	1,9	2,4	2,3	1,55
P 14	1,5	1,3 ^{a2}	1,9	2,95*
P 21	1,2	1,2	1,3 ^{c2}	7,16**
DU 0	1375,0	562,5	842,9	1,84
DU 7	5000,0 ^{a2}	4316,0 ^{a2}	2600,0	1,5
DU 14	6016,7	6050,0	5340,0	0,1
DU 21	4800,0	3350,0 ^{c2}	4640,0	1,49

*** $p < 0,05$; ** $p < 0,01$; ^{a1} – $p < 0,05$, 0. dan; ^{a2} – $p < 0,01$, *vs* 0. dan; ^{b1} – $p < 0,05$ *vs* 7. dan; ^{b2} – $p < 0,01$,*vs* 7. dan; ^{c1} – $p < 0,05$ *vs* 14 dan; ^{c2} – $p < 0,01$ *vs* 14 dan; Hg – koncentracija hemoglobina (g/L); Kr – koncentracija serumskog kreatinina (umol/L); Ur – koncentracija serumske ureje (mmol/L); TP – ukupni proteini (g/L); Alb –koncentracija albumina (g/L); AST – aspartat aminotransferaze (IU/L); ALT – alanin aminotransferaze (IU/L); Na, Ca, P – natrijum, kalcijum, fosfor (mmol/L); DU – diureza (mL/24h); 0, 7, 14, 21 – dani hospitalizacije.**

Korelacija između težine kliničke slike i broja trombocita, broja leukocita, koncentracije hemoglobina, serumskog albumina, serumskog kalcijuma, serumske alanin aminotransferaze (ALT) i aspartat aminotransferaze (AST) prikazana je u tabeli 3. U cilju ispitivanja udruženog dejstva laboratorijskih parametara na težinu kliničke slike multivarijantnom analizom na dan prijema, bolesnike smo podelili u podgrupe prema intervalima nezavisnih parametara kako je prikazano u Tabeli 4. Pojedinačno i udruženo dejstvo ispitivanih parametara u momentu prijema na težinu kliničke slike dalo je značajnosti prikazane u tabeli 5.

Tabela 3

Spearmanova korelacija između laboratorijskih parametara i težine kliničke slike

Parametri	Koeficijent korelacije	*p*
Leukociti	0,415	0,023
Hemoglobin	-0,481	0,007
Trombociti	-0,687	0,000
Albumin	-0,150	ns
Aspartat aminotransferaza	0,449	0,013
Alanin aminotransferaze	0,427	0,018
Kalcijum	-0,319	0,05

ns – nije signifikantno

Tabela 4

Distribucija bolesnika prema intervalima nezavisnih parametara na dan prijema

Parametri	Intervali	Bolesnici [n (%)]
Trombociti ($\times 10^9$/L)	< 40	7 (23,3)
	> 40	23 (76,7)
Leukociti ($\times 10^9$/L)	< 14	17 (56,7)
	14–30	11 (36,6)
	> 30	2 (6,7)
Hemoglobin (g/L)	< 100	7 (23,3)
	> 100	23 (76,7)
Albumin (g/L)	< 30	22 (73,3)
	> 30	8 (26,7)
Kalcijum (mmol/L)	< 1,9	19 (63,3)
	> 1,9	11 (36,7)
Aspartat aminotransferaze (U/L)	< 27	9 (30,0)
	> 27	21 (70,0)
Alanin aminotransferaze (U/L)	< 30	10 (33,3)
	> 30	20 (66,7)

Tabela 5

Uticaj nezavisnih parametara i njihovih kombinacija na težinu kliničke slike

Parametri	F	*p*
Aspartat aminotransferaza	9,73	0,006
Alanin aminotransferaza	0,217	ns
Kalcijum (Ca)	1,247	ns
Trombociti (PLT)	13,25	0,002
Leukociti (WBC)	0,491	ns
Hemoglobin (Hg)	1,998	0,05
PLT – WBC	0,522	ns
PLT – Hg	3,746	0,05
WBC – Hg	0,166	ns
PLT – WBC – Hg	2,921	ns

ns – nije signifikantno

Diskusija

U našoj studiji nađena je veća učestalost težih kliničkih oblika bolesti (23,3%) u odnosu na podatke iz susednih zemalja na Balkanu, u kojima se teška klinička slika javlja kod oko 5%, a veoma teška, sa razvojem multiorganske disfunkcije i smrtnim ishodom, u oko 1% obolelih [12]. Objašnjenje za veću učestalost ispoljavanja teške kliničke slike bolesti može biti u većoj zastupljenosti infekcija sojevima virusa koji su odgovorni za teže kliničke forme oboljenja, dok je samo kod oko 20% bolesnika dijagnostikovana infekcija umala virusom koji izaziva blaže forme oboljenja. Učestalost infekcija Pumala serotipom virusa je u saglasnosti sa rezultatima drugih studija iz Srbije prema kojima su pozitivna antitela na Pumala virus prisutna kod 20% bolesnika, a antitela prema serotipu Beograd kod 35% [13]. Dodatni razlog za veću učestalost teške kliničke slike može biti i to što je naša ustanova tercijarnog ranga i ima zadatak da zbrinjava najteže bolesnike, dok su lakši slučajevi delom lečeni u regionalnim centrima. Većoj smrtnosti bolesnika u našoj studiji (20%) doprinosi veći procenat bolesnika sa teškom kliničkom slikom i upućivanje u našu ustanovu nakon višednevnog zadržavanja u regionalnom centru, kada su se pojavile komplikacije bolesti (teške sekundarne infekcije i multiorganska disfunkcija). Smrtnost bolesnika lečenih hemodijalizama nije se statistički značajno razlikovala od konzervativno lečenih bolesnika (21,1% *vs* 18,2%), pošto su uzroci smrti bili akutni respiratorni distres sindrom (*acute respiratory distress syndrome* – ARDS) i teške sekundarne bakterijske infekcije, a u slučaju jednog bolesnika lečenog konzervativno smrtni ishod je nastupio kao iznenadna smrt u fazi oporavka. Kod svih bolesnika lečenih hemodijalizama primenjene su bikarbonatne hemodijalize sa polisulfonskom *low flux* membranom F6HPS (Fresenius Medical Care, Srbija). Lečenje hemodijalizama je najčešće započinjano neposredno nakon prijema, ali su bolesnici upućivani u našu ustanovu u različitim vremenskim intervalima u odnosu na početak bolesti. Zbog toga je ograničena mogućnost donošenja relevantnog zaključka u pogledu uticaja ranih hemodijaliza na ishod bolesnika. Zbog malog broja umrlih bolesnika po grupama sa različitom težinom kliničke slike, ograničena ja i mogućnost izvođenja statistički relevantnog zaključka u pogledu povezanosti težine kliničke slike sa ishodom.

U našoj studiji, kod oko 80% bolesnika bila su prisutna antitela za više serotipova hanta virusa, za razliku od drugih studija u kojima je procenat koreakcija manji zbog korišćenja specifičnijeg ELISA testa za njihovo određivanje [13]. Visok procenat koreakcija može se samo delimično objasniti koegzistiranjem više serotipova virusa, a najvećim delom je posledica manje specifičnosti metode primenjene za njihovo određivanje.

Od posebnog značaja za razlikovanje težine kliničke slike su parametri čije se vrednosti razlikuju u ranom toku oboljenja i na osnovu kojih se već u momenu prijema mogu razlikovati bolesnici sa potencijalno težom kliničkom slikom i potrebom za brižljivijim praćenjem (kontrolom). To može biti odlučujuće kada je u pitanju donošenje odluke o daljem lečenju u regionalnom centru ili transportu u ustanovu višeg ranga. Naši rezultati pokazuju da više vrednosti transaminaza, izraženija hipoalbuminemija i hipokalcemija mogu usmeriti pažnju na bolesnike kod kojih će se klinička slika razviti u pravcu težih formi. Posebno bi izdvojili porast serumskih transaminaza, o čijem značaju u određivanju težine kliničke slike ima nedovoljno podataka, mada pojedine studije ipak ukazuju da se procenat bolesnika sa oštećenjem jetre povećava parelelno težini kliničke slike [14]. Blago do umereno povišene transaminaze ima više od 75% hospitalizovanih bolesnika, a hipoalbuminemiju njih oko 33% [15]. Oštećenje funkcije jetre nastaje u proseku početkom druge nedelje oboljenja, kada su naši bolesnici i hospitalizovani. Hipoalbuminemija je posledica gubitka belančevina preko creva i bubrega, povećane propustljivosti krvnih sudova i smanjene sintetske funkcije jetre, pa kako su svi ovi poremećaji često udruženi, nije iznenađujuće da je hipoalbuminemija povezana sa težinom kliničke slike. Statistički značajne promene koncentracije ukupnih proteina treba očekivati kod bolesnika sa srednje teškom i teškom, a serumskih albumina sa teškom kliničkom slikom (u podgrupama gde su njihove vrednosti bile značajnije snižene).

Elektrolitski disbalans je prisutan kod većine bolesnika u obliku hiponatremije, hipokalcemije, hiperfosfatemije i sklonosti hiperkalemiji. Poremećaj metabolizma kalcijuma i fosfora povezan je sa težinom bubrežne slabosti [16]. Hipokalcemija nastaje zbog snižene serumske koncentracije 1,25 dihidroksi vitamina D3 [17]. Doprinosi joj smanjen unos hrane i hipoalbuminemija. Hiperfosfatemija je umerenog stepena.

Razlike prema težini kliničke slike postoje i kada su u pitanju parametri koje uočavamo u kasnijem toku oboljenja (koncentracija serumskog kreatinina, natrijuma, kalcijuma i fosfora 14. dana hospitalizacije), ponekad i na samom završetku akutne faze oboljenja (kreatinin 21. dana ili hemoglobin 21. dana).

Nakon početnog utvrđivanja stanja bolesnika važno je pratiti dinamiku daljeg toka bolesti i prepoznati odstupanje od predviđenog toka događaja, koje može da sugeriše razvoj komplikacija. Statistički značajan pad koncentracije serumskog kreatinina treba očekivati u prvoj nedelji hospitalizacije (između nultog i sedmog dana prisutan je bez obzira na težinu kliničke slike). Kako je prema podacima iz literature azotemija prisutna u proseku između 4. i 15. dana od početka febrilne faze, nije iznenađenje da u daljem toku, između 7. i 14. i 14. i

21. dana nismo potvrdili dalji statistički značajan pad koncentracije serumskog kreatinina [17]. Izuzetak je podgrupa bolesnika sa srednje teškom kliničkom slikom, kod kojih je pad koncentracije serumskog kreatinina kasnije nastupio zato što smo u nekim slučajevima odlagali primenu hemodijalize (uglavnom je bila prisutna neoligurična forma akutne bubrežne slabosti). U grupi sa lakšom kliničkom slikom brzo nakon prijema nastupio je oporavak uz primenjenu konzervativnu terapiju, a u grupi sa teškom kliničkom slikom u lečenje su uključene i rane hemodijalize (samo 28,6% bolesnika sa srednje teškom kliničkom slikom imalo je više od pet hemodijaliza, za razliku od 71,4% bolesnika sa teškom kliničkom slikom).

Volumen diureze statistički značajno se menjao samo kod bolesnika sa lakšom i srednje teškom kliničkom slikom između nultog i 7. dana, što odgovara podacima iz literature prema kojima se oligurija očekuje između 3. i 10. dana od početka febrilne faze [17]. Kod bolesnika sa težom kliničkom slikom na manji volumen diureze uticalo je duže trajanje oligurične faze koja je bila prisutna u drugoj nedelji bolesti. Od uticaja je i prijem bolesnika sa teškom kliničkom slikom u ranijoj fazi bolesti (u proseku 3 dana ranije u odnosu na početak simptoma kod ostalih grupa). Početak poliurije kod pojedinih bolesnika ove grupe vremenski se podudario sa produženom oliguričnom fazom kod preostalih bolesnika iste grupe, pa kod ove grupe bolesnika nije ni došlo do naglog porasta volumena diureze u periodu kada je u podgrupama bolesnika sa blagom i srednje teškom kliničkom slikom poliurija već bila prisutna.

Statistički značajne promene koncentracije natrijuma u serumu bile su prisutne između 7. i 14. dana bolesti u svim grupama bolesnika bez obzira na težinu kliničke slike, što se poklapa sa podacima iz literature prema kojima je hiponatremija prisutna između 4. i 19. dana bolesti [17]. Vrednosti kalcemije statistički su se značajno menjale kod bolesnika sa lakšom i srednje teškom kliničkom slikom između nultog i 14. dana hospitalizacije, a kod bolesnika sa srednje teškom i teškom kliničkom slikom između 14. i 21. dana. Kako su vrednosti kalcijuma na prijemu korisne u otkrivanju bolesnika sa težom kliničkom slikom, očigledna je i različita dinamika oporavka hipokalcemije u daljem kliničkom toku.

Aktivnost serumskih transaminaza čiji je prediktivni značaj u momentu prijema kod naših bolesnika značajan, u daljem toku nije pokazala drugačiji trend kretanja kod bolesnika sa lakšom i težom kliničkom slikom. Prema podacima iz literature porast transaminaza se očekuje između 3. i 16. dana bolesti (u našoj studiji 16. dan bolesti se poklapa sa 8. danom hospitalizacije), što je moguće objašnjenje za ovakvu tendenciju [17, 18].

Statistički značajne promene koncentracije hemoglobina između nultog i 21. dana hospitalizacije registrovane su kod bolesnika sa srednje teškom i teškom kliničkom slikom. Kod njih je hemokoncentracija na početku bolesti izraženija. Prema podacima iz drugih studija hemokoncentracija je prisutna između 3. i 8. dana bolesti i može usloviti porast koncentracije hemoglobina za 20–30 g/L, što znači da su u momentu prijema u našu ustanovu neki bolesnici, posebno oni sa blažom kliničkom slikom, već bili van tog perioda [17]. Trombocitopenija je kod svih bolesnika korigovana u prvih sedam dana, a kod teže kliničke slike oporavak je nastavljen i posle 14. dana, što se poklapa sa podacima iz drugih studija prema kojima trombocitopenija postoji između 3. i 14. dana, sa minimalnim vrednostima između 6. i 10. dana. Multivarijantna analiza je potvrdila poseban značaj kombinacija parametara i njihovih intervala vrednosti za određivanje težine kliničke slike.

Zaključak

Na osnovu kliničkog i laboratorijskog nalaza prilikom prijema možemo razlikovati bolesnike kod kojih će se ispoljiti različita težina kliničke slike. Statistički značajna razlika između grupa sa blagom, srednje teškom i teškom kliničkom slikom nađena je u koncentraciji serumskih proteina, albumina, kalcijuma i transaminaza na prijemu. Analizom laboratorijskih parametara na dan prijema ustanovljena je statistička značajnost udruženog dejstva trombocitopenije i anemije na težinu kliničke slike.

Statistički značajna razlika između grupa sa blagom, srednje teškom i teškom kliničkom slikom nađena je u koncentraciji serumskog natrijuma i kalcijuma 14. dana hospitalizacije, koncentraciji hemoglobina 21. dana hospitalizacije i koncentraciji kreatinina i fosfora 14. i 21. dana hospitalizacije, što upućuje na mogućnost prepoznavanja različite dinamike bolesti različitog stepena težine. U sedmodnevnim intervalima praćenja uočena je i različita statistička značajnost promena prosečnih vrednosti biohemijskih parametara. Nađena je statistički značajna korelacija između težine kliničke slike i broja trombocita, broja leukocita, koncentracije hemoglobina, serumskog kalcijuma i aktivnosti transaminaze u serumu.

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Model of psychotherapeutic crisis intervention following suicide attempt

Model psihoterapijske intervencije u krizi nakon pokušaja samoubistva

Gordana Dedić*†

***Clinic for Psychiatry, Military Medical Academy, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia**

Key words:
crisis intervention; suicide, attempted; psychotherapeutic processes.

Ključne reči:
kriza, psihoterapeutska intervencija; samoubistvo, pokušaj; psihoterapeutski procesi.

Introduction

There is a strong evidence that suicide attempters need a psychiatric crisis intervention immediately after suicide attempt [1–3]. Mental illness, in general, has become less stigmatized in recent years, but suicide remains nearly as stigmatized as ever diminishing motivation of some subjects to ask for psychiatric help after suicide attempt [4].

In some recent meta-analysis study cohorts it was noted that a year after suicide attempt and subsequent problem-oriented psychotherapy, the repeated suicide attempt rate was reduced for about 30% [5]. After psychotherapeutic crisis intervention the number of hospitalizations was also reduced, but the number of those treated after the attempt in outpatient clinics was increased [6–8]. All this suggests positive results in suicide recidivism reduction after psychotherapy.

On the other hand, some reviews and meta-analyses of the therapeutic effect of psychotherapeutic crisis intervention suggest that about one half of patients are resistant when referred to the psychiatrist. The background of this is fear of being stigmatized as a psychiatric patient, but also subjective self-assessment of unnecessary psychiatric consultation. The doctors who do not regularly refer their patients after suicide attempt to psychiatric control examinations also have an important role in this. The problem is even more evident when after hospitalization a patient is left to self-decision concerning psychiatric consultations [9, 10].

Many reports on treatments of suicidal patients claim effectiveness in reducing suicidal behavior but fail to demonstrate which treatment interventions diminish suicidality.

The literature on a treatment model formation for suicidal patients is scanty. There are two types of these models: the first one is intervention in crisis which comprises actual dealing with the patient's suicidal ideations and the other one comprises continuous therapy emphasizing a long-term care of suicidal patients' feelings. This means that intervention in crisis is active, immediate intervention, while the continuous one is a long-lasting process. Yet, continuous treatment of patients after suicide attempt is advantageous because it offers a long-term improvement treating a patient as a responsible person and perceives suicidal behavior within the scope of a complete personality [11, 12].

In psychotherapeutic approach to a patient various methods and techniques such as behavioral, cognitive, dynamic etc. have been applied [13]. In cases of acute crisis, a supportive cognitively focused approach should be applied and in the chronic ones – an expressive, insight-oriented psychotherapy with elements of supportive approach [14, 15]. Dialectical behavior therapy devised by Linehan at al. [16] has been proved as the most effective one in the treatment of adult borderline patients after suicide attempt. However, only a limited number of studies report outcome of psychodynamic approach [17].

The aim of the paper was to explain our model of psychotherapeutic crisis intervention following suicide attempt, an empirically supported psychological treatment-specific manual for suicidal patients. In this paper our findings, from an outcome study on the basis of experience and a few extensive clinical trials of the treatment of suicidal behavior are described. We studied the efficacy of our model of psychotherapeutic crisis intervention following suicide attempt by self-poisoning using psychodynamic approach with supporting elements.

Our model of psychotherapeutic crisis intervention following suicide attempt includes: conceptual frame for assessment and treatment of persons after the suicide attempt; psychodynamic approach in psychotherapeutic crisis intervention following the suicide attempt; assessment of the degree of support given by the family and broader social environment in the treatment of a patient after a suicide attempt.

Correspondence to: Gordana Dedić, Clinic for Psychiatry, Military Medical Academy, Crnotravska 17, 11 040 Belgrade, Serbia.
E-mail: sdedic@sezampro.rs

In Serbia, all persons after a serious suicide attempt have been sent to the Clinic for Emergency and Clinical Toxicology, the Military Medical Academy (MMA) in Belgrade, which is a part of the National Poison Control Center. After being admitted to the Emergency Center, all admitters are hospitalized and treated in the Intensive Care Unit or at the appropriate department in dependence on the self-poisoning severity. Psychiatric consultation is possible only when the patient is restored to life.

Every patient after suicide attempt is first examined by a psychiatrist within the consultative psychiatric service of the Military Medical Academy. At the end of an examination of suicidal patients, a psychiatrist must define a conceptual frame for assessment and treatment of a person following suicide attempt.

Conceptual frame for assessment and treatment of persons following suicide attempt

Conceptual frame for assessment and treatment of persons after a suicide attempt includes: choice of the treatment method, selection of patients for psychotherapeutic crisis intervention and psychological assessment of persons following suicide attempt.

Choice of the treatment method

Within the consultative psychiatric service, a psychiatrist chooses the best treatment method (hospitalization, outpatient clinic treatment, psychotherapy and/or pharmacotherapy) for a suicidal patient. Pharmacotherapy in treatment of a suicide attempter is administered when necessary. It should be taken into consideration that pharmacotherapy is the only one among other therapeutic methods and that a registered drug for suicide prevention does not exist today. When choosing a drug, it is very important to have very detailed data on the type of a disorder, dominant symptoms excluding suicidal ideas, data on living conditions, environment support, side effects, as well as effect of the administered therapy.

Selection of patients for psychotherapeutic crisis intervention

In the therapeutic procedure with a suicidal patient one of the most important expertness is reflected in the assessment of indications for psychotherapy and intervention should be done according to this selection of patients for psychotherapeutic crisis.

Individual psychotherapeutic intervention is used in subjects who meet criteria for selection of patients for psychotherapeutic crisis intervention application [6]. We excluded the patients with diagnosis from F 00 to F 09, F 10 to F 19 (except F1x.0), F 20 to F 29 and F 30 to F 31 and F 32.3 satisfying ICD 10 (World Health Organization – WHO-criteria) [18].

Psychological assessment of persons following suicide attempt

In psychological assessment of persons following suicide attempt the following psychological tests are used: Hamilton Depression Rating Scale (HAMD), Center for Epidemiological Studies–Depression Scale (CES-D), Defensive Questionnaire Scale (DSQ-40), Scaling of Life Events (Paykel) and Pierce Suicide Intent Scale (SIS) [19].

Suicide attempters are depressed (HAMD = 22.60 ± 5.93), (CES – D = 29.67 ± 7.99), with medium suicide risk factor (SIS = 4.5 ± 4.17), use immature (projection, dissociation, devaluation, acting-out) and neurotic (altruism) defenses mechanisms. The most important motives for suicide attempt are separation problems, problems with parents and problem of loneliness. Commonest feelings and thoughts of a subject preceeding suicide attempt are wish to escape from unbearable situation, loss of control, desire to show love for partner and wish to be helped. After suicide attempt 90% of persons feel relief because it failed, while almost half of them intend to repeat it. Risk of the repeated suicide attempt is 1.8 (90% CI, 0.09–37.70; $p < 0.001$) times higher if values on the SIS Total Score are increased and 1.62 (90% CI, 0.03–81.39; $p < 0.001$) times higher if values on the Circumstances Score (SIS 1) subscale are increased, too [19].

Psychodynamic approach in psychotherapeutic crisis intervention following the suicide attempt

In the psychotherapeutic crisis intervention applied in our patients after the suicide attempt we use psychodynamic approach, which helps a patient to understand his/her pathologic behavior. Although there are two different modalities, crisis intervention and psychoanalytical psychotherapy are not antagonistic, but extremely compatible.

In our study we applied individual therapy of one séance in which the psychotherapist had to have appropriate method for a short psychotherapy for each individual case structured as a complete therapy for that very moment, because it was not certain whether the next one would be possible, at all.

We can say that psychotherapeutic crisis intervention following suicide attempt is analogous to the early phase of psychotherapy. The most important processes in both analyst's and patient's internal world develop in the mutual relationship between the conscious and unconscious. The nature of the analyst's intervention depends on what is happening in a patient's mind.

Psychotherapeutic crisis intervention following suicide attempt should be carried out in a soundproof room simply equipped with a table and two armchairs. Calm atmosphere is convenient for conversation lasting up to 50 minutes with each patient.

Psychotherapeutic crisis intervention following suicide attempt is oriented toward the need for a patient's relations with his/her surrounding to remain preserved and that connections between the crisis and the life history will be specified toward reconstruction and redefinition of relations with important persons and also toward development of a new network of relations. In this way crisis can lose its characteristic of existential break and instead of this it can get a dynamic value contradictory to that existence as much as it refers to the crisis itself.

This intervention should be carried out in an unfrightening tone and atmosphere in which a patient feels safe and the therapist's empathy for him. It also requires formulation of a clear model of intervention, which would enable work with a patient in a short period of time.

A model of psychodynamic approach in psychotherapeutic crisis intervention following suicide attempt is given in Figure 1.

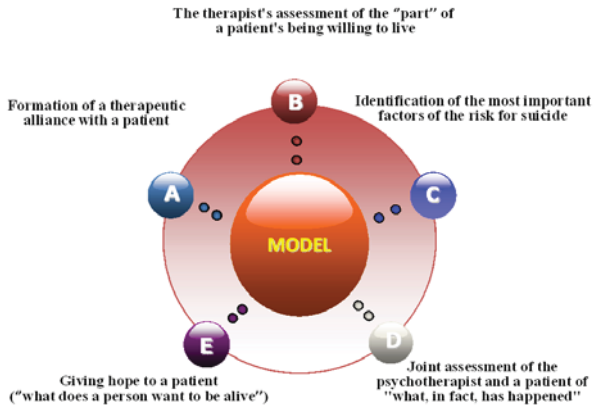

Fig. 1 – Psychodynamic approach in psychotherapeutic crisis intervention following suicide attempt

Formation of a therapeutic alliance with a patient

In psychoanalytical psychotherapy the working alliance is emphasized. The first contact between the psychiatrist and a patient after suicide attempt is of great importance. Alliance realized in the first several minutes develops on the level of intuition and it is very important for further relationship between psychotherapist and a patient.

Successful psychotherapy with a suicidal patient requires a complete therapist's emotional and active engagement. A real relationship, not transfer, should be emphasized. The therapist should be available as a firm, safe object that the patient can be identified with. The therapist's attitude is an expression of favor, not of neutrality. Alliance should be created on the therapist's attention paid to the patient's capabilities and qualities necessary for a successful, mature functioning.

The goal of psychotherapeutic crisis intervention is to relieve the patient's suffering and to find out the way to improve his/her adaptation ability to a new situation. In a setting in which both patient and therapist should feel comfortable, the therapist offers emotional containing and support, helps in modulation of the painful affects, confirmation, reality testing and education.

Therapist's assessment of the patient's "part" of personality willing to live

The therapist communicates with the patient's "part" of personality willing to live and assesses elements of his/her survival and mental status. Crisis causes decrease in one's intellectual capacities, first in a sense of using something concrete and absence of the abstract thinking. Confusion in a person after suicide attempt arises a feeling that alternatives and choices do not exist at all.

The basic principle in psychotherapeutic work with a patient following suicide attempt is that death does not solve the problem and that it is behind the patient. Live solves the problem because changes are possible only in that way. The therapist's patience, knowledge and appropriate approach are necessary for that.

Identification of the most important risk factors

The psychotherapist should assess dynamic causative factors of the suicide attempt. Taking into consideration that deconstruction of the basic models of understanding the world has been developed, of essential importance is regression to lower, more primitive levels of functioning as well as partial regression of the transference readiness and capability which includes intensification of desire for dependence. In transfer, it is important to recognize negative and positive responses and limitations during the subsequent regression, which can lead to a longer adaptation period. Therefore, the therapist plays the role, particularly in serious cases, of a primary object having a task to help in establishment of the patient's cognitive and emotional organization and to clear the way to the life-giving powers.

Suppressed neurotic conflicts and defect in ego organization influence upon a person's vulnerability to specific stressors. For this reason, selection of focus in crisis intervention is derived from the recognition of rigid defensive ways and problems in adaptation, which are partly reduced or dispelled by the newly occurred stress. With the help of the old problem in a new situation the crisis is allowed to develop out of symptoms and to enable solution of the conflict and the possibility of activity.

Psychotherapy can solve a feeling of aggression, envy, and jealousy of the introjected image, disturbed omnipotent control and of interpersonal relations and skills deficit. The therapist's task is to transform suicidal behavior into the reactivation of aggression toward the therapist.

A person after suicide attempt should be assisted to verbalize experience and to give it meaning. To change the experienced helplessness it is a focus of every psychotherapeutic effort. The offered therapist's support does not lessen a patient's loneliness, but provides contact with reality and conviction that the world, the same as it was before, still exists and that the therapist is ready to help him/her to return to it.

Joint assessment of the psychotherapist and a patient about "what did really happen"

By using professional focusing on the problem the therapist explains critical situation to every individual patient giving him/her opportunity to perceive in another way the problem resulting in suicide attempt.

Immediate crisis intervention is focused exclusively on the presence; it is focused on situation, not on the person. Its goals are close, direct and help is provided to persons who were healthy a day or two ago. They are even at that moment considered healthy, but they only reacted to serious traumatic experience in their own lives "like typical humans".

Emergency comprises urgent intervention in order to make the person return to normal life easier. Expectancy that recovery will be soon and effective and that the person will soon return to routine activities are present from the very beginning. In this way the possibility that a person after suicide attempt gets accustomed to the role of the patient is reduced, taking into consideration that it really is not a reaction of a sick person who can think of himself/herself in that way.

Giving hope to a patient ("what does the subject want to survive")

Finally, most persons in crisis are focused only on how to regain condition they previously used to function. Since only that is impossible, the therapist offers alternatives, which open the way out at least temporarily – offered, are activities enabling relaxation and control of some aspects of situation with the aim to eliminate the feeling of helplessness and hopelessness.

Crisis intervention should help a person to overcome the crisis and also to be something else in the following period – a guide, advice, and education. By crisis intervention actual relations within the family and with friends can be evaluated as well as, if possible, relations with persons important in a patient's past. This also suggests the need to evaluate methods of solving previous crisis by patient's education, profession, marriage and through social achievements; which were its advantages, values and what does the subject expects of the help. A person tries to examine own strength, which provides understanding of planning of possible activity levels necessary for a successful coping with crisis.

Psychotherapeutic crisis intervention following suicide attempt is carried out through:

a) Showing empathy, confidence and unlimitedness of time – the therapist shows empathy for despair of a suicidal person which most often uses mechanism of the emotional suffering avoidance through suicide rather than to share problems with other individuals. The psychotherapist has to send a message that suicide is some sort of solution, but not the only one and, by all means, not the best one. Of special importance is to inform a suicidal person that the therapist has empathy and understanding for him/her, that he does not want a repeated suicide attempt and finally, that he/she is always at the attempter's disposal.

b) Testing the degree of despair – using data obtained in the interview and from analysis of the Scaling of Life Events (Paykel), the therapist initiates conversation directing it toward change. In this test the therapist should not be scared of questions reviving feelings of despair and fatalism

c) Influence upon change in the way of thinking particularly in the segment where suicide is considered to be the single solution – to change the way of thinking that suicide is a single possible solution by simple comparisons familiar with and understandable to a suicidal person. To explain that suicide should not be treated as a single solution not giving any chance to see the possibility of any other one. Of special importance is to face a person with the fact that a long-lasting situation can be temporary and after several weeks the problem may seem quite different. In this way the time is saved, the response is delayed and a space of time is provided.

d) Help in problem solving – it is important to help a suicidal person to find alternatives. Following-up his/her process of thinking the psychotherapist helps such person also to perceive other situations. Also, it is of a particular importance to find out together some other ways in facing the problem.

e) Help in finding out possible solutions – it is very important to help a person after suicide attempt to start to believe in himself/herself and to develop self-confidence which will result in finding out a proper solution [20–23].

Assessment of the degree of support by the family and a broader social environment in treatment of a patient after suicide attempt

The psychotherapist should also assess sources of the external support that a person after suicide attempt could rely upon. The role of family support is a defender who relieves effect of the stressful events. It represents a very important source of the strength in overcoming the actual crisis, as well. Recognition that the subject is accepted, respected, loved, supported end that there are persons he/she can rely upon and get their help, enables regaining of self-respect and own image. All this helps to overcome even the most difficult life circumstances in an easier and faster way with less unfavorable consequences. On the contrary, hostile attitude of the family members can cause momentary withdrawal from the primary or secondary family of a person after suicide attempt. Family members often use denial and suppression as a mechanism of defense to protect themselves from terrifying thoughts and the feeling of guilt because a member of their family did that. Closeness of suicide as a frightening and terrifying possibility urges them to deny their connection with that act or to express empathy, or even to defend them against it. They also give it the status of extraterritoriality, foreign body, proclaiming it mental disease not affecting common people. In such case the therapist should intervene and include the family as cooperators in the treatment of their member.

Concerning a prevention plan the most can be done at the level of social community through activities oriented toward the reduction of the risk group, persons, and, isolationism, organization of various activities, groups, communities in which every person will feel safe and respected. Only positive activities are promoted, but negative ones influencing directly or indirectly upon possible suicide should be eliminated. Together with this, very important is, care for the feeling of belonging and change in the experience "I do not belong to anywhere". Through education of a complete population about useful ways of facing stress and positive communication, positive way of thinking could be influenced upon and mass-media have great importance in all this. Legal support should also be provided for persons in crisis.

Comments

The model of psychotherapeutic crisis intervention following suicide attempt assesses actual mental status of an attempter comprising the therapist's rapid assessment of depression seriousness, degree of the suicidal risk, suicidal plan characteristics, reasons and motives of suicide, assessment of

actual fear of stigmatization and also of patients attitude toward acceptance of the psychiatric help after the suicide attempt. Assessment of conscientious and unconscientiously conflicts leading to a suicide attempt represents initial basis for therapist's work with patient after the suicide attempt and for application of psychotherapeutic crisis intervention. Suicide attempters are depressed with medium suicide risk factor, use immature and neurotic defenses mechanisms. After the suicide attempt most of them feel relief because the attempt failed, while almost half of them intend to repeat it [19].

In therapeutic procedure we have contained patient's feeling of worthlessness, helplessness and feeling of guilt that we have transferred from the patient after suicidal attempt to us, psychotherapists. We have also tried to give him/her hope for life even though it was present only with us during the whole period of therapy. Patients were given alternatives suggesting values of life, which could be comprehended as realistic, and patients have learnt that there are ways to continue to live with pain instead to commit suicide. It is important to emphasize that both psychodynamic factors per se and psychopathology are not sufficient in assessment of a suicidal risk. Only by combination of all mentioned factors suicidal risk assessment in every phase of the treatment [24].

The most important motives for suicide attempt are separation problems, problems with parents and problem of loneliness. Commonest feelings and thoughts of a subject preceding the suicide attempt are wish to escape from unbearable situation, loss of control, desire to show love for partner and wish to be helped [19].

During our work with patients who attempted suicide and wanted to die we have tried through empathy to understand his/her suicidal fantasies, recognize released stimulating feelings of power but not underestimating their destructiveness. Together with all this we had in our mind that we should help him/her to overcome the actual situation [25].

Patients who have attempted suicide establish ambivalent relationship with their psychotherapist making him/her great countertransferential problems. In the course of psychotherapy patient often uses the therapist as a self-object, an experience which changes patient's narcissistic balance. Suicidal patients create a self-object transfer by attacking therapist, similarly to relations they had with important figures in their childhood. Concealed attacks are very unpleasant for the therapist's feelings of self-estimation. Unwillingness of the suicidal patient to confide a secret to therapist causes his/her ambivalence toward both therapist and life, in general. Behavior of the suicidal patient is additionally complicated by his/her emotional reactions and demands posed to the therapist, by the therapist's own reaction and by influence of some other important ones. Apart from this, therapist must not take over the whole patient's life on himself/herself only to support the patient. Therapist may be in the situation in which patient demands his availability in any moment aiming to include him into the wide range of own problems. Suicidal patient intends to get into a symbiotic relationship with the therapist, from which both partners can hardly get out without generating anxiety in each other. Degree to which the therapist yields patient in his/her dependent need or, on the contrary, to which he encourages patient to learn to be responsible, is a matter of clinical assessment [26].

Psychotherapist has to be permanently cool and ready for conversation with a suicidal person in all circumstances. However, to be able to fulfill that task the therapist himself must solve the own attitude toward death. If the therapist is scared of death he/she will neither be able to recognize signs which undoubtedly, lead the patient to suicide, nor to be on the side of value of even life defense together with the patient. Opinion not very rare even among psychiatrists that the failed suicide attempt means that, in fact, there was no serious suicidal intention has to be rejected. Therapist has to initiate conversation about suicidal intentions with his patient including detail of his/her suicidal plan.

On the other hand, therapist can play the role of the patient and experience his/her painful feelings. Because of the risk for therapist to be succumbed by the patient's way of thinking and to make or strengthen false mental structures which will create him/her problems, countertransferential supervision of the therapist's reactions is necessary [27].

A special problem in countertransference can be therapist's reaction of the patient and his/her withdrawal from analysis.

After the psychotherapeutic crisis intervention none of our patients was referred to the hospital treatment, but psychotherapy without any financial compensation was recommended to all of them. Only 16.7 % of our patients, however, came to psychiatric consultation to the outpatient clinic, at the Department for Mental Health and Military Psychology of the Military Medical Academy.

Fear of stigmatization in connection with psychiatric treatment transfers to fear of stigmatization related to psychiatric aid to patients after suicide attempt. Previously mentioned investigations speak in favor of the fact that a large number of patients after suicide attempt self-initiatively do not ask for psychiatric helps either during the actual hospitalization or after hospital treatment because they do not recognize the need to accept psychiatric aid in their situation. The same happened with our patients. Therefore, it can be seen that psychotherapeutic crisis intervention applied in patients after suicide attempt during their hospitalization is their only contact with a psychiatrist, which is, in fact, its greatest importance.

The absence of motivation and refusal to continue psychotherapy confirm that we cannot have the omnipotent role in making decisions instead of our patients, either in present or in future, either in their lives or death. We also cannot bear responsibility for possible repeated suicide attempt of our patients. The only possible thing that we can do in psychotherapeutic crisis intervention is to convince our patients in vainness of escape into suicide, in, for them, already known refuge.

After the psychiatric crisis intervention 6.7 % of our patients repeated suicide attempt during the following year. One of them repeated suicide attempt by serious self-harming in the beginning of psychotically decompensation, and was hospitalized in the Clinic of Psychiatry; second repeated suicide attempt for the same reasons (financial prob-

lems) he had had at the moment of previously suicide attempt. Both of them did not ask psychiatric help before their suicide attempt.

In spite of a pessimistic prognosis that patients accept psychiatric aid with difficulty, effects of the psychiatric crisis intervention applied in the work with our patients represent great stimulus for our further professional efforts.

Conclusion

Assessment of conscientious and unconscientious conflicts leading to suicide attempt represents initial basis for therapist's work with a patient after suicide attempt and for application of psychotherapeutic crisis intervention. In psychotherapeutic crisis interventin the psychotherapist renders help to the person who attempted suicide with the aim to relieve his/her suffering and to integrate painful feelings which can be helpful in coping with them in a more constructive way and find out how to enhance own capacities of adaptation to newly created situation, so that the person could regain normal mental functioning level.

Suicide attempters are depressed with a medium suicide risk factor, so it is very important to use an integrative therapeutic approach, combining pharmacotherapy and psychotherapy in psychotherapeutic crisis intervention following suicide attempt.

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CURRENT TOPIC

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Are the carotid kinking and coiling underestimated entities?

Da li su morfološke abnormalnosti karotidne arterije (*kinking* i *coiling*) beznačajne?

Djordje Radak[*†‡], Srdjan Babić[*†], Slobodan Tanasković[*†], Predrag Matić[*†], Vuk Sotirović[*], Predrag Stevanović[*§], Predrag Jovanović[*†], Predrag Gajin[*†]

[*]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [†]Dedinje Cardiovascular Institute, Clinic for Vascular Surgery, Belgrade, Serbia; [‡]Serbian Academy of Sciences and Arts, Belgrade, Serbia; [§]Clinical Hospital Center "Dr. Dragiša Mišović", Belgrade, Serbia

Key words:
carotid artery, internal; carotid artery diseases; risk assessment; cerebrovascular disorders; ultrasonography; angiography; vascular surgical procedures.

Ključne reči:
a.carotis interna; aa. carotis, bolesti; rizik, procena; cerebrovaskularni poremećaji; ultrasonografija; angiografija; hirurgija, vaskularna, procedure.

Introduction

The terms "kinking" and "coiling" were first thoroughly explained and presented to the professional public in the early sixties by a group of authors – Weibel et al. [1] and Metz et al. [2] (Table 1). According to this classification coiling (loop) is defined as the elongation of the internal carotid artery (ICA), which causes the appearance of S- or C-shape angulation or the appearance of circular formations. Kinking is one of the variants of a coiling, or angulation of one or more segments of the ICA and could be associated with local or global cerebral symptoms (Figure 1).

The occurrence of carotid abnormalities (CAs), verified by arteriography varies between 10% to 43% of the cases [1–3]. Kinking occurs in 5%–16% of patients [4, 5], mostly elderly men, and is associated with atherosclerotic pathology, while coiling is more common in younger women [6]. Up to 75% of morphological abnormalities were localized 2–4 cm proximal to the carotid bifurcation [2]. The use of ultrasound examination in the ongoing clinical practice has enabled rapid, morphological and also functional studies of CAs [7]. In the study of Del Corso et al. [8] more than half of the number of patients with cerebrovascular symptoms had some forms of CAs diagnosed by ultrasound technique.

Table 1

Modified criteria of the morphologic abnormalities of internal carotid artery (ICA) (Wiebel-Filds and Metz)

Type of CAs	Forms of morphologic abnormalities of ICA	Symptoms
Kinking	Mild – angulation of elongated ICA with an angle ≥ 60 °	-
	Medium – angulation of elongated ICA with angle between 30 ° – 60 °	±
	Severe – angulation of elongated ICA with angle < 30 °	+
Coiling	Angulation of elongated ICA with the formation of S or C shape, or appearance of circular formations	±

CAs – carotid abnormalities

CAs are rarely observed in children and young, and could be explained by congenital etiology in these cases. During the third trimester of intrauterine development occurs the lowering of the heart in the chest (*descensus cordis*) and any difference in speed of growth of the skeleton and supraaortic branches can lead to the associated vascular abnormalities of blood vessels, which are usually bilateral [8, 9]. These disorders of embryonic development explain the presence of CAs in newborn babies and fetuses [1]. Beigelman et al. [10] in a series of 885 patients, aged 1 to 90 years, showed no difference in the prevalence of kinking or coiling among age groups, favoring the embryogenic mechanism of the development of CAs.

Correspondence to: Srđan Babić, Dedinje Cardiovascular Institute, Milana Tepića 1, Belgrade, Serbia. Phone.: +381 65 33 03 000, E-mail: sdrbabic@sezampro.rs

Fig. 1 – Multidetector computed tomography show high "Z" shaped kinking of right internal carotid artery (left) and typical 360º coiling of left internal carotid artery located in proximal part of artery (right)

Among children coiling is often the reason for reduced cognitive capacity, slow neuropsychological development as well as focal or grand mal convulsions [11].

In contrast to congenital, acquired form of kinking and coiling is most commonly associated with aging, hypertension and traditional risk factors for atherosclerosis [2, 8, 12]. It is proved that the arterial blood vessels are prone to deformation when exposed to elevated blood pressure [13]. Hypertension causes the extension of smooth muscle cells of the media of blood vessels, which is associated with elastin loss and fragmentation of elastomers. Progression of this process eventually leads to abnormal elongation of blood vessels [13–17]. Pancera et al. [12] showed that the prevalence of hypertension in patients with kinking is significantly higher than with patients without morphological abnormalities of blood vessels ($x = 6 : 44$, $p < 0.02$). However, a clear link between vascular risk factors and kinking and coiling is still not fully understood.

Clinical features and diagnosis of carotid abnormalities

The appearance of symptoms of kinking and coiling of the carotid arteries is associated with intracranial and extracranial occlusive disease, frequent and sudden variations in blood pressure as well as the unfavorable position of the head and neck [1, 18]. In the chain of pathological dynamics, associated atherosclerotic stenotic changes represent the second link, but their development can transform kinking in the hemodynamically significant anomaly [8, 19, 20]. It is sometimes difficult to prove the connection, but isolated CAs can lead to cerebral symptoms, without the presence of atherosclerotic changes.

Symptoms presentation most commonly appear due to transitory hypotension during sleep or sudden and extreme movement of the head and neck [1, 21, 22]. In the majority of patients, symptomatology generally withdraws with the return of the head in neutral position. However, kinking without atherosclerotic plaque, although often present, rarely can be considered as the cause of stroke, as compared with carotid stenotic diseases [23, 24]. Ischemic cerebrovascular accident occurs in about 11%–33% of cases with CAs [6].

It is pathognomonic that typical (stereotypical) movements of the head and neck can induce ischemic symptoms, with ipsilateral rotation of the head usually leading to the biggest reduction of the carotid flow [25]. Extreme flexion or extension of the neck can manifest a pre-existing kinking leading to almost complete occlusion of viable arteries. Hemodynamic mechanism of brain ischemia involves episodic or permanently reduction in perfusion through the anomalous part of the artery. If baroreceptor activity is preserved, due to specific rotation of the head and neck, the reduction of lumen of kinking or coiling occurs and the increased pressure level proximal to the compression may appear. As a result, a decrease in perfusion pressure occurs with symptoms of a global ischemia of the brain. It has been proven that a reduction regional cerebral flow in extracranial elongation of carotid segments appears with 30–35 mL per min (normal range 50–60 mL per min per 100 g. brain tissues). Importance of kinking becomes significantly increased if there is associated stenosis of carotid bifurcation [23, 24, 26].

In the diagnostic process of CAs, duplex ultrasonography as an initial diagnostic tool is most commonly used. However, for these patients who have an ultrasound verified kinking or coiling with the angulated segment speeds over 100 cm/s, as well as ones with cerebrovascular symptoms, additional diagnostics procedures are required. Angiography [multidetector computed tomography angiography and magnetic resonance imaging (MRI)] allows visualization of the intracranial and extracranial part of carotid vessels [1, 2], while selective angiography is reserved for CAs of non-atherosclerotic origin, because of their frequent association with anomalies in other arterial segments [9, 10]. Hemodynamically significant kinking is the one with angulation less than 60°, and with the flow rate within a limited segment of over 200 cm/s, while the coiling is significant if there is a full cir-

cle segment formed (360°). Computed tomography (CT) and MRI of the brain provide information about ischemic changes in brain structure and serve as a differential diagnostic tool, which can exclude similar symptoms, but of another etiology.

Treatment of carotid abnormalities: indications and surgical techniques

Choosing the right method for treatment of CAs is still a subject of numerous debates. A large number of studies [3, 5, 9, 11, 21, 24, 27–30] have shown the efficiency and safety of surgical correction of kinking and coiling. However, the first randomized, prospective study that to some extent clarified this dilemma was published in 2005 by Ballotta et al. [31]. They concluded that the surgical correction of symptomatic CAs is better in preventing stroke compared with best medical therapy, as well as it completely eliminates the symptoms in patients with non-hemispheric symptoms.

Similar with these findings, Radak et al. [32] underlined that operative management is best therapeutic option for patients with near total occlusion of ICA. Surgical correction of symptomatic kinking and/or coiling makes up about 5% of all reconstructive procedures for cerebrovascular insufficiency [24, 33].

Surgical correction of CAs is indicated for: patients with transient ischemic attacks (focal, hemispheric ischemic simptoms); patients in whom angiography demonstrated hemodinamically significant kinking and/or coiling; if CT and MRI examination excludes other significant ischemic brain injury; and in symptomatic and asymptomatic patients with one-sided CAs and occlusion of contralateral carotid artery; bilateral kinking and/or coiling, with the correction of one side first, if the symptoms do not disappear, then the other side as well, and patients with simultaneous lesions of vertebral artery [6, 31, 34, 35]. Kinking and/or coiling are predisposing factor for ICA dissection (Figure 2). Even associated with dramatic ultrasound finding, treatment of these lesions remains medical in the majority of cases, with anticoagulants and antiplatelet drugs [36]. However, bilateral high kinking with distal dissection of ICA is indicated for surgical repair but only in cases with confirmed cerebral symptoms. This type of intervention is associated with frequent peripheral nerve lesions and high mortality rate [36].

The surgical technique of resection of tortuous segment, with dilatation and reimplantation has become the method of choice in treating carotid kinking and coiling. If there are atherosclerotic changes associated with CAs in the same procedure eversion carotide endarterectomy can be done [21, 31, 35]. Correction of kinking and coiling is performed with peroperative mortality rate below 1% and low postoperative morbidity [11, 21, 26, 27]. Similarly, Radak et al. [37] reported low total mortality rate after endarterectomy procedures of carotid artery [37]. Neurological symptoms of cerebral ischemia retreat even in 85% of patients. The lowest percentage of improvement occurs in patients with global (nonspecific) neurological symptomatology, as well as in the case of severe preoperative neurological deficit [23, 38, 39]. Recurrences of kinking and coiling are rare and can appear in patients with uncontrolled hypertension [8, 19, 40, 41].

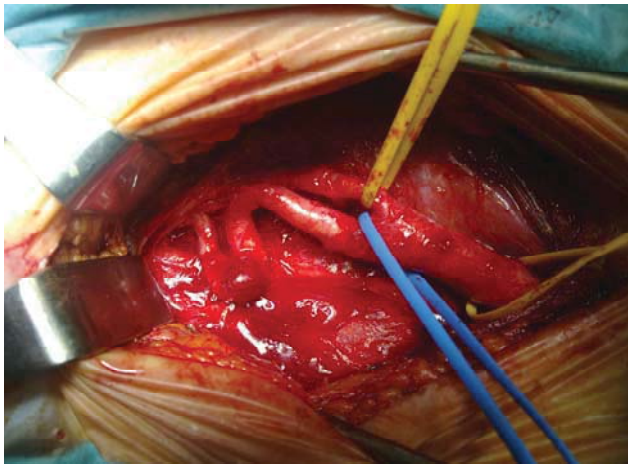

Fig. 2 – Kinking with dissection of internal carotid artery

Conclusion

Morphological CAs, kinking and coiling, are common in the general population, with still unexplained etiopathogenesis and the course of the disease.

Despite the great success of surgical reconstructions, because of the lack of multicentric, randomized, prospective studies, appropriate therapeutic treatment is still subject of numerous debates.

The purpose of this work was systematization of current data for preparation our multicentre, randomized, prospective trail.

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CASE REPORT

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Fabry disease, do we think enough about this multisystemic disorder? – A presentation of three cases in a Serbian family

Fabrijeva bolest, razmišljamo li dovoljno o ovom multisistemskom poremećaju? Prikaz tri bolesnika iz jedne porodice u Srbiji

Dejan Sakač*, Goran Koraćević†, Tatjana Pavlica‡, Slobodan Sekulić§

***Clinic of Cardiology, Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia; †Clinic of Cardiology, Clinical Center Niš, Niš, Serbia; ‡Department of Biology and Ecology, School of Natural Scienes and Mathematics, University of Novi Sad, Novi Sad, Serbia, §Clinic of Neurology, Clinical Center of Vojvodina, Novi Sad, Serbia**

Abstract

Background. Fabry Disease is a rare, X-chromosomal inherited lysosomal storage disease with a consequent intracellular accumulation of neutral glycosphingolipids in various tissues. This can cause skin and ocular lessions, progressive renal, cardiac or cerebrovascular disorders. If a person in a family has Fabry disease, other family members including even extended relatives, may also be at risk. **Case report.** We presented three cases pointed out various manifestation of Fabry disease, that illustrate a possible cause for otherwise unexplained cardiac hypertrophy and various rhythm and conduction abnormalities. **Conclusion.** Although most symptoms begin in childhood, various manifestations often lead to misdiagnosis and clinical diagnosis is frequently delayed for many years, even decades. Enzyme replacement therapy has become available, pointing out the importance of early diagnosis so that treatment can be initiated before irreversible organ damage.

Key words:
fabry disease; chromosome aberrations; genetic diseases, inborn; diagnosis, differential.

Apstrakt

Uvod. Fabrijeva bolest je retka, X-hromozomno nasledna lizozomna bolest nakupljanja sa posledičnim intraćelijskim nagomilavanjem neutralnih glikosfingolipida u različitim tkivima. To može da uzrokuje patološke promene kože i očiju, progresivne bubrežne, srčane ili cerebrovaskularne poremećaje. Ako jedna osoba u porodici ima Fabrijevu bolest, i drugi članovi porodice, uključujući čak i širu rodbinu, takođe mogu biti ugroženi. **Prikaz bolesnika.** Prikazana su tri bolesnika iz jedne porodice sa ciljem da se ukaže na vrlo različite manifestacije Fabrijeve bolesti i na moguć uzrok, inače, neobjašnjive hipertrofije miokarda i poremećaje srčanog ritma i provođenja. **Zaključak.** Iako većina simptoma počinje u detinjstvu, različite manifestacije bolesti često dovode do pogrešne dijagnoze i otkrivanje bolesti često kasni mnogo godina, čak i decenija. Enzimska supstituciona terapija postala je dostupna, ističući važnost ranog utvrđivanja bolesti, tako da se lečenje može započeti pre nastanka ireverzibilnih oštećenja organa.

Ključne reči:
fabrijeva bolest; hromosomi, anomalije; nasledne bolesti; dijagnoza, diferencijalna.

Introduction

Fabry disease (FD), also known as morbus Anderson-Fabry, is a rare X-chromosomal inherited lysosomal storage disease caused by mutations in the galactosidase alpha gene (GLA gene) that result in deficient activity of the lysosomal enzyme α-galactosidase A. The ensuing enzyme deficiency results in intracellular accumulation of neutral glycosphingolipids (primarily globotriaosylceramide) in the vascular endothelium, particularly in kidneys, heart, nervous system, skin or in other cell types [1, 2]. The incidence of FD is estimated to range from 1 : 40,000 to 1 : 117,000 worldwide, but these figures likely underestimate the burden of disease because its manifestations often lead to misdiagnosis and underreporting [3]. Although most symptoms begin in childhood, clinical diagnosis is frequently delayed. Female carriers are at risk of developing disease, but this tends to be milder and more slowly progressive than in males. In males, symptoms can begin in the first decade of life with acroparesthesia and pain, febrile crises, hypohidrosis, heat intolerance, gastrointestinal disturbance and cutaneous angiokeratomas. From the second decade onward, patients can develop proteinuria and

Correspondence to: Dejan Sakač, Institute of Cardiovascular Diseases of Vojvodina, Institutski put 4, 21 204 Sremska Kamenica, Serbia. Phone: +381 21 480 5 100. E-mail: dejsakac@open.telekom.rs

neurologic manifestations [4]. Data about enzyme replacement therapy suggest that it has the potential to attenuate and possibly reverse some aspects of organ involvement [5, 6].

Case report

There is no documentation about index patient (grandmother), but there are data about her son from the second marriage – case 1, her granddaughter – case 2, as well as for her son from the first marriage – case 3 (Figure 1).

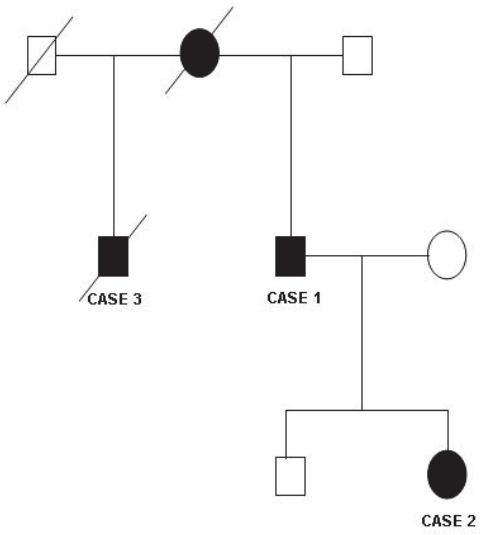

Fig. 1 – Family history of three patients with Fabry disease (cases 1–3). Males are denoted by squares, females by circles. Filled symbols indicate those with Fabry disease. Open symbols indicate unaffected subjects. The dashes indicate deceased patients

fibrillation with hypertrophy of the left ventricle (Figure 2). The patient was normotensive, but echocardiogram revealed concentric hypertrophy of the left ventricle (interventricular septum thickness 1.5 cm, posterior wall thickness 1.4 cm in end-diastole) with normal ejection fraction. Then, signs of forgetfulness and dormancy has been noticed. Magnetic resonance imaging of the endocranium was without pathological findings. As palpitations repeated, the patient underwent ergometry (to the 3rd minute, 100W, Bruce protocol), with the normal finding. During laboratory screening proteinuria was also registered (997.3 mg/L; referent values < 140 mg/L) while creatinine levels were normal. Finally, data of positive family history of an early death of his half-brother raised suspicion of inherited disease. Blood tests to measure the level of alpha-galactosidase A activity were performed at the Institute of Medical Biochemistry, Clinical Center of Serbia, Belgrade, and revealed low activity (0.81 nmoL/h/mg, referent values > 60 nmoL/h/mg proteins from leucocytes). Measurement was repeated in Hamburg University Medical Center, Germany, which registered activity below its referent range (16.92 pmoL/spot; referent values 200–2000 pmoL/spot, from dried blood). A subsequent genetic analysis was performed in the University Medical Center, Ljubljana, Slovenia (genomic DNA was extracted from peripheral blood, DNA regions of the α-galactosidase A gene were analyzed by polymerase chain reaction after amplifying each of α-galactosidase A exons and sequencing the opposite strand), where a hemizygous nucletid substitution c.334C > G was registered, resulting in change of aminoacid arginine to glycine (p.R112G). This confirmed the diagnosis of FD (Table 1).

Case 2 – the daughter of the case sensed paresthesia at the age of 14, now aware of inherited disease in the family,

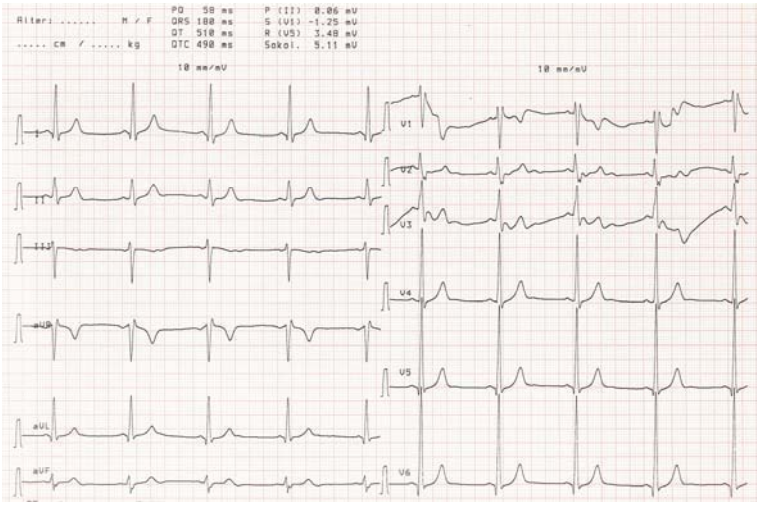

Fig. 2 – A standard 12-lead electrocardiogram demonstrating left ventricular hypertrophy by voltage criteria and incomplete right bundle branch block

Case 1 – a 21-year-old male, sensed upper abdominal pain with occasional episodes of diarrhea. He repeatedly underwent gastrointestinal investigation, including gastroscopy, which found no abnormalities. At the age of 40 he felt palpitations, electrocardiogram (ECG) registered paroxysmal atrial

she went through ophthalmology evaluation which registered discrete signs of corneal opacities (*cornea verticillata*) and radial lens opacities. A subsequent genetic analysis was performed in Slovenia which confirmed nucletid substitution, as her father's findings.

Table 1

Gold-standard methods for confirmation Fabry disease

Gender	Diagnostic step 1	Diagnostic step 2
Male	Alpha-galactosidase A activity in peripheral leucocytes (or plasma)	Alpha-galactosidase A gene sequencing and identification of disease - causing mutation
Female	Alpha-galactosidase A gene sequencing and identification of disease - causing mutation*	

*** Alpha-galactosidase A activity in peripheral leucocytes is not preferred and plasma levels are unreliable**

Case 3 – finally, family got the part of medical documentation of the grandmother's oldest son, of her first marriage, who at that time had started living with his father. The father noticed signs of intellectual deterioration, impared memory and lethargy in his late teens. The deterioration was progressive with new signs, such as balance disturbances and ataxia. Clinical investigation was performed in the United Kingdom (in 1982) where urine examination showed a markedly increased concentration of ceremide trihexoside and ceremide dihexoside while brain biopsy showed accumulation of Periodic acid-Schiff stain (PAS) positive, birefringent and sudanophilic material. Soon, at the age of 32, the patient died.

Discussion

Historically, FD has been believed to be a rare disease [1–3]. However, a recent study using an alpha-galactosidase A assay on blood spots from 37,104 consecutive Italian male neonates, has demonstrated a prevalence of 0.03% and an incidence of alpha-galactosidase A deficiency of 1 in 3,100. These data are in accordance with the findings of studies that have reported a prevalence of 0.2–1.2% in patients with end-stage renal disease on hemodialysis and 4.9% in men with cryptogenic stroke [4]. Although many symptoms occur in childhood, a proper diagnosis can be delayed by as much as 10–15 years. Because of typical skin lesions, dermatologists are often the first to make the diagnosis. Cardiac involvement is present early in life, but is not detected clinically until the third or fourth decade [7, 8]. Cardiac abnormalities in FD are usually presented as left myocardial hypertrophy, various rhythm and conduction disturbances. In all cases with unexplained cause of cardiac hypertrophy or various rhythm and conduction abnormalities, always think about FD as a differential diagnosis. Enzyme replacement therapy (ERT) for FD was introduced in Europe in 2001. ERT has been shown to clear accumulated glycosphingolipids (Gb 3) in blood vessels as well as from other organs [9, 10]. ERT is recommended in all male with FD, children and female carrier with signs and symptoms of FD. Follow-up and additional studies are necessary to fully evaluate long term efficacy of ERT in children with FD [8, 10, 11]. There are no reliable data about the incidence of FD in Serbia, so further investigation and screening are desirable.

Conclusion

Although most symptoms begin in childhood, various manifestations often lead to misdiagnosis and confirmation of FD is frequently delayed. The incidence is obviously underestimated. Prenatal screening, screening of asymptomatic relatives and predictive testing provide an opportunity to detect preclinical disease and start treatment to prevent long-term complications.

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CASE REPORT

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Portal hypertension caused by postoperative superior mesenteric arteriovenous fistula

Portna hipertenzija prouzrokovana gornjom mezenteričnom arteriovenskom fistulom

Dušan Dj Popović*, Milan Špuran*, Lazar Davidović†‡, Tamara Alempijević*‡, Milenko Uglješić*‡, Igor Banzić†, Dragica Jadranin†, Nada Kovačević*‡, Mirjana Perišić*‡, Momčilo Čolić†, Miodrag Krstić*‡

***Clinic for Gastroenterology, †Clinic for Vascular Surgery, Clinical Center of Serbia, Belgrade, Serbia; ‡Faculty of Medicine, University of Belgrade, Belgrade, Serbia**

Abstract

Introduction. Arteriovenous fistula of the superior mesenteric blood vessels is a rare complicaton in abdominal surgery. **Case report.** We presented a 49-year-old man with cramp-like abdominal pain, abdominal distension and weight loss symptoms, with a history of previous small bowel resection and right colectomy, due to Crohn disease, 16 years ago. Clinical examination revealed a paraumbilical pulsation with systolic murmur and thrill. Ultrasonography and computed tomography revealed cystic dilatation of the superior mesenteric vein, hepatomegaly and ascites. Upper endoscopy revealed grade I esophageal varices with portal hypertensive gastropathy. The diagnosis of arteriovenous fistula between superior mesenteric artery and vein was confirmed by angiogram of the superior mesenteric vessels and resection of the fistula was performed. Control examination after nine months showed no signs of portal hypertension. **Conclusion.** Early diagnosis and treatment of mesenteric blood vessel arteriovenous fistula prevents portal hypertension development and its complications.

Key words:
arteriovenous fistula; mesenteric arteries; mesenteric veins; diagnosis; surgical procedures, operative; prognosis; hypertension, portal.

Apstrakt

Uvod. Razvoj arteriovenske fistule mezenteričnih krvnih sudova je retka komplikacija abdominalnih hirurških intervencija. **Prikaz bolesnika.** Bolesnik, star 49 godina, primljen je u našu ustanovu zbog bolova u trbuhu, nadimanja i gubitka telesne mase. Bolesnik je 16 godina ranije imao resekciju tankog creva i desnu hemikolektomiju zbog Kronove bolesti. Fizikalnim pregledom u trbuhu, paraumbilikalno otkrivena je pulsirajuća rezistencija sa čujnim sistolnim šumom. Ultrasonografijom i kompjuterizovanom tomografijom otkriveni su aneurizmatska dilatacija gornje mezenterične vene, hepatomegalija i ascites. Endoskopskim pregledom viđeni su variksi jednjaka I stepena i hipertenzivna portna gastropatija. Angiografskim pregledom verifikovana je arteriovenska fistula između gornje mezenterične arterije i vene, te je sprovedena resekcija fistule. Na kontrolnom pregledu nakon devet meseci, bolesnik nije imao znakove portne hipertenzije. **Zaključak.** Ranim otkrivanjem i lečenjem arteriovenskih fistula mezenteričnih krvnih sudova sprečava se razvoj portne hipertenzije i njenih komplikacija.

Ključne reči:
arteriovenska fistula; aa. mesentericae; vv. mesentericae; dijagnoza; hirurgija, operativne procedure; prognoza; hipertenzija, portalna.

Introduction

Arteriovenous fistula (AVF) affecting superior mesenteric vessels are uncommon, and have usually been observed in patients who have undergone abdominal surgery or have abdominal trauma [1–7]. Due to localisation in the portal circulation, it increses blood flow in the portal vein and may produce portal hypertension with its complications. We presented a patient with superior mesenteric AVF, which developed 16 years after small bowel resection and right colectomy.

Case report

A 49-year-old-male patient was admited to our hospital due to cramp-like abdominal pain, abdominal dystension, malaise, fatigue and weight loss of 8 kg for one month. Symptoms appeared one month before admission. Sixteen

Correspondence to: Dušan Dj. Popović, Clinical Center of Serbia, Clinic for Gastroenterology, Str. Koste Todorovića 6, 11 000 Belgrade, Serbia. Phone: +381 11 366 37 34. E mail: dr.popovic@ptt.rs

years ago, the patient had small bowel resection and right colectomy for ileus caused by ileitis terminalis (Morbus Crohn). He had no complains until the present illness. At physical examination, the patients was subicteric. Abdominal examination revealed a soft, mobile, pulsating mass in the paraumbilical region. The abdominal, systolic murmur was heard and thrill was palpated. Laboratory tests showed elevated leucocyte count 12 × 10^9/L (4.0–10.0 × 10^9/L), erythrocyte sedimentation rate 32 mm/h (2–10 mm/h), fibrinogen 7.9 g/L (2–4 g/L), total bilirubin 28.7 μmol/L (3–22 μmol/L), conjugated bilirubin 15.5 μmol/L (0–7 μmol/L), aspartate aminotransferase 155 U/L (14–50 U/L), alanine aminotransferase 477 U/L (21–72 U/L), alkaline phosphatase 310 U/L (38–126 U/L) and gamma-glutamyl transpeptidase 287 U/L (8–78 U/L). Other biochemical parameters were within the reference range. Other causes of liver diseases were excluded (no history of alcohol consumption, negative viral markers, autoantibodies and laboratory tests for metabolic diseases). Ultrasonography and computed tomography (CT) of the abdomen showed hepatomegaly, ascites around the liver and a small polyp in the gallbladder. The superior mesenteric vein (VMS) was dilated, aneurismatic (8 × 5 × 12 cm) (Figure 1). Doppler ultrasonography revealed dilatation

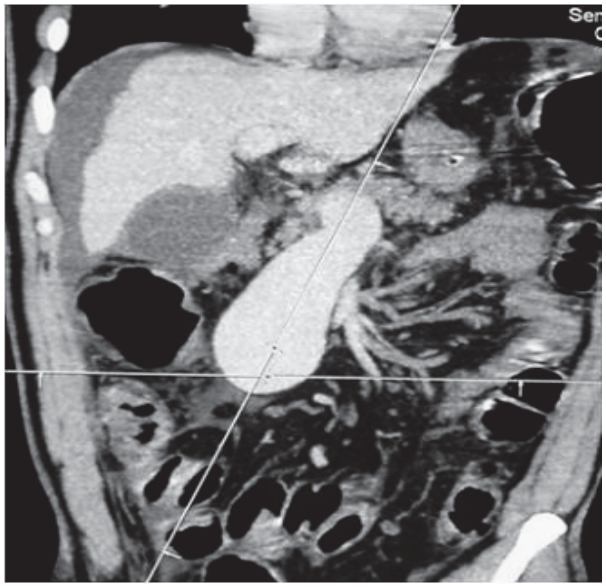

Fig. 1 – Computed tomography showed dilatation of the superior mesenteric vein

of portal vein (28 mm) with hyperkinetic flow (v = 31 cm/s). The lienal vein was considered normal, as well as diameter and its flow. Upper endoscopy revealed grade I esophageal varices without „red cherry spots“. Portal hypertensive gastropathy also often described as snake-skin appearance was detected in the fornix and corpus of the stomach. Colonoscopy did not detect recidive of Crohn`s disease. Selective arteriography of the superior mesenteric artery (AMS) demonstrated dilatation of AMS, aneurismatic dilatation of VMS and its early filling directly from the AMS (Figure 2). Midline laparotomy was performed. Fistulous communication between the AMS and VMS was demonstrated (Figure 3). An AVF had a thick wall and external appearance of the

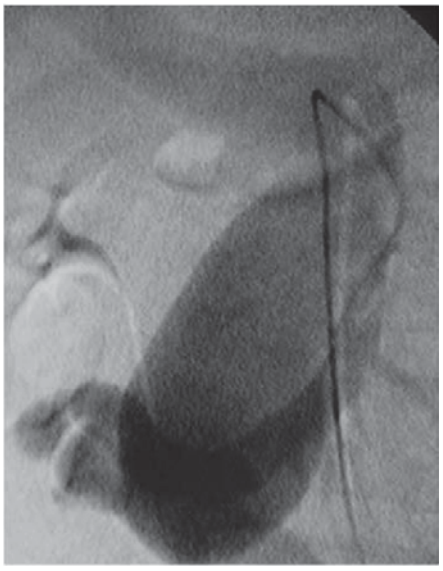

Fig. 2 – Selective arteriography of superior mesenteric artery (AMS) demonstrated dilatation of AMS and aneurismatic dilatation of the superior mesenteric vein

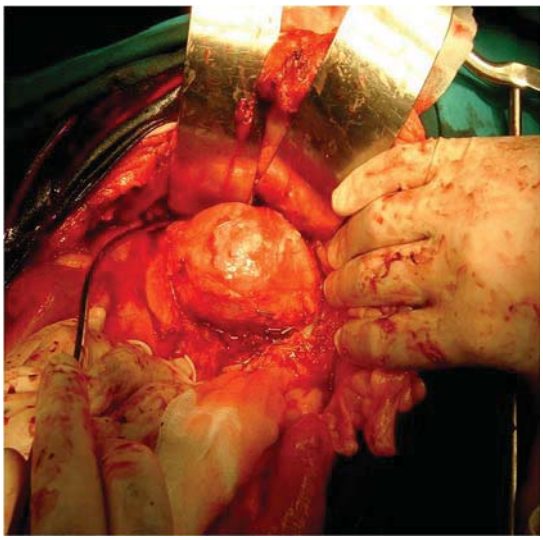

Fig. 3 – A fistulous communication between the superior mesenteric artery and vein after midline laparotomy and its release

large artery and vein. After occlusion of the AMS and VMS proximally and distally, transverse incision was made into the artery aspect of the AVF. Communication between AMS and VMS, was about 15 mm in diameter. After closure of the AVF with continuous suture, partial resection of arteriovenous aneurysm has been performed followed by venous closure. After release of clamps, the veins in the mesentery of the small bowel decreased in size. The postoperative course was uneventful. The patient was discharged on the 10th postoperative day. On control examination after nine months the patient had no complains. He gained 13 kg weight, biochemical parameters were within the reference range. Doppler ultrasonography and upper endoscopy were without sign of portal hypertension.

Discussion

Portal hypertension is characterized by an increase in portal vein pressure as a result of impediment to portal flow [8]. According to the level of impediment it may be prehepatic, intrahepatic and posthepatic. AVF is a patological, direct communication between an artery and a vein, when blood bypasses a capilary bed. An AVF may be congenital or acquired: congenital one is a result of persistent embryonic blood vessels that fail to differentiate into arteries and veins [9], while an acquired occurs as a consequence of surgery or injures [9–12]. AVF of the superior mesenteric blood vessels is a rare complication of abdominal surgery. The first case was described in 1960 by Movitz and Finne [13]. Delays in diagnosis after surgery have been reported up to 20 years [14]. In case of our patient, the AVF became symptomatic 16 years after the surgery. Clinical presentation varies from asymptomatic to manifest, most commonly as cramping abdominal pain with or without diarrhea [3, 7, 12, 15, 16]. Pain is a result of ischemic bowel, as blood is "stolen" by the portal system leaving the segment distal to the fistula with a compromised arterial circulation. Diarrhea is probably related to impaired perfusion of the mucosa [17]. Portal hypertension, congestive heart failure, or gastrointestinal tract hemorrhage have also been reported [14, 15, 17–21]. In the presented patient, the first symptoms were abdominal dystension and cramp-like abdominal pain, as a result of portal hypertension. Clinical examination is performed to detect paraumbilical pulsation and systolic murms with thrill, such was in our patient. Abdominal ultrasonography and CT indicate the presence of AVF between AMS and VMS, with portal dilatation vein [3, 21]. However, selective arteriography AMS, allows the determination of exact location and extensiveness of AVF. In the presented patient, AVF was diagnosed by ultrasonography and CT of the abdomen, and the diagnosis was confirmed by selective arteriography of AMS. There are two modalities of the therapy: surgery and interventional radiology methods (percutaneous catheter embolisaton) [3–5, 7, 19, 20, 23, 24]. Surgery has traditionally been the method of choice for treating AVF involving superior mesenterial vessels, but significant morbidity and mortality associated with surgical treatment has made interventional radiology methods priority, except in patients with relative or absolute contraindications for surgery [25, 26]. The presented patient had achieved complete recovery after operative treatment. Early diagnosis and treatment of mesenteric blood vessel AVF prevents the development of portal hypertension and liver damages with its sequelae of variceal bleeding and ascites [21].

Conclusion

AVF of the superior mesenteric blood vessels is a rare complicaton of abdominal surgery. This disease should be kept in mind in patients who present with cramping abdominal pain, diarrhea and signs of portal hypertension, who in the past had abdominal surgery or trauma. Early diagnosis and treatment prevents the development of liver and heart damages, with all eventual complications.

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CASE REPORT

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Tolosa-Hunt syndrome – Diagnostic problem of painful ophthalmoplegia

Tolosa-Hunt sindrom – dijagnostički problem bolne oftalmoplegije

Jelena Paović*, Predrag Paović*, Ivica Bojković†, Mirjana Nagulić‡, Vojislav Sredović§

***Institute for Eye Disease, ‡Institute for Neurosurgery, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Department of Ophthalmology, General Hospital, Zrenjanin, Serbia, §Health Centre Inđija, Inđija, Serbia**

Abstract

Background. Tolosa-Hunt syndrome (THS) is an uncommon disease caused by non-specific inflammation of the cavernous sinus, superior orbital fissure and the apex of the orbit. The disease is characterized by periorbital pain, paresis of the bulbomotor and quick response to steroid treatment. The orbital process may lead to optic nerve atrophy. According to the International Headache Society Classification of 2004, the diagnostic protocol includes magnetic resonance imaging (MRI) and biopsy. **Case reports.** We presented 46-year old male patient, with THS. The patient had unilateral periorbital pain, inflammatory process in the cavernous sinus, the apex of the orbit and the paranasal sinuses. Inflammatory process had spread into the fascia of the bulbomotor and performed compression to the optic nerve, causing paresis of the bulbomotor, protrusion of the eyeball and atrophy of the optic nerve. Pulse doses of corticosteroids were effective. Regarding the presented patient, diagnostic dilemmas arose from nonspecific sinusitis. The initial ophthalmological diagnosis, based on periorbital pain, drop in visual acuity and the narrow chamber angle was angular glaucoma, which resulted in a delayed diagnosis of THS and the beginning of the treatment. MRI and positive response to the treatment with corticosteroids were relevant for making the diagnosis. **Conclusion.** According to the International Headache Society Classification of 2004, THS is an entity that occurs rarely, its etiopathogenesis is unknown, it is manifested clinically by unilateral orbital pain associated with simple or multiple oculomotor paralyses, which resolves spontaneously but may recur. MRI orbital phlebography and biopsy are the recommended methods for making diagniosis. In our patient MRI findings and positive response to the corticosteroide treatment were relevant for making the diagnosis.

Key words:
tolosa-hunt syndrome; diagnosis; diagnosis, diferential; radiosurgery; drug therapy; treatment outcome.

Apstrakt

Uvod. Tolosa-Hunt sindrom (THS) je nespecifično inflamatorno oboljenje kavernoznog sinusa, gornje orbitalne fissure i vrha orbite. Oboljenje se karakteriše periorbitalnim bolovima, parezama bulbomotora i povoljnim efektom na kortikosteroidni tretman. Orbitalni proces može da dovede do atrofije optičkog nerva. U skladu sa Internacionalnim društvom za klasifikaciju glavobolja od 2004. godine dijagnostički protokol uključuje nuklearnu magnetnu rezonancu i biopsiju. **Prikaz bolesnika.** Prikazan je bolesnik, star 46 godina, sa THS. Bolesnik je imao unilateralni periorbitalni bol, zapaljenski proces u kavernoznom sinusu, vrhu orbite i paranazalnim šupljinama. Zapaljenski proces je zahvatio fascije bulbomotora i doveo do kompresije optičkog nerva, pareze bulbomotora, protruzije očne jabučice i atrofije optičkog živca. Pulsne doze kortikosteroida bile su efikasne. Dijagnostička dilema je bila nespecifični sinusitis. Početna oftalmološka dijagnoza zasnovana na periorbitalnim bolovima, značajnom padu vida, povećanom intraokularnom pritisku i plitkoj prednjoj očnoj komori bila je angularni glaukom, a posle ispitivanja magnetnom rezonancom (MR) započeto je lečenje kortikosteoridima na koje je bolesnik dobro odreagovao. **Zaključak.** Prema Međunarodnoj klasifikaciji Društva za glavobolje iz 2004. godine, THS predstavlja entitet nepoznate etiopatogeneze. Klinički se manifestuje unilateralnim orbitalnim bolom udruženim sa pojedinačnom ili multiplom paralizom okulomotora, koja spontano može nestati ili se ponovno pojaviti. Dijagnostički protokol ovog sindroma obuhvata MR, orbitalnu flebografiju i biopsiju. U ovom slučaju odlučujući nalazi za dijagnozu THS bili su nalaz MR i pozitivan odgovor bolesnika na primenu kortikosteroida.

Ključne reči:
tolosa-hunt sindrom; dijagnoza; dijagnoza, diferencijalna; radiohirurgija; lečenje lekovima; lečenje, ishod.

Correspondence to: Jelena Paović, Institute for Eye Disease, Clinical Center of Serbia, Belgrade, Serbia. Phone.: +381 63 245 552. E-mail: velikiceda@yahoo.com

Introduction

Tolosa-Hunt syndrome (THS) is a condition caused by nonspecific granulomatous inflammation of the cavernous sinus, superior orbital fissure and/or the apex of the orbit. The disease is characterized by periorbital pain, headaches on the same periorbital side and diplopia. Clinical signs of the disease are slight protrusion, limited movements of the eyeball due to paresis of the oculomotor nerve and sensitive outbreaks in the area of V1 and V2 branch of the trigeminal nerve [1–15]. The disease is recurrent and it responds well to steroid treatment [5–7, 16]. According to the redefined diagnostic criteria, THS is unspecific granulomatous inflammation diagnosed by nuclear magnetic imaging and biopsy [7, 16–18, 19]. We presented a male patient with THS, previously diagnosed with angular glaucoma.

Case report

A 46-year old male patient referred to the ophthalmologist within one week due to decreased vision in his right eye and pain on the right side of the head. The ophthalmologist made a diagnosis of angular glaucoma based on increased intraocular pressure (TOU = 22 mmHg) and gonioscopic findings of the narrow chamber angle. Visual acuity was normal (VOU = 1.0). The therapy was antiglaucomatous (dorzolamide hydrochloride/timolol maleate ophtholmic solution 2 times per day).

One month later, in February 2009 the patient referred to the ophthalmologist again due to severe periorbital pain, drop in vision of the right eye and double vision. During ophthalmological examination, protrusion of the right eyeball was detected as well as limited movements and diplopia. Intraocular pressure was normal (TOU = 18 mmHg), the vision of the right eye decreased and visual acuity was 0.4, while the visual acuity of the left eye was normal. Computed tomography (CT) head scan and otorhinolaryngological (ORL) findings spoke in favour of non-specific chronic sinusitis (both maxillary sinuses, left frontal sinus and right sphenoidal sinus), without visible orbital tumor mass. The therapy was antiglaucomatous. In the period from February 2009 to April 2009 the vision of the right eye was 0.1. The patient had severe periorbital headache on the right side.

In April 2009 the functional endoscopic sinus biopsy was performed in the ORL Clinic. The histological finding was: polyposis without description. Based on this histological finding the decision to perform maxillary sinus surgery was made.

In May 2009 maxillary sinus surgery was performed in the ORL Clinic. During the operation a tissue filling in the right maxillary sinus, expanding to the adjacent tissues, was detected and the surgery was given up. The biopsy was not made. After the surgery, the ophthalmologist sent the patient to the tertiary ophthalmological institution. The patient had severe periorbital headache on the right side and could not see on his right eye.

In June 2009, after ophthalmological examination it was established that the visual acuity of the right eye was VOD = L+ P+ and of the left eye VOS = 1.0. Intraocular pressure was normal, TOU = 12 mmHg. The right pupil reacted more sluggishly to the light. Atherosclerotic changes in the blood vessels were observed in the fundus. The right papilla was atrophyc with clear borders. Due to CT and ORL findings it was presumed that the patient suffered from Wegener's granulomatosis, THS or pseudotumour of the orbit of some other etiology. The patient had to undergo laboratory examinations and nuclear magnetic resonance imaging. Laboratory tests such as erythrocyte sedimentation rate and basic biochemical analysis were within the normal limits, except C-reactive protein (CRP), the levels of which were higher and amounted to 23.3 units. The value of circulating immune complexes (CIC), cANCA, pANCA, were within the normal limits.

Magnetic resonance imaging (MRI) scan of the endocranium performed in July 2009 primarily proved the inflammation of the right cavernous sinus with the protrusion of inflammatory process through the superior orbital fissure into the intraconic section of the orbit in which it caused pseudotumor spreading along the same-sided maxillary nerve and the mandibular nerve. In making the differential diagnosis, THS should be considered, although it is not possible to exclude the spreading of inflammatory process from the sphenoidal sinus “per continuitatem” (Figure 1).

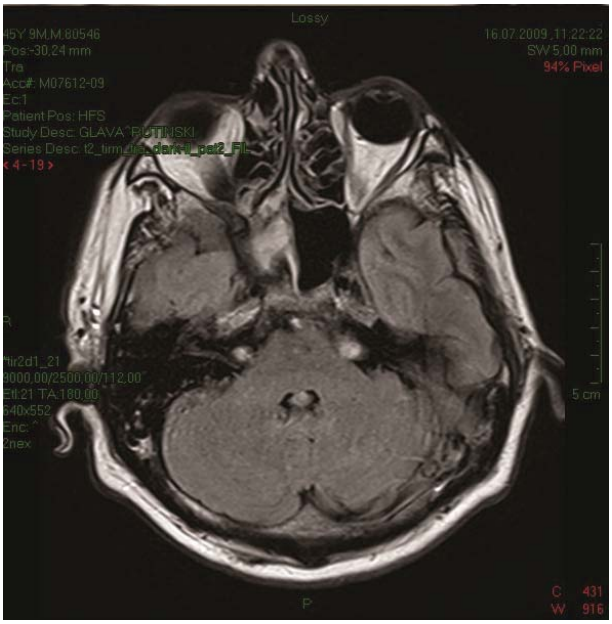

Fig. 1 – Magnetic resonance imaging (MRI) scan in July 2009 (before corticosteroid treatment)

The patient received pulse doses of corticosteroids (1000 mg methylprednisolon administered intravenously for five days), and then, he received 80 mg of methylprednisolon *per os* and the dose was gradually decreased for 2 months. After the applied treatment the patient did not feel pain. The mobility of his eyeball and intraocular pressure were normal, visual acuity was VOD=L+ P+. In the following course the patient had periods of an impairment of the disease characterized by headaches due to which he received pulse doses of

corticosteroids. The ophthalmological finding was unchanged.

A control MRI scan of the endocranium performed 7 months later as compared to the previous result revealed the following: obvious reduction in the retrobulbar intraocular substrate by about 40%, which was most markedly reflected in the lateral aspect with the persistently lower circumferential perineural zone, and still persistent zone of paracavernous inflammation to the same extent (Figure 2). The ophthalmological course in the following year was unchanged. The clinical aspect showed an improvement of the disease.

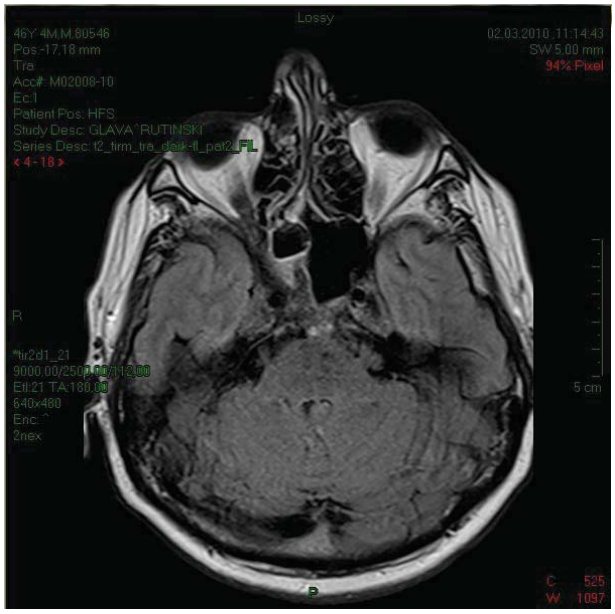

Fig. 2 – Magnetic resonance imaging (MRI) scan in March 2010 (7 months later following corticosteroid treatment)

Discussion

Tolosa-Hunt syndrome is uncommon disease. In the period from 1988 through 2002 only 124 cases of the disease were analysed and published [3]. In the period from 2009 to 2011 twenty five cases were described [11–14, 16, 18–36] three of them were children [20, 24, 31].

THS is characterized by initial and recurrences episodes of painful ophthalmoplegia due to idiopathic granulomatous inflammation of the cavernous sinus and orbita [1–15]. In our case the propagation of pseudo inflammatory process from the cavernous sinus into the retrobulbar space and paranasal cavities was interpreted by the otorhinolaryngologist as non-specific sinusitis. The confirmation of chronic non-specific sinusitis was obtained from a histological result: polyposis. The initial diagnosis was angular glaucoma due to a shallow front anterior eye chamber and increased intraocular pressure. It was treated with an antiglaucomatous therapy.

Further on, the disease manifested itself by severe periorbital pain, diplopia, limited movements of the eyeball and eyeball protrusion which was an indication of an inflammatory orbital process. Anisocoria was present – the right pupil was wider and it reacted more sluggishly than the left pupil. There was a drop in visual acuity and the atrophic papilla of the optic nerve indicated inflammatory process spreading around the optic nerve and that some compression made on it. Diseases that might be included in the differential diagnosis, such as Wegener's granulomatosis were excluded. The key diagnostic procedure was MRI which proved inflammatory process spreading in the cavernous sinus, along the superior orbital fissure into the retrobulbar space, reaching the fascia of the bulbomotor and spreading around the second half of the intraorbital section of the optic nerve on the same side. In 2004, the International Headache Society (IHS) redefined the diagnostic criteria for THS specifying that granuloma, demonstrated by magnetic resonance imaging or biopsy is required for diagnosis.

Steroid therapy dramatically reverses symptoms and clinical signs [5–7, 16].

Because they also may respond to steroids, tumors such as lymphoma and meningioma [15, 23, 37], and orbital tumors can make differential diagnosis difficult. MRI findings before and after systemic corticosteroid treatment are important diagnostic criteria to make the final diagnosis of THS and to diferentiate it from other cavernous sinus lesions that stimulate THS [17].

The pulse doses of corticosteroids resulted in a significant withdrawal of the inflammatory process and discomforts that the patient felt [5–7, 16]. The atrophy of the optic nerve and poor vision acuity remained as definite ophthalmological findings due to the delayed diagnosis and the delayed initiation of appropriate treatment.

In the differential diagnosis, diseases similar to THS are diseases of various etiology, such as neoplasms, and infectious diseases [23, 28, 32, 38]. The cases of granulomatous pachymeningitis spreading into the cavernous sinus and secondary spreading to the hypophysis were described [39]. The simultaneous occurrence of THS and fibrillary glomerulonephritis was reported [35]. It is speculated that bacterial infection might cause clinical features mimicking THS [40].

THS could be diagnosed in patients with carotid-cavernous fistula [29, 30, 34, 36]. The case of recurrent alternating THS was described [27].

Conclusion

According to the International Headache Society Classification of 2004, THS is an entity that occurs rarely, its etiopathogenesis is unknown, it is manifested clinically by unilateral orbital pain associated with simple or multiple oculomotor paralyses, which resolves spontaneously but may recur. MRI, orbital phlebography and biopsy are the recommended methods for making diagniosis.

In this case MRI and positive response to the treatment with corticosteorids were relevant for making the diagnosis.

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CASE REPORT

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Primary leptomeningeal melanocytosis – A case report with an autopsy diagnosis

Primarna leptomeningealna melanocitoza

Živković Nikola, Mihailović Dragan, Žaklina Mijović, Maja Jovičić Milentijević

Institute of Pathology, Faculty of Medicine , University of Niš, Niš, Serbia

Abstract

Introduction. Primary melanocytosis of the leptomeninges is a rare tumor, most likely originating from the melanocytes in the leptomeninges. The average survival is only about 5 months. **Case report.** A 61- years-old woman presented with headache, amaurosis and hallucinations lasted for two months, and she had been treated at the Clinic for Psychiatry and Clinic for Infectious Diseases. The cerebrospinal fluid analysis showed a lower level of glucose and a higher level of proteins. Small shaded areas of basal leptomeninges and hydrocephalus were found by computed tomography and magnetic resonance imaging. The autopsy showed a dark brown mass on basal leptomeninges with blurred boundaries. No pigmented skin lesions were found. Histopathological analysis revealed a primary leptomeningeal melanocytosis. **Conclusion.** Primary leptomeningeal melanocytosis is a rare tumor, difficult to diagnose. This case is being presented for its specificity, since this diagnosis is not frequently seen in practice.

Key words:
meningeal neoplasms; diagnosis; tomography, x-ray computed; magnetic resonance imaging; autopsy; 6 enzyme-linked immunosorbent assay.

Apstrakt

Uvod. Primarna melanocitoza leptomeningi predstavlja redak tumor, koji najverovatnije nastaje od melanocita koji se nalaze u leptomeningama. Prosečno vreme preživljavanja iznosi samo oko pet meseci. **Prikaz bolesnika.** Prikazana je bolesnica stara 61 godinu koja je imala dvomesečne tegobe – glavobolju, amaurozu i halucinacije, a lečena je u Klinici za psihijatriju i Klinici za infektivne bolesti. Analizom cerebrospinalne tečnosti nađen je snižen nivo glukoze i povišen nivo proteina. Kompjuterizovanom tomografijom i magnetnom rezonancijom viđena su mala zasenčenja bazalnih leptomeningi i hidrocefalus. Obdukcijom na bazalnim leptomeningama uočena je tamnobraon masa sa nejasnim granicama. Pigmentne kožne lezije nisu nađene. Histopatološkom analizom dijagnostikovana je primarna leptomeningealna melanocitoza. **Zaključak.** Primarna leptomeningealna melanocitoza je redak tumor koji se teško dijagnostikuje. Specifičnost ovog rada je u tome da prikazuje bolesnicu sa oboljenjem koje se retko sreće u praksi.

Ključne reči:
meninge, neoplazme; dijagnoza; tomografija, kompjuterizovana, rendgenska; magnetska rezonanca, snimanje; autopsija; elisa.

Introduction

Primary melanocytic neoplasms of the central nervous system originate from melanocytes of leptomeninges, and can occur as diffuse or solitary, benign or malignant tumors. This group of tumors also includes diffuse melanocytosis and melanomatosis, melanocytoma and malignant melanoma [1].

Limas and Tio [2] first described these lesions in 1972, while before, they had been referred to as melanotic meningioma. Approximately 110 cases of meningeal melanocytosis have been reported [3, 4]. The annual incidence of meningeal melanocytoma is estimated to be one case per 10 million population, and females are affected more often than males (female: male ratio 1.5 : 1) [1, 5]. Meningeal melanocytosis may manifest at any age, but most patients are in the 5th decade of life [6, 7].

This case is being presented for its specifity, since the disease is not frequently seen in practice.

Case report

The problems of a 61-year-old female patient had lasted for two months, accompanied with headache, amaurosis and hallucinations. At the beginning of February, she was transferred to the Clinic for Infectious Diseases, Clinical Centre Niš, from the Clinic for Psychiatry, Gornja Toponica,

Correspondence to: Živković Nikola, Maksima Gorkog 5/62, 18 000 Niš, Serbia. Phone: +381 18 429 2400, +381 63 10 45 645.
E-mail: nikolazivkovich@gmail.com

doubting of an inflammation process of the central nervous system (lumbar punition: glycorachy 0.0 mmol/L). A month before admission to the Clinic for Infectious Diseases, the patient had complained of an occipital headache, low back pain and pain in the right leg. The patient had an outpatient treatment with symptomatic therapy. In the meantime, the patient started speaking with no fenency, hallucinations appeared and people around her noticed she could not see. Diagnosed with acute hallucinatory syndrome, the patient was observed at the Clinic for Psychiatry, where, apart from a lumbar puncture, computed tomography and nuclear magnetic resonance of the brain were done showing reductive changes without focal lesions.

At the Clinic for Infectious Diseases, the following results were obtained: sedimentation values were 4, 12, 22 mm/h, urea, creatinine, electrolytes without major changes, the value of lactate dehydrogenase (LDH) was 966 U/L, leukocytes 30.9 × 10^9/L, and neutrophils 86.5%, 89.0%, 90.1%; hematocrit value was 31.27%. The patient was anti-HIV negative. A lumbar puncture was done for three times and the cytological results were normal. The first time the level of glycorachy was 0.5 mmol/L with serum glucose 5.3 mmol/L, and proteinorachy was 0.85 g/L; the second time the level of glycorachy was 0.3 mmol/L with serum glucose 6.8 mmol/L; the third time the level of glycorachy was 1.1 mmol/L with serum glucose 6.1 mmol/L. Bone marrow biopsy discarded hematological malignancy. The control computed tomography of the brain revealed dilated ventricular system (the third and lateral ventricle) and small shaded areas of basal leptomeninges. At a consultative examination, a neurosurgeon determined there were no indications for a neurosurgical intervention. The neurologist determined spastic paraparesis, sphincter incontinence and amaurosis as a consequence of hydrocephalus. Finally, an ophthalmologist determined cortical amaurosis. The enzime-linked immunosorbent assay (ELISA) test on tuberculosis (TB) (liquor) was done and proved to be negative.

During hospital treatment, antibiotic, tuberculostatic, antiedematous and symptomatic therapy had been given. For a short period of time, the patient was taking psychiatric medication. Due to the received therapy, the hallucinatory syndrome started to wear off, but instead spastic-type paraparesis and incontinence developed, which indicated a control computed tomography of the brain. She was afebrile all the time. At the beginning of March, the general condition got worse, tension decreased with tachycardia 120/min. After tension correction, she still had tachycardia with hypoproteinemic edema and her state of mind worsened to sopor state with tachy/dyspnea (to 38/min). In a week's time, the state of the patient worsened, she fell into coma, with acid-base imbalance and significant tachycardia. In spite of reanimation measures, cardio-respiratory failure occurred accompanied with fatal outcome (*exitus letalis*).

At autopsy, a dark brown mass with blurred boundaries was found on basal leptomeninges (Figure 1). No pigmented skin lesions were found, as well as any changes on other organs. Histopathological analysis revealed a leptomeningeal melanocytosis (Figure 2). Immunohistochemical analysis

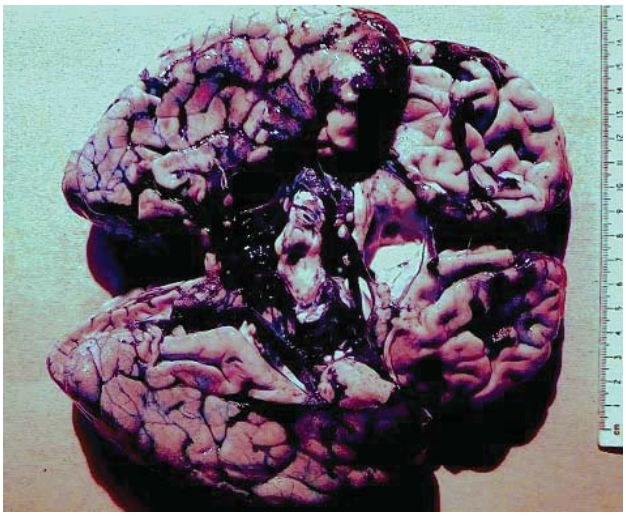

Fig. 1 – Dark brown areas on the leptomeninges of the brain basis

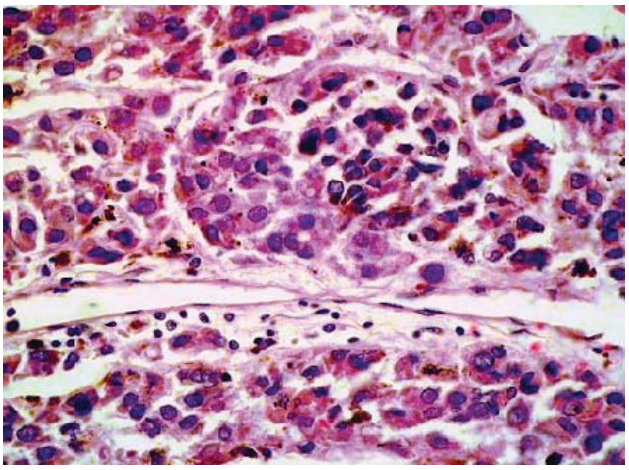

Fig. 2 – Melanin presented in the cytoplasm of tumor cells (hematoxylin and eosin, ×40)

demonstrated the expression of melanocytic marker proteins, melan A (Figure 3) and β-hydroxy β-methylbutyrate (HMB) 45 (Figure 4), but an absence of meningothelial cell markers, endothelial monocyte antigen (EMA) (Figure 5). The Ki-67 index was approximately 10% (Figure 6).

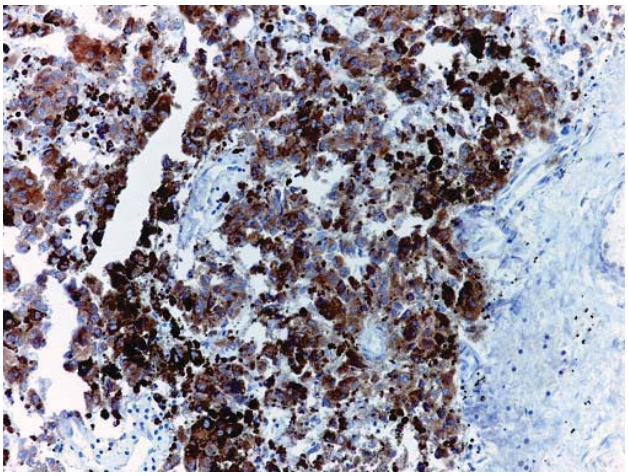

Fig. 3 – Melan A positivity of tumor cells (×20)

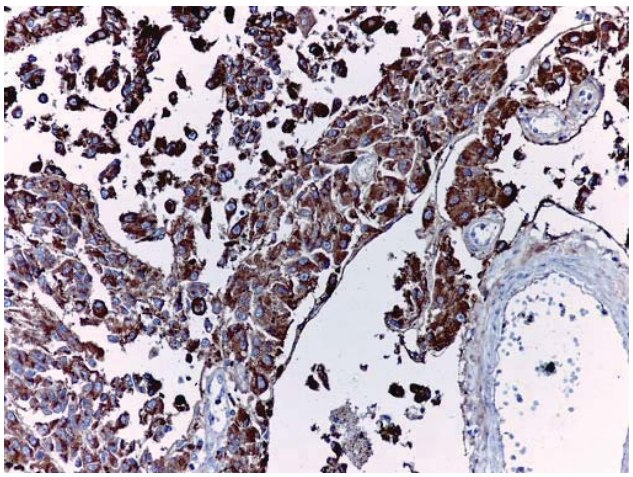

Fig. 4 – β-hydroxy β-methylbutyrate (HMB) 45 positivity of tumor cells (×20)

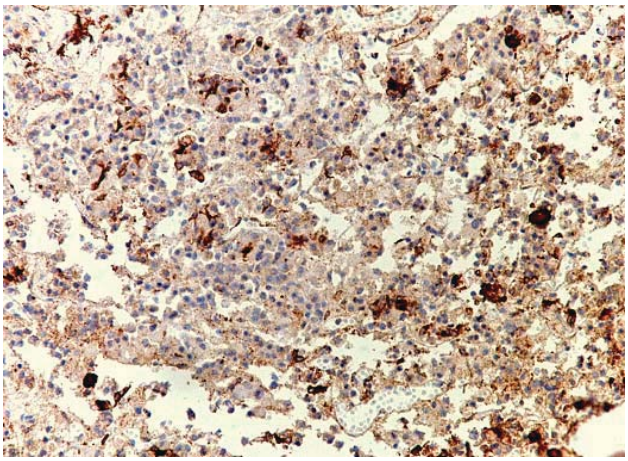

Fig. 5 – The tumor cells were negative for endothelial monocyte antigen (EMA) (×20)

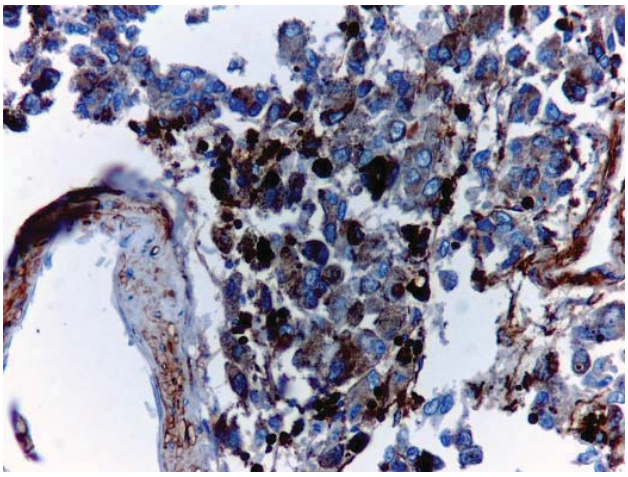

Fig. 6 – The Ki-67 index was approximately 10% (×40)

Discussion

Leptomeningeal malanocytosis is a very rare tumor of the central nervous system. The pathogenesis has not been clear enough yet, but it is supposed that melanocytes populate this area from the neural crest, so it is their proliferation that causes the disease [8, 9]. Certainly, there is a predisposition from birth, but it is a question of time when it is going to manifest clinically. Very often, these lesions in the central nervous system go together with skin changes, but they can also be solitary as in our case [10, 11].

There are diffuse and solitary forms of this tumor. Diffuse tumors are more often found in children, opposite to solitary ones, that are found in adults [12, 13]. Diffuse forms of melanocytoses and melanomatoses infiltrate supra- and infratentorial leptomeninges and the surface of the brain parenchyma. The areas they are localized the most are cerebellum, pons, medulla and temporal lobe [1].

Diffuse melanocyte lesions are presented as dense black content in the subarachnoid area or as a dark blurry change on the menings. Melanocytomas and a malignant melanoma are solitary masses which can occur as black, red-brown, blue or macroscopic non-pigmented changes [1].

In terms of diagnostics, encephalography, myelography, arteriography and computed tomography are used, but the best results are achieved with magnetic resonance. Cerebrospinal fluid analysis showed higher values of proteinorachy, lower values of glycorachy, a greater number of lymphocytes, but tumor cells also.

In terms of differential diagnostics, it can be doubted of a meningeoma, schwannoma, medulloblastoma, choroid plexus papilloma and astrocytoma [11].

The microscopic characteristics of the primary leptomeningeal melanocytosis are basically identical to melanocytosis in other places. The tumor consists of epithelial cells or spindle cells in their characteristic nest arrangement [13]. Most of benign and malign melatocytic lesions contain melanin pigment, finely distributed in tumor cells or roughly in the tumor stroma – in the cytoplasm of macrophages (melanophages). Rarely, melanocytoses and primary melanoma do not contain melanin; in such cases the diagnosis is given with the help of the electronic microscope or immunohistochemical methods.

At most published cases, the diagnosis was given postmortally [9]. It is accompanied with a number of symptoms by vegetative, motor and central nervous system, in terms of headache, vomiting, visual field loss, lethargy and hemiparesis. Very often, the meningeal signs are positive, most often Kernig's one. As a consequence of high intracranial pressure, hydrocephalus may occur [10, 11].

Our 61-year-old patient had had problems for two months, including headaches, amaurosis and hallucinations. The cerebrospinal fluid analysis showed a higher value of proteinorachy and a lower value of glycorachy. Some shaded areas on the brain basis and hydrocephalus were found by computed tomography. At autopsy, histopathological and immunohistochemical analysis revealed leptomeningeal melanocytosis.

The tumor was composed of epithelial cells in a characteristic nest arrangement. The grains of melanin were present in the cytoplasm. Infiltration of the surrounding tissue was not present.

Meningeal melanocytoma is characterized by positive immunoperoxidase staining for HMB-45, S-100 protein,

melan A and vimentin antibodies, and by a negative reaction to EMA [1, 14–16]. In general, melanocytoma is a solitary tumor with discrete margins, lack of mitoses, and a low Ki-67 index (< 12%) [16].

In 1999, Brat et al. [17] analyzed 33 of these rare tumors (comprising nearly half of the reported tumors at that time) and proposed a three-tiered grading system. Approximately half of their cases consisted of well-differentiated lesions (melanocytomas), characterized by variably pigmented cells arranged in nests and fascicles. This group of tumors demonstrated rare mitotic figures, inconspicuous nucleoli, and absence of parenchymal invasion. With a medium follow-up period of 3 years, none of these tumors recurred. Most of the other half of the tumors in the study were composed of poorly organized, mitotically active cells, with more prominent nucleoli, necrosis, and parenchymal invasion. This group of tumors was classified as primary central nervous system melanoma. Although half of these tumors recurred between 2 and 76 months after surgery, all but one were alive at the time of this publication. In addition, 4 out of 5 totally resected melanomas did not recur. Three (10%) of the tumors in the study could not be easily situated within either category and received the designation of intermediate-grade melanocytic tumor. Therefore, although the grading system proposed for primary central nervous system melanocytic tumors may be helpful in predicting the biologic behavior of these rare tumors, there is very significant overlap. In addition, with longer follow-up intervals, low-grade melanocytomas have shown a tendency toward radiographic recurrence [17, 18].

Conclusion

Primary pigmented lesions can be manifested both as benign and malignant neoplasms. Leptomeningeal melanocytosis is a rare tumor difficult to diagnose and treat.

Acknowledgment

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LETTER TO THE EDITOR/PISMO UREDNIKU UDC: 82-36:[159.944.4:616.12-008.331.1(044.4)

A doctor, actor and hypochondriac: a fancy mixture

Lekar, glumac, hipohonder: zgodna kombinacija

For all the time of my practice in the Department of Cardiovascular Diseases, Clinical Center Niš, I have been watching catastrophic consequences of stress upon an individual's health (*e.g.* stress as a trigger of acute aortic dissection). The importance of stress has been often underestimated. Stress may be easily produced in susceptible persons, sometimes due to an obvious reason, but on another occasion due to a trivial thing and with interesting repercussions.

"Finally!" – said my friend, a good man and a colleague – "I've to play my first role in a real movie!" His palms were sweating ("The cost of being famous", he thought). Therefore, he, a careful physician, decided to use his fancy device for blood pressure (BP) self-measurement, "Just to check it". However, checking was shocking: 240/120 mmHg! Fear came quickly into his heart of a devoted hypochondriac. He repeated the measurement with a traditional apparatus carefully, but he heard mixed sounds from the device and lub-dubs from his own heart.

"My dear, I am dying!" – he said desperately to his wife, with a hint of Shakespeare in his acting. ("Why should I die? Just too young to die… Just in front of the door of glory… What a loss for art! Oh, it is all so mixed in my head, like in fever.")

"I need help immediately!" – it flashed through his mind, "but where?"

"Cardiology Department" – sounded encouraging and promising to him – "If they do not know, who will?" – was the reasoning meritorious of a suddenly awoken emergency physician in him. Besides, all he had to do was walk just 100 meters flat.

Halfway there, he (as a doctor himself) remembered that he was expected, quite logically, to experience some symptoms with that high BP. "What symptom? I am already unhappy with my trouble, and it is not enough, I have to recall symptoms. Life is not fair!" Having the gift from God, for acting, he managed to do it. Suddenly, his walking stability disappeared, but he somehow managed to clutch at an old linden. "Take care of our children" – said he, a trendy hypochondriac, to his scared wife – like a pledge (resembling "Promise Me This", a movie from his "brother-in-film" Emir Kusturica).

Step by step, stumbling and falling, he reached his safety in our Department. Blood pressure was 140/90 mmHg. My friendly and relaxing diagnosis was "hypochondriacal storm".

The story is to illustrate the importance of both stress and accurate measurements in medicine. ("But BP was twice as high just a few minutes ago! Whom to believe? Even BP devices are not as precise as they used to be anymore …"). Another mixture of feelings: glad to be alive, but a little bit ashamed. "How to express it as an actor – with style?"

Goran P. Koračević
Faculty of Medicine, University of Niš, Department of Cardiovascular Diseases, Clinical Center Niš, Niš, Serbia
E-mail: gkoracevic@yahoo.com

IZVEŠTAJ SA STRUČNOG SKUPA

17. kongres Balkanskog komiteta vojne medicine, 29. maj – 1. jun 2012, Beograd, Srbija.

The 17th Congress of Balkan Military Medical Committee, 29 May-1 June 2012, Belgrade, Serbia.

Pod pokroviteljstvom Ministarstva odbrane Republike Srbije, Uprava za vojno zdravstvo i Vojnomedicinska akademija Beograd, organizovali su prvi puta u našoj zemlji Balkanski kongres vojne medicine. Srbija je punopravni član Balkanskog komiteta vojne medicine (BKVM) od 2008. godine, zajedno sa zemljama osnivačima – Bugarskom, Grčkom, Rumunijom i Turskom. Balkanski komitet vojne medicine oformljen je sa idejom da se unapredi saradnja zemalja Balkanskog poluostrva na polju vojne medicine. Shodno usvojenom Memorandumu o sporazumevanju, razmena iskustava i znanja na svim poljima vojne medicine tokom održavanja Kongresa BKVM, predstavlja jednu od najvažnijih aktivnosti BKVM. Prvi kongres BKVM održan je 1995. godine i u njegovom radu učestvovale su zemlje osnivači BKVM. Od momenta kada je naša zemlja postala kandidat za punopravno članstvo, do danas, sanitetska služba Vojske Srbije učestvovala je sa svojim delegatima na svim kongresima BKVM. Porodici zemalja BKVM, kao punopravni član, prid-ružila se i Albanija 2011. godine sa svojom sanitetskom službom.

Nakon ispunjenja svih proceduralnih uslova,vezanih za punopravno članstvo i organizaciju pretkongresnih sastanaka BKVM, MO RS prihvatilo je organizaciju 17. kongresa BKVM i odredilo mesto i datum održavanja kongresa. Pretkongresni sastanak održan je krajem marta 2012. u Bukureštu i tokom njega usaglašen je Program 17. kongresa BKVM, koji je planiran da se održi od 29. maj do 1. jun 2012. u Beogradu.

Glavne teme kongresa bile su ateroskleroza i vaskularne bolesti u hirurgiji, internoj medicini i neurologiji, uz ratnu traumu, teme iz preventivne medicine i vojne toksikologije.

Tokom pripreme kongresa Naučni odbor kongresa primio je 331 rad, koji su selektovani u 17 naučnih sesija, plenarnu sesiju o aterosklerozi, jedan okrugli sto i sesiju studenata vojnomedicinskih fakulteta i srednjih medicinskih škola. Za predsednika kongresa izabran je načelnik Uprave za vojno zdravstvo, puk. prof. dr Zoran Popović, za predsednika Naučnog odbora prof. dr Marijan Novaković, načelnik VMA, a za predsednika Organizacionog odbora kongresa puk. prof. dr Đoko Maksić, predsednik Srpskog nacionalnog upravnog odbora (SNO) BKVM.

U radu kongresa učestvovala su 273 delegata iz Bugarske, Grčke, Rumunije, Srbije i Turske. Delegati Albanije nisu prisustvovali iz opravdanih razloga, uprkos činjenici da su na vreme prijavili svoje radove.

Učešće u usmenim izlaganjima na engleskom jeziku, koji je službeni jezik BKVM, uzela su 137 delegata iz svih prisutnih zemalja članica, a tokom pet poster sesija prikazano je dodatno još 194 rada.

Naučni odbor kongresa uz pomoć nacionalnih komiteta zemalja BKVM nagradio je po jedan najbolji rad iz svake zemlje saopšten tokom usmenih i poster izlaganja, kao i najbolji izloženi rad kongresa. Svi nagrađeni dobili su potvrde za najbolje radove, a ostali delegati potvrde o učešću na kongresu koji je, inače, bio akreditovan od strane Zdravstvenog saveta Republike Srbije.

Saradnja zemalja članica BKVM na polju vojne medicine bila je i tema sastanka šefova vojnomedicinskih službi i načelnika vojnomedicinskih akademija. Tokom tog sastanka, koji je održan u sali nastavnonaučnog veća VMA Beograd, istaknut je značaj kontinuiranog obrazovanja pripadnika sanitetskih službi, potreba za razmenom stručnjaka i povezivanjem vojnih bolnica pomoću telemedicine. Posebno je naglašen značaj formiranja zajedničkih medicinskih snaga zemalja BKVM u cilju učestvovanja u neodložnoj medicinskoj pomoći u slučaju različitih prirodnih katastrofa.

Tokom svečanog zatvaranja 17. kongresa BKVM predsedavanje BKVM predato je Turskom nacionalnom odboru, čija je zemlja naredni domaćin 18. kongresa BKVM 2013. godine.

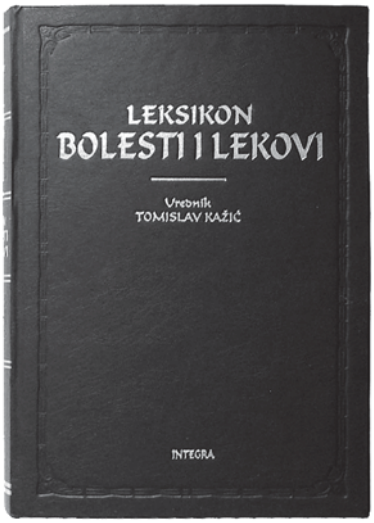
Postkongresni sastanak održan je od 1. do 3. juna 2012. u Beogradu, na kome je izvršena detaljna analiza svih kongresnih aktivnosti. Opšta ocena predsednika svih nacionalnih odbora u pogledu stručnog kvaliteta kongresa bila je odlič-na i posebno je istaknut visok naučni nivo predavanja o aterosklerozi u plenarnoj sesiji.

Zadovoljstvo svih delegata kongresa organizacijom kongresa, njegovim stručnim dometima i uspostavljenim novim profesionalnim i prijateljskim vezama između delegata BKVM opravdalo je sav uloženi trud zemlje domaćina koja je još jednom pokazala svoje mogućnosti na polju vojnomedicinske organizacije i saradnje.

Predsednik SNO/BKVM
puk. prof. dr sc. Đoko Maksić

P R I K A Z K N J I G E

LEKSIKON – BOLESTI I LEKOVI



Urednik: Tomislav Kažić
Izdavač: Integra, Beograd
Godina izdanja: 2012.
Strana: 700, latinica
Tiraž: 600 primeraka
Povez: Tvrdi, sa zlatotiskom. Tabaci šiveni koncem.
Format: 17cm x 25cm

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Kada je farmakolog i klinički farmakolog, prof. dr Tomislav Kažić, procenio da bi za naše studente i lekare trebalo prirеđivati udžbenike i priručnike, postepeno je sve više stvarao takvu literaturu. Sreća je što je prof. Kažić bio izuzetno dobar poznavalac lekova i lečenja, a istovremeno veoma dobar pisac. Tako je nastalo tridesetak knjiga, ogroman opus koji je autor dao našoj medicini. Najznačajnija mu je knjiga „Klinička kardiovaskularna farmakologija“ koja je objavljena u pet izdanja. To svojevrsno delo bilo je dugi niz godina, a još uvek jeste, najbolji izvor naučnih podataka za one koji spremaju ispit iz kardiologije i nekih drugih specijalizacija, ali i štivo koje unapređuje praksu lekara praktičara i znanje studenata. Koncept te knjige je jedinstven u svetu i da nije bilo našeg rata, to pozamašno delo bilo bi prevedeno na engleski jer je naručilac iz inostranstva svojevremeno hteo da to organizuje.

Ko ne poznaje profesora Kažića, pitaće se otkuda toliki altruizam – da jedan veoma uspešan naučnik–istraživač odvoji toliko vremena i snage za edukaciju lekara, studenata i zdravstvenih radnika. Tomislav Kažić, kao učenik gimnazije i student medicine, bio je učesnik četiri omladinske radne akcije (ORA) na kojima je dobrovoljno u toku leta radio po mesec dana na izgradnji autoputa „Bratstvo-jedinstvo“. Učesnici ORA su zauvek zavoleli svoju zemlju i davali su joj više od mnogih drugih.

Drugo izdanje knjige „Leksikon: Bolesti i lekovi“, Kažić je priredio sa svojim saradnicima (M. Bajčetić, Lj. Gojković-Bukarica, S. Radulović, Z. Todorović i S. Vučković) neposredno pre svoje iznenadne smrti. Tako su ovo značajno delo i njegov pregledni članak „Statini – neželjena dejstva i interakcije“ (Scripta Medica Vol. 42, No. 2, 2011, www.scriptamedica.com) objavljeni nakon smrti autora.

Ovo izdanje Leksikona, nastalo pet godina posle prvoga, za skoro 100 strana je opširnije od prethodnog. Obim knjige je povećan jer su u međuvremenu pronađeni novi lekovi, a među autorima se našao novi član (M.B.) koji se bavi farmakoterapijom kod dece. Prvo izdanje ove knjige predstavio sam u Srpskom arhivu (2007;135:245–6); zato ću ovde navesti samo najvažnije odlike knjige i ukazati na dobre i slabije strane ovog ogromnog posla koji su obavila samo šest autora.

Većina tekstova pisana je na osnovu savremenih bazičnih i kliničkih istraživanja koja se kategorizuju u tzv. medicinu zasnovanu na dokazima (*evidence-based medicine*). Takav pristup ima snažan i dugotrajan uticaj na medicinske stručnjke, ali i na sve one koji su zainteresovani za prevenciju masovnih nezaraznih i zaraznih bolesti, mehanizam nastanka raznih bolesti, lečenje lekovima, dijagnostičke postupke i terapijske intervencije koje se odvijaju na supcelularnom, biohemijskom, elektrofiziološkom, imunološkom i genetskom nivou. Da bi korisnici knjige lakše shvatili neke bolesti i njihovo lečenje, prikazan je niz anatomskih, histoloških, biohemijskih, patoloških i opštih farmakoloških podataka. Na stotine odrednica sadrže najnovija saznanja o nastanku oboljenaja, njihovom lečenju i o samim lekovima. Tako se u knjizi nalaze opisi apneje u snu, metaboličkog sindroma, posttraumatskog stresnog poremećaja (PTSD), sindroma nemirnih nogu, karcinoma, radijacione bolesti, sepse i septičnog šoka, insuficijencije rada srca, statitna,

citotoksičnih lekova, antagonista AT_1 receptora, antagonista kalcijuma i mnogih drugih.

Svi tekstovi (odrednice) u knjizi raspoređeni su abecedno, uz ubačena tri slova iz engleskog alfabeta: W, X i Y. Čitalac, tako, i bez predmetnog registra, može brzo pronaći većinu termina u knjizi. No, izostavljanje predmetnog registra (indeksa reči) ima i nedostatak, jer neki se pojmovi iz teksta teže nalaze. Na primer, tekst o svrabu može se naći samo pod odrednicom „*pruritus*“, dok se neki pojmovi u tekstu pominju, ali ih među posebnim odrednicama nema. Izrada predmetnog indeksa bi značajno opteretila knjigu dodatnim stranama pa je zato takav pristup izostavljen.

Tekst je pisan veoma jasnim, lepim i ujednačenim stilom, što je očigledno zasluga urednika. Pojedine reči su označene zvezdicom, što ukazuje gde se o njima može naći dodatni tekst. Taj pristup dobrim delom nadoknađuje nedostatak pomenutog indeksa. Većina odrednica ima naziv na našem jeziku, posrbljenom latinskom jeziku (na primer, encefalitis, nefritis, nauzeja), zaštićenim nazivom leka (na primer, Ketosteril, Macmiror Complex, Viagra, Viatromb), a veoma retko se koriste latinski nazivi – uglavnom za bakterije, viruse i parazite. Međutim, gde god je moguće, u zagradi su dati nazivi na engleskom jeziku. To je verovatno učinjeno da bi zainteresovani mogli lakše naći dodatne podatke o tom pojmu na internetu. Zanimljivo je da su baš lekari-farmakolozi, koji su od srednjeg veka pa skoro do danas pisali recepte i učili studente medicine, stomatologije i farmacije kako se (na latinskom jeziku) pišu recepti, skoro potpuno izbacili taj jezik iz većine odrednica Leksikona. Sigurno je glavni razlog za to prodor engleskog jezika u stručnu terminologiju drugih jezika, ali i to što je taj jezik, nakon Drugog svetskog rata, postao *lingua franca* u svim vidovima komuniciranja, pa i u nauci i medicinskoj praksi. Imajući to u vidu, vredelo bi da su u knjigu unete odrednice za neke od glavnih baza podataka (na primer, Medline, tj. PubMed, Ovid, Biosis, Embase, Toxline).

U ovom, kao i u prethodnom, izdanju knjige ilustracije su lepe, jasne i pregledne, a prikazane hemijske formule značajno pomažu čak i onima koji imaju samo osnovno znanje iz hemije. Ovo izdanje sadrži niz novih lekova; na primer, dabigatran (Pradaxa), vareniklin (Champix) i aliskiren (Rasilez). Neke odrednice ne sadrže jasnu poruku o mogućem ishodu poremećaja. Tako, u odrednici sinkopa ne navodi se da je ona kod skoro 50% slučajeva iznenadne smrti jedini znak upozorenja (White, Beograd, septembar 2009, str. 32-3). U Americi, gde se takvi podaci uredno prikupljaju, godišnje ima 400 000 žrtava iznenadne smrti. U pomenutoj odrednici (sinkopa) navodi se ugradnja pejsmekera kod bolesnika s jakom bradikardijom, ali se kod terapije sinkope, ako je izazvana određenim tipovima aritmije, ne navodi ablacija i ugradnja kardiovertera/defibrilatora. U knjizi postoji odrednica „ablacija retine“, ali nema odrednice za ablaciju kod lečenja aritmija srca. Mada je reč o leksikonu koji je mahom posvećen lekovima, elektrofiziološkom pristupu terapiji za poremećaje srčanog ritma danas treba posvetiti nužnu pažnju.

Autorima Leksikona treba odati priznanje za uspešan enorman trud. Ovu knjigu trebalo bi da poseduju lekari i farmaceuti, studenti medicine, farmacije i više medicinske škole, ali i mnoga domaćinstva. Pošto knjiga služi kao brza referenca studentima, vredelo bi da se nađe u studentskim učionicama i bibliotekama odgovarajućih fakulteta i škola.

Prof. Dr. Rajko Igić,
Senior Scientist
Department of Anesthesiology and Pain Management
John Stroger Hospital of Cook County
Chicago, IL 60612, USA
E-mail:igicrajko@gmail.com

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Priprema rada

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

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

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2. ***Apstrakt i ključne reči***

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

3. ***Tekst članka***

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

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

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

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Primeri oblika referenci:

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

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

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

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

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

Tabele

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

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

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

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Examples of references:

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

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

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

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

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

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