

UDK 61(05)=862=20
GOD. 53/2023, 3

ISSN 0351-0093
Coden: MEJAD6

medica jadertina



Med. Jad. God 53. Br. 3 Str. 169-242 Zadar 2023.

Nakladnik
Opća bolnica Zadar

Publisher
Zadar General Hospital

UDK 61(05)=862=20

ISSN 0351-0093

GOD. 53/2023, 3

Coden: MEJAD6

Med. Jad.

God 53.

Br. 3

Str. 169-242

Zadar 2023.

Nakladnik

Publisher

Opća bolnica Zadar

Zadar General Hospital

Nakladnik
Opća bolnica Zadar

Publisher
Zadar General Hospital

Urednički odbor – *Editorial Board*

Ivan Bačić, Željko Čulina, Boris Dželalija, Robert Karlo, Ivo Klarin, Alan Medić, Jakov Mihanović, Jure Pupiće-Bakrač,
Nataša Skitarelić, Neven Skitarelić, Tatjana Šimurina, Dražen Zekanović

Glavni i odgovorni urednik – *Editor-in-Chief*
NEVEN SKITARELIĆ

Urednik – *Editor*
NEVEN SKITARELIĆ

Tajnik – *Secretary*
ROBERT NEZIROVIĆ

Lektor za hrvatski jezik – *Croatian language proof reading*
ROBERT NEZIROVIĆ

Lektor za engleski jezik – *English language proof reading*
JASMINKA BAJLO

Grafički urednik – *Graphic editor*
PREDRAG JELIČIĆ

Savjet časopisa – *Council of the Journal*

Klaudio Grdović, Mile Gverić, Albino Jović, Mate Kozić, Boris Labar, Petar Lozo, Neven Ljubičić, Želimir Maštrović,
Zlatko Matulić, Antun Mazzi, Maja Maržić-Mazzi, Šime Mihatov, Miro Morović, Marko Mustać, Boris Petričić,
Mladen Srzentić, Tatjana Vukelić-Baturić

Adresa uredništva – *Address of the Editorial Office*

MEDICA JADERTINA – Opća bolnica Zadar, 23000 Zadar, Bože Peričića 5
Telefon (023) 315-508; 505-270, fax: (023) 312-724, e-mail: opca-bolnica-zadar@zd.t-com.hr

Časopis MEDICA JADERTINA objavljuje uvodnike, izvorne znanstvene i stručne članke, prethodna priopćenja, pregledne članke, prikaze bolesnika, izlaganja sa znanstvenih skupova i druge priloge iz temeljnih i kliničkih medicinskih znanosti.

The journal MEDICA JADERTINA publishes editorials, original scientific and professional articles, earlier announcements, reviewed articles, case reports, presentations from scientific conferences and other enclosures basic and applied medical sciences.

Medica Jadertina izlazi četiri puta godišnje. Godišnja pretplata iznosi 14 €. Broj žiro računa: HR5924020061100879223 kod Erste&Steiermärkische Bank d.d., s naznakom: Za Medica Jadertina i adresom 23000 Zadar, B. Peričića 5, p.p. 291.

Medica Jadertina is published four times a year. The annual subscription is 14 € payable to Erste&Steiermärkische Bank, account number HR5924020061100879223, SWIFT: ESBCHR22 for Medica Jadertina and the address Croatia, 23000 Zadar, B. Peričića 5, p.p. 291.

Medica Jadertina je indeksirana u EMBASE/Excerpta Medica, Scopus.
Medica Jadertina is indexed in EMBASE/Excerpta Medica, Scopus.

Digitalna verzija časopisa ISSN 1848-817X (Online) dostupna je na portalu znanstvenih časopisa Republike Hrvatske: <https://hrcak.srce.hr/medica-jadertina>
The digital version of the magazine ISSN 1848-817X (Online) is available at the portal of the scientific papers of Croatia: <https://hrcak.srce.hr/medica-jadertina>

Rješenje i priprema korica: NILO KARUC
Priprema: PREDRAG JELIČIĆ
Tisak: FG GRAFIKA, Zadar
Naklada 85 primjeraka
Printed in Croatia

SADRŽAJ

Contents

IZVORNI ZNANSTVENI ČLANCI

Original scientific papers

- Marta Knežević, Nikola Kolja Poljak, Dora Knežević, Nancy Poljak
PROMJENA TRENDA U PRISTUPU LIJEČENJU STRANIH TIJELA JEDNJAKA U KLINIČKOM
BOLNIČKOM CENTRU SPLIT173
Change in trend in the management of esophageal foreign bodies at University Hospital of Split

PREGLEDNI ČLANCI

Review

- Tommy Nazwar Alfandy, Farhad Bal 'afif, Donny Wisnu Wardhana, Mustofa Mustofa
EMERGING MANAGEMENT OF CHRONIC SUBDURAL HEMATOMA (CSDH) IN HIGH
INCOME COUNTRY (HIC) AND LOW-INCOME COUNTRY (LIC): A REVIEW181
*Novo liječenje kroničnog subduralnog hematoma (CSDH) u zemlji s visokim (HIC) i u zemlji s niskim
prihodima (LIC): pregled*

Milan Ivanišević

- OFTALMOLOG ALBRECHT VON GRAEFE (1828.-1870.) I NJEGOVI ASISTENTI I UČENICI.....199
Ophthalmologist Albrecht von Graefe (1828-1870) and his assistants and pupils

STRUČNI ČLANCI

Professional papers

- Ivo Dilber, Sara Bilić Knežević, Mirisa Tokić, Jakov Mihanović, Josipa Jović Zlatović
UTJECAJ COVID-19 PANDEMIJE NA BOLESNIKE S NOVOOTKRIVENIM KOLOREKTALNIM
KARCINOMOM U OPĆOJ BOLNICI ZADAR207
*The impact of the COVID-19 pandemic on patients with newly diagnosed colorectal cancer in Zadar
General Hospital*

- Ivan Vučković, Ivana Pajić Matić, Tomislav Stojadinović, Damir Sauerborn, Karolina Veselski,
Antonija Mišković, Josip Samardžić
KARCINOM PARATIROIDNE ŽLIJEZDE – PRIKAZ BOLESNICE.....213
Parathyroid gland carcinoma – a case report

- Fatima Juković-Bihorac, Hakija Bečulić, Emir Begagić, Rasim Skomorac
LOCALLY AGGRESSIVE GIANT BASAL CELL CARCINOMA OF THE HEAD WITH FOCUS
ON SURGICAL TREATMENT – A CASE REPORT219
*Lokalno agresivni gigantski bazocelularni karcinom vlasišta s posebnim osvrtom na kirurško liječenje –
prikaz bolesnika*

Zdeslav Benzon, Jasminka Rešić, Zoran Meštrović, Indira Kosović, Sandra Benzon MANAGEMENT OF FETAL SUPRAVENTRICULAR TACHYARRHYTHMIA – CASE REPORT.....	225
<i>Postupak kod dijagnosticirane fetalne supraventrikularne tahiaritmije – Prikaz bolesnice</i>	
Ante Štefić, Vanja Đuričić, Valentin Kordić, Sara Đuričić, Maristela Šakić, Melita Jukić DISSOCIATIVE AMNESIA WITH FIGUE FEATURES IN A PATIENT WITH HUNTINGTON'S DISEASE.....	229
<i>Disocijativna amnezija s obilježjima fuge kod bolesnika s Huntingtonovom bolešću</i>	
UPUTE AUTORIMA.....	235
<i>Instructions for authors</i>	

Promjena trenda u pristupu liječenju stranih tijela jednjaka u Kliničkom bolničkom centru Split

*Change in trend in the management of esophageal foreign bodies
at University Hospital of Split*

Marta Knežević, Nikola Kolja Poljak, Dora Knežević, Nancy Poljak*

Sažetak

Uvod: Strana tijela jednjaka predstavljaju jedno od hitnih stanja koja su česta u otorinolaringološkoj praksi i kao takva predstavljaju izazov zdravstvenim djelatnicima. Glavni cilj ovoga istraživanja bio je prikazati smanjenje broja ezofagoskopija krutim ezofagoskopom zbog sumnje na strano tijelo, uz prikaz broja fleksibilnih ezofagogastroduodenoskopija (EGDS) učinjenih zbog sumnje na strano tijelo.

Bolesnici i metode: Provedena je retrospektivna studija u koju je uključeno 855 ispitanika kojima je u KBC-u Split učinjena ezofagoskopija krutim ezofagoskopom ili fleksibilna EGDS zbog sumnje na strano tijelo tijekom razdoblja od 2001. do 2021. god. Prikupljeni podaci za bolesnike s Klinike za bolesti uha grla i nosa s kirurgijom glave i vrata uključivali su: dob, spol, datum obavljenog zahvata, prisutnost stranog tijela, vrstu stranog tijela, lokalizaciju stranog tijela, postojanje komplikacija i novootkrivenih medicinskih stanja. Za bolesnike s Odjela gastroenterologije dostupni su bili podaci za razdoblje od 2016. do 2021. god. Za usporedbu kategorijskih varijabli proveli smo hi-kvadrat test pri razini značajnosti od $p < 0.05$.

Rezultati: Na Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata učinjeno je ukupno 559 zahvata ezofagoskopije krutim ezofagoskopom, u razdoblju od 2001. do 2021.god. Od 2016. do 2021.god. učinjeno je 139 ezofagoskopija krutim ezofagoskopom. Od 2016. do 2021. god. na Odjelu gastroenterologije Klinike za unutarnje bolesti učinjeno je 296 fleksibilnih EGDS. Postoji statistički značajna razlika u broju zahvata fleksibilne EGDS i ezofagoskopije krutim ezofagoskopom u razdoblju 2016. do 2021.god., $p < 0.05$. Strano tijelo pronađeno je u 63% zahvata ezofagoskopije krutim ezofagoskopom. Ingestija stranog tijela češća je kod muškaraca. Medijan dobi ispitanika u Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata bio je 45,5 godina. Najveći broj ispitanika u pedijatrijskoj populaciji su predstavljala djeca do druge godine života. Najzastupljenija dobna skupina odrasle dobi bili su bolesnici u šestom desetljeću života. Najčešća razina opstrukcije u više od četvrtine bolesnika bilo je prvo suženje jednjaka. Kod četvrtine bolesnika sa stranim tijelom najčešću vrstu stranog tijela predstavljao je bolus hrane.

Zaključci: Ovim je istraživanjem potvrđena promjena trenda u pristupu rutinskom vađenju stranih tijela jednjaka tijekom razdoblja od 2016. do 2021. god., u kojemu je prva metoda izbora bila fleksibilna EGDS. Ezofagoskopija krutim ezofagoskopom ostaje i dalje metoda izbora kod bolesnika kojima se fleksibilnom endoskopijom ne uspije odstraniti strano tijelo prilikom sumnje na oštro strano tijelo, te kod stranih tijela na razini gornjeg sfinktera jednjaka ili hipofarinksa.

Ključne riječi: jednjak, strano tijelo, ezofagoskopija, ezofagogastroduodenoskopija

Summary

Introduction: Foreign bodies in the esophagus are one of the most common emergencies in ENT practice and thus pose a challenge to medical staff. The main objective of this study was to demonstrate the

* (Marta Knežević, dr.med.); **KBC Split, Klinika za otorinolaringologiju i kirurgiju glave i vrata** (Izv.prof.prim.dr.sc. Nikola Kolja Poljak, dr.med.); **Sveučilište u Zagrebu, Edukacijsko-rehabilitacijski fakultet** (dr.sc. Dora Knežević, mag.logoped); **Dom zdravlja Splitsko-dalmatinske županije** (Nancy Poljak, dr.med.dent.)

Adresa za dopisivanje/ *Correspondence address:* Marta Knežević, dr.med., Ul. Jure Kaštelana 8, 21 000 Split E-mail: marta.knezevic7@gmail.com

Primljeno/Received 2023-02-27; Ispravljeno/Revised 2023-09-12; Prihvaćeno/Accepted 2023-10-25

reduction in the number of esophagoscopies performed with a rigid esophagoscope when a foreign body is suspected, and at the same time to show the number of flexible esophagogastroduodenoscopies (EGD) performed when a foreign body is suspected.

Patients and methods: A retrospective study was conducted involving 855 participants who underwent esophagoscopy with a rigid esophagoscope or flexible EGD for suspected foreign body between 2001 and 2021 at Split University Hospital. Data collected for the patients from the Ear, Nose and Throat Clinic with Head and Neck Surgery included: age, sex, date of surgery, presence of foreign body, type of foreign body, location of foreign body, presence of complications and newly detected medical conditions. For the patients from the Department of Gastroenterology data are available for the period from 2016 to 2021. For the comparison of the categorical variables, we performed the chi-square test with a significance level of $p < 0.05$.

Results: 559 procedures were performed from 2001 to 2021 with a rigid esophagoscope in the Ear, Nose and Throat Clinic with Head and Neck Surgery. 139 esophagoscopies were performed from 2016 to 2021 with a rigid esophagoscope. Flexible EGD were performed in the Gastroenterology Department of the Department of Internal Medicine. There is a statistically significant difference in the number of flexible EGD procedures and esophagoscopy with a rigid esophagoscope from 2016 to 2021, $p < 0.05$. A foreign body was found in 63% of rigid esophagoscopy procedures. Ingestion of a foreign body is more common in men. The median age of respondents in the Ear, Nose and Throat Clinic with Head and Neck Surgery was 45.5 years. Most participants in the pediatric population were children aged up to two years. The most represented adult age group was patients in their sixth decade of life. The most common level of obstruction, in more than a quarter of patients, was first esophageal narrowing. The most common type of foreign body was a food bolus, in a quarter of the patients with a foreign body.

Conclusion: This study confirms a shift in the approach to routine removal of foreign bodies in the esophagus from 2016 to 2021, with flexible EGD being the first method of choice. Esophagoscopy with a rigid esophagoscope remains the method of choice for patients in whom flexible endoscopy cannot remove a foreign body, for suspected sharp foreign bodies and for foreign bodies at the level of the upper esophageal sphincter or hypopharynx.

Keywords: Esophagus, foreign body, esophagoscopy, esophagogastroduodenoscopy

Med Jad 2023;53(3):173-180

Uvod

Strana tijela jednaka predstavljaju jedno od hitnih stanja koje je relativno često u otorinolaringološkoj praksi i kao takva predstavljaju izazov zdravstvenim djelatnicima. Veliki broj studija pokazuje da strana tijela kod odraslih najčešće predstavljaju bolusi hrane, i to uglavnom komadi mesa i kosti, dok je kod djece riječ o dijelovima igrački i kovanicama. Većina progutanih stranih tijela (80-90%) ne zahtijeva intervenciju i prolaze spontano, no određeni dio ipak zahtijeva endoskopsku ekstrakciju (10-20%), a iznimno (1%) je potreban vanjski, kirurški pristup.¹ Nadalje, istraživanja pokazuju da je prevalencija viša kod muškaraca, kako među odraslima, tako i među djecom. Osim fizioloških suženja značajne čimbenike rizika predstavljaju i prethodne operacije grkljana, kongenitalne malformacije, poremećaji motiliteta jednjaka ili eozinofilni ezofagitis.² Također, neki autori spominju i sezonsku varijaciju kod pojave stranih tijela. Naime, riječ je o većoj incidenciji tijekom državnih praznika i nacionalnih sportskih događanja, prvenstveno zbog neumjerenosti u prehrani i prekomjernoj konzumaciji alkoholnih pića.³

U jednjaku postoje tri fiziološka suženja koja su sama po sebi najčešća mjesta opstrukcije.⁴ Prvo suženje predstavlja krikofaringealni mišić, drugo suženje nalazi se na mjestu križanja jednjaka s lijevim bronhom i lukom aorte, dok treće suženje predstavlja mjesto prolaska jednjaka kroz dijafragmu.⁴ Od tri spomenuta mjesta, otprilike 75 % stranih tijela dovodi do opstrukcije na razini prvog suženja,⁵ što se objašnjava jakom muskulaturom donjeg konstruktora ždrijela i slabijom mišićnom aktivnošću donjeg dijela jednjaka, a to rezultira otežanom daljnjom pasažom.⁵

Osnovni simptom predstavlja smetnja pri gutanju.⁴ Simptomi se razlikuju ovisno radi li se o djelomičnoj ili potpunoj opstrukciji. Ako je jednjak u cijelosti zatvoren stranim tijelom, onemogućeno je uzimanje hrane ili tekućine.⁴ Potpuna opstrukcija rezultira nakupljanjem pljuvačke i javljanjem posljedičnog kašlja, dok su usna šupljina i ždrijelo ispunjeni sekretom.⁴ Bol pri gutanju također je jedan od čestih simptoma. Zaostajanje stranog tijela ispod prvog suženja može rezultirati osjećajem gušenja koji je uglavnom vezan uz osjećaj straha i obilje sekreta.⁴

Kao kod svakog medicinskog stanja (hetero)anamneza i fizikalni pregled su inicijalni dijagnostički postupci. Starija pedijatrijska

populacija i osobe bez intelektualnih teškoća uglavnom mogu prepričati tijek događaja i ponekad lokalizirati mjesto nelagode i bolnosti.⁵ Specifično mjesto bolesnikove nelagode, međutim, ne mora nužno biti u korelaciji sa stvarnim mjestom opstrukcije.⁶ Simptomi se ne moraju pojaviti odmah nakon impakcije, već nakon nekog vremena, zajedno s komplikacijama koje se razlikuju ovisno o vrsti stranog tijela.⁷ U odraslih može biti riječ o retrosternalnoj boli (78%), odinofagiji (43,4%), disfagiji (48%), mučnini ili povraćanju.¹ Kod djece je stanje često praćeno gušenjem/grčenjem (49%), povraćanjem (47%) i disfagijom/odinofagijom (42%), no međutim čak 76% djece ne mora imati nikakve simptome.⁶

Vitalni znakovi kao što su hipoksemija, tahikardija i hipertenzija, mogu se pojaviti u epizodama kod produljene, potpune opstrukcije jednjaka.⁸ Fizikalni pregled može otkriti oticanje vrata, osjetljivost, eritem ili krepitacije s orofaringealnim ili proksimalnim ezofagealnim perforacijama.⁸ Distalnije rupture jednjaka mogu rezultirati peritonitisom i medijastinitisom, kao i drugim sistemskim bolestima i komplikacijama.⁸

Iako se mnoge dijagnoze mogu postaviti anamnezom i fizikalnim pregledom, radiografska procjena (RTG) može biti iznimno vrijedna u određenim slučajevima, kao na primjer kod gutanja metalnog stranog tijela ili za procjenu pneumoperitoneuma ili pneumomedijastinuma.⁵ Preferirana početna slikovna dijagnostika je obična radiografija grudnog koša sa stražnjim i bočnim pogledom. Bočne i kose projekcije razlikuju položaj jednjaka i dušnika, te omogućuju evidenciju više stranih tijela koja se, zbog preklapanja, ne bi nužno vidjela na frontalnoj projekciji.⁹ Značajna uloga jednostavne radiologije je ona u probiru komplikacija.¹⁰ Ako je početni RTG nalaz negativan, ili ako se sumnja na perforaciju jednjaka, sljedeća slikovna dijagnostika koja se preporučuje je kompjutorizirana tomografija (CT).⁵ CT pokazuje bolju osjetljivost od obične radiografije, osobito u kombinaciji s trodimenzionalnom rekonstrukcijom s intravenskim kontrastom.⁵ CT može također procijeniti oblik stranog tijela, veličinu, mjesto i povezane komplikacije, kao što su perforacija, medijastinitis, apsces i fistula.⁵

Procjena dišnog puta bolesnika je prvi korak u evaluaciji bolesnika. Bolesnici s respiratornim distresom ili nemogućnošću disanja zahtijevaju hitnu intervenciju s endotrahealnom intubacijom.⁵ Bolesnik koji ne može upravljati vlastitim izlučevinama je pod visokim rizikom od aspiracije i također zahtijeva intervenciju.^{1,8} Evaluacija u bolesnika sa stranim tijelom u obliku bolusa hrane koji je stabilan,

drugačija je od bolesnika s neprehrambenim stranim tijelom. U bolesnika s bolusom hrane, stabilnom hemodinamikom i respiratornim statusom probavni put može se pokušati osloboditi fizičkim radnjama u kombinaciji s lijekovima.⁵ Radnja se sastoji od ponovljenih ekstenzija vrata zajedno s pokretima gutanja, koji se mogu kombinirati sa šumećim agensima i lijekovima.⁵ Endotrahealna je intubacija nerijetko potrebna bolesnicima s progutanim predmetima koje je teško ukloniti, za one bolesnike s više stranih tijela, te kada je potrebna ezofagoskopija krutim ezofagoskopom.⁸

Šumeći agensi (tj. tvari koje sudjeluju u stvaranju plina) također su razmatrani za upotrebu kod impakcije jednjaka, iako nisu pokazali značajnu efikasnost.⁵ Ovi lijekovi dovode do proizvodnje ugljikovog dioksida i tako povećavaju intraluminalni tlak i forsiraju bolus niz jednjak u želudac.⁵ Glukagon se smatra jednim od lijekova prve linije.⁵ U teoriji dovodi do opuštanja distalnog jednjaka i omogućuje prolaz bolusa hrane.⁵ Veliki broj bolesnika pri intervenciji primi glukagon u kombinaciji s drugim metodama, tako da je teško odrediti njegovu izoliranu učinkovitost.⁵ Druge mogućnosti liječenja uključuju hioscinbutilbromid, benzodiazepine, blokatore kalcijevih kanala, i nitrate.⁵

Potreba za endoskopskom intervencijom ovisi o dobi bolesnika, kliničkoj slici, vrsti, veličini i obliku stranog tijela, anatomskom položaju opstrukcije i vremenu koje je prošlo od incidenta.⁸ Pedijatrijski i odrasli bolesnici s visokim rizikom od aspiracije, potpunom opstrukcijom, ili dokazima perforacije (npr. groznica, tahikardija, loš opći dojam) zahtijevaju hitnu endoskopsku intervenciju.⁵ Oštri predmeti zahtijevaju hitno endoskopsko uklanjanje, kako za pedijatrijsku, tako i za odraslu populaciju.⁵ Jedno od najopasnijih stranih tijela u odraslih predstavljaju zubne proteze zbog metalnih kopčica koje mogu oštetiti sluznicu jednjaka i dovesti do perforacije jednjaka.^{9,10}

Ukoliko lijekovi nemaju nikakav učinak, endoskopiju treba obaviti unutar 24 sata jer je prisutnost stranog tijela dulja od tog razdoblja povezana s većom incidencijom komplikacija.⁵ Uklanjanje stranog tijela unutar 24 sata može smanjiti lokalno oštećenje sluznice jednjaka uzrokovano pritiskom.¹¹ Jedno istraživanje pokazalo je veće stope ulceracija jednjaka s odinofagijom ukoliko je strano tijelo uklonjeno endoskopski nakon razdoblja od 24 sata.¹² Izravna laringoskopija opcija je za uklanjanje predmeta smještenih iznad ili u razini krikofaringealnog mišića.⁸

Fleksibilna ezofagoskopija je također metoda koja se koristi za dijagnozu i uklanjanje stranih tijela jednjaka.⁵ Uklanjanje stranih tijela fleksibilnim

endoskopom ima visoku stopu uspješnosti i može se izvoditi uz svjesnu sedaciju kod većine odraslih osoba.⁸ Bolji oporavak bolesnika, niža stopa postinterventne disfagije i komplikacija (perforacija jednjaka), te nepostojanje potrebe za općom anestezijom, stavljaju fleksibilnu ezofagoskopiju kao metodu izbora ispred ezofagoskopije krutim ezofagoskopom.¹³ Ezofagoskopija krutim ezofagoskopom ima svoje mjesto kao "druga linija", tj. kada fleksibilna endoskopija ne uspije, a osobito kada kod bolesnika prevladavaju respiratorni simptomi.¹³ Preporučuje se i kod sumnje na oštro strano tijelo.⁴ Također, od veće je pomoći za strana tijela na razini gornjeg sfinktera jednjaka ili hipofaringealne regije.^{8,13} Ako se strano tijelo ne uspije odstraniti ezofagoskopijom ili propasirati dalje u probavni sustav, preporučuje se odstranjenje stranog tijela vanjskim kirurškim pristupom lateralnom faringotomijom.⁴

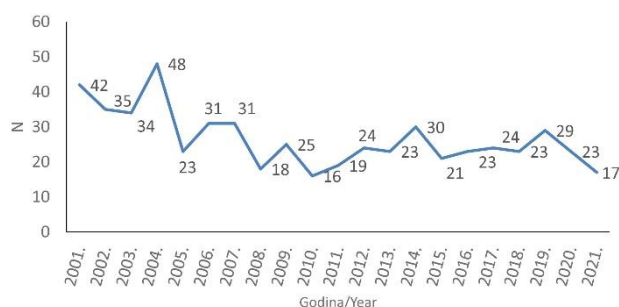
Bolesnici i metode

Provedeno je retrospektivno istraživanje za razdoblje od 01.01.2001. do 31.12.2021.god. u Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata i Klinici za unutarnje bolesti Kliničkog bolničkog centra Split (Odjel za gastroenterologiju). Ispitanici uključeni u ovo istraživanje bili su svi bolesnici sa sumnjom na strano tijelo hipofarinksa i jednjaka kojima je učinjena ezofagoskopija krutim ezofagoskopom u razdoblju od 01.01.2001. do 31.12.2021. god. ili ezofagogastroduodenoskopija (EGDS) u razdoblju od 01.01.2016. do 31.12.2021. god. Podaci o ispitanicima prikupljeni su iz pismohrane Klinike za bolesti uha, nosa i grla s kirurgijom glave i vrata i Klinike za unutarnje bolesti Kliničkog bolničkog centra Split (Odjel za gastroenterologiju). Prikupljeni podaci uključivali su: dob, spol, datum obavljenog zahvata, prisutnost stranog tijela, vrstu stranog tijela, lokaciju stranog tijela, postojanje komplikacija i novootkrivenih medicinskih stanja (maligne novotvorine, stenoze jednjaka). Za bolesnike s Odjela gastroenterologije dostupni su podaci po spolu i datumu obavljenog zahvata, dok ostali podaci nisu bili dostupni. U ovo istraživanje uključeno je 855 ispitanika (559 bolesnika s Klinike za bolesti uha nosa i grla s kirurgijom glave i vrata i 296 bolesnika s Odjela za gastroenterologiju, Klinike za unutarnje bolesti). Kriterij uključivanja u istraživanje bio je izvršena ezofagoskopija krutim ezofagoskopom ili EGDS zbog sumnje na strano tijelo, te dokaz o istome u knjigama hitnih protokola. Za usporedbu kategorijskih varijabli proveli smo hi-kvadrat test pri razini značajnosti od $p < 0.05$. Etičko povjerenstvo

KBC-a Split odobrilo je istraživanje rješenjem br. 500-03/22-01/112.

Rezultati

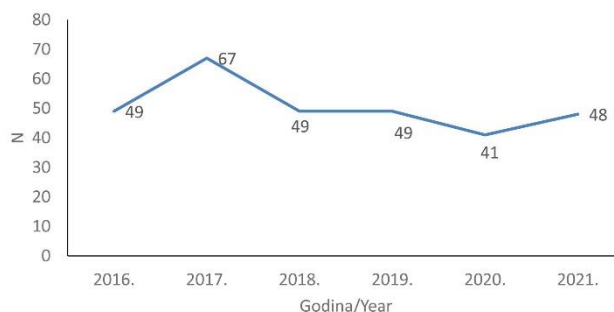
U istraživanje je uključeno 855 ispitanika. Kod njih 559 provedena je ezofagoskopija krutim ezofagoskopom u Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata, dok je u njih 296 provedena fleksibilna EGDS u Klinici za unutarnje bolesti (Odjel za gastroenterologiju).



Slika 1. Incidencija ezofagoskopija od 2001. do 2021. god na Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata

Figure 1 Incidence of esophagoscopy from 2001 to 2021 at the Ear, Nose and Throat Clinic with Head and Neck Surgery

Slika 1. Prikazuje incidenciju ezofagoskopija krutim ezofagoskopom u Klinici za bolesti uha, nosa i grla s kirurgijom glave i vrata u razdoblju od 21 godine. Ukupno je učinjeno 559 ezofagoskopija krutim ezofagoskopom. Od toga broja, 139 ih je učinjeno u razdoblju od 2016. do 2021.god. Općenito broj ezofagoskopija krutim ezofagoskopom je u padu od 2004.god. u odnosu na prethodno razdoblje. Također, broj ezofagoskopija ponovno pada nakon 2014.god.u odnosu na prethodno razdoblje. Trend pada se dodatno nastavlja u zadnjim godinama istraživanja.



Slika 2. Incidencija EGDS zbog sumnje na strano tijelo od 2016. do 2021. god.na Klinici za unutarnje bolesti (Odjel gastroenterologije)

Figure 2 Incidence of EGDS due to suspected foreign body from 2016 to 2021 at the Clinic for Internal Diseases (Department of Gastroenterology)

Slika 2. Prikazuje incidenciju EGDS zbog sumnje na strano tijelo od 2016. do 2021. god. u Klinici za unutarnje bolesti. Iako se radi o kraćem vremenskom razdoblju, vidljivo je da je pri Odjelu gastroenterologije godišnji broj EGDS zbog sumnje na strano tijelo relativno stabilan i kreće se u prosjeku oko 50 intervencija godišnje. Ukupan broj EGDS u razdoblju od 2016. do 2021.god. iznosio je 296 endoskopskih zahvata. U istom vremenskom razdoblju učinjeno je 139 ezofagoskopija krutim ezofagoskopom (Slika 1.). Razlika između broja učinjenih EGDS i ezofagoskopija krutim ezofagoskopom zbog sumnje na strano tijelo statistički je značajna tijekom ispitivanog razdoblja od šest godina (296 vrs 139, $p < 0.05$).



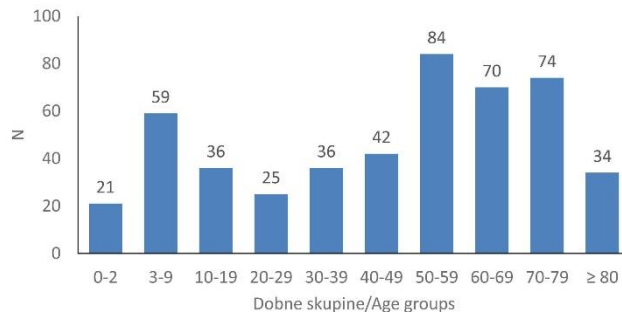
Slika 3. Incidencija ezofagoskopija po mjesecima
Figure 3 Incidence of esophagoscopy by months

Na Slici 3. prikazana je incidencija ezofagoskopija krutim ezofagoskopom tijekom mjeseci. Uočavamo da ih je najviše učinjeno tijekom ljetnih mjeseci srpanj (n=57) i kolovoz (n=65), dok je najmanja incidencija bila u studenom (n=24).



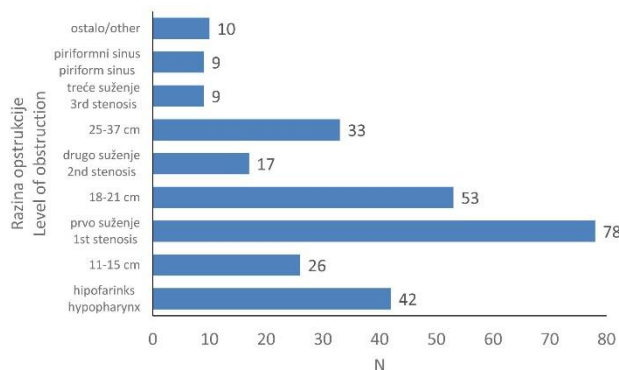
Slika 4. Incidencija EGDS po mjesecima
Figure 4 Incidence of EGDS by months

Slika 4. prikazuje incidenciju EGDS tijekom mjeseci. Najviše zahvata obavljeno je u lipnju (n=33) i rujnu (n=33), dakle tijekom ljetnih mjeseci, što odgovara i distribuciji ezofagoskopija krutim ezofagoskopom. Najmanja incidencija zahvata je ponovno bilo u zimskim mjesecima.



Slika 5. Prikaz raspodjele ispitanika po dobi, sa stranim tijelom i ezofagoskopijom krutim ezofagoskopom
Figure 5 Presentation of the distribution of subjects by age, with a foreign body and esophagoscopy with a rigid esophagoscope

Na Slici 5. prikazana je dobna raspodjela bolesnika s učinjenom ezofagoskopijom. Dob oboljelih kretala se od 6 mjeseci do 91 godinu starosti, a medijan je iznosio 45,5 godina. Iz raspodjele po dobnim skupinama vidljivo je da je ezofagoskopija najčešća u dječjoj dobi do 18. godine života, a potom slijedi odrasla populacija u dobi između 50. i 59. godine života. Najmanje ezofagoskopija učinjeno je u grupi bolesnika između 20. i 29. godine života.



Slika 6. Razine opstrukcije stranog tijela prilikom ezofagoskopije
Figure 6 Different levels of foreign body obstruction during esophagoscopy

Slika 6. prikazuje anatomska lokalizaciju zaostalog stranog tijela. Za 78 bolesnika nije bilo moguće dobiti podatke o visini opstrukcije. Od poznatih stranih tijela (n=277) najčešće mjesto opstrukcije predstavlja prvo suženje jednjaka (78 ili 28,2%), potom područje između prvog i drugog suženja (53 ili 19,1%), odnosno hipofarinks (42 ili 15,2%). U kategoriju ostalo (10 ili 1,9%) spadaju strano tijelo bazeepiglotisa, baze jezika, lingvalna tonzila i tamponada većeg dijela jednjaka. Najmanje stranih tijela (9 ili 3,2%) nađeno je na razini trećeg suženja i piriformnog sinusa.

Tablica 1. Vrste stranih tijela
Table 1 Overview of different foreign body types

Vrsta stranog tijela <i>Types of foreign bodies</i>	Broj <i>Number</i>	Postotak <i>Percentage</i>
Bolus <i>Bolus</i>	144	25,8%
Kost <i>Bone</i>	93	16,6%
Nepoznato <i>Unknown</i>	59	10,6%
Kovanica <i>Coin</i>	22	3,9%
Čačkalice <i>Toothpick</i>	9	1,6%
Metalni predmet <i>Metal object</i>	9	1,6%
Zubna proteza <i>Denture</i>	5	0,9%
Plastični predmet <i>Plastic object</i>	4	0,7%
Tableta <i>Tablet</i>	3	0,6%
Baterija <i>Battery</i>	2	0,4%
Tkanina <i>Fabric</i>	2	0,4%
Kamenčić <i>Small stone</i>	1	0,2%

Tablica 1. prikazuje vrste pronađenih stranih tijela prilikom ezofagoskopije. U 144 bolesnika (25,8%) radilo se o bolusu hrane kao najčešćoj vrsti stranog tijela, a potom slijedi kost kod 93 bolesnika (16,6%). Od neorganskih stranih tijela najzastupljenije su bile kovanice, kod 22 bolesnika (3,9%).

Strano tijelo je pronađeno kod 353 bolesnika (63%), dok kod 205 (37%) bolesnika ono nije pronađeno. Novootkrivena stenoza jednjaka potvrđena je kod 9 (2%) bolesnika, dok je sumnja na zloćudnu tvorbu postavljena kod 6 (1%) bolesnika.

U našem istraživanju dokumentirana je samo jedna komplikacija na 559 zahvata krute ezofagoskopije, a odnosila se na aspiraciju stranog tijela.

Rasprava

Rezultati ovog istraživanja pokazali su da je prilikom ezofagoskopije strano tijelo pronađeno u 63% bolesnika. Rezultati sličnih studija u svijetu su raznoliki. Primjerice, u istraživanju provedenom na Taiwanu postotak pronađenih stranih tijela bio je 57,2%, dok u drugoj studiji Li i suradnici ističu da je strano tijelo pronađeno u čak 90,8% bolesnika koji su bili podvrgnuti zahvatu.^{11,13}

Gledajući raspodjelu po spolu, od ukupnog broja

ispitanika u našem ispitivanju 41% su bile žene, a 59% muškarci. Dobiveni rezultati u skladu su s podacima domaće i strane literature. Naime, mnoge studije ističu da je prevalencija stranog tijela jednaka veća u muškaraca nego u žena, što se potvrdilo i ovim istraživanjem. Tako je primjerice u istraživanju Sperry-a i suradnika postotak muškaraca bio 59%, žena 41%, baš kao i u našem istraživanju.¹⁴ Wu i suradnici su pokazali nešto veću prevalenciju kod muškaraca (63%).¹¹ Postoje studije u kojima je bio nešto veći postotak žena od muškaraca.^{15,16}

Medijan dobi svih ispitanika u ovom istraživanju bio je 45,5 godina. Najmlađi ispitanik imao je šest mjeseci, dok je najstariji imao 91 godinu. Najzastupljeniju dobnu skupinu činila su djeca do 18. godine života. Dobiveni rezultati u skladu su sa svjetskom literaturom koja ističe da je upravo pedijatrijska populacija jedna od najrizičnijih dobnih skupina za intervencije zbog sumnje na strano tijelo jednjaka.² U našem istraživanju druga najzastupljenija dobna skupina bili su bolesnici u šestom desetljeću života, što odgovara istraživanju Pudara i suradnika.¹⁵ Za razliku od Pudara i suradnika, u našem je istraživanju najmanje zastupljena dobna skupina bila od 20. do 29. godine života.

Što se tiče incidencije po mjesecima, uočavamo da su ezofagoskopija i EGDS češće u ljetnim mjesecima. Shuja i suradnici u svojoj su studiji pokazali povećanu incidenciju stranih tijela jednjaka tijekom nacionalnih praznika i značajnih sportskih događanja.³ To se događa prvenstveno zbog neumjerenosti u prehrani, te istovremenoj upotrebi alkohola.³ Naši rezultati u skladu su sa spomenutim istraživanjem jer su upravo ljetni mjeseci zastupljeni većim brojem okupljanja, druženja i zabava na otvorenom, koje sa sobom donose i blagovanje većih količina hrane i pića.

Nadalje, jedno od istraživanih obilježja ezofagoskopija su vrste odstranjenih stranih tijela. Prema Damghaniju i suradnicima, najzastupljenija vrsta stranog tijela bila je kost (37%), zatim kovanice (18,7%) i mesni bolus (8,1%).¹⁷ Pudar i suradnici kao strano tijelo u 42,36% slučajeva nalaze kost, zatim bolus (33%) i kovanicu (11,33%).¹⁵ U našoj studiji 25,8% stranih tijela čini bolus koji obuhvaća bilo kakav oblik hrane (mesnog i nemesnog porijekla), 16,6% čini kost i 3,9% kovanica. Baš kao i u spomenutim studijama, u našoj je studiji najzastupljeniji oblik stranog tijela bio bolus hrane, dok je najzastupljenije neorgansko strano tijelo bila kovanica.

Gledajući mjesto opstrukcije, najviše stranih tijela zastalo je na prvom suženju i to kod gotovo trećine bolesnika. Nakon toga slijedi dio jednjaka između prvog i drugog suženja u gotovo petine bolesnika, te

hipofarinks u 15,2 % slučajeva. Do sličnih podataka je došao i Aiolfi meta-analizom.² Long i suradnici u svojoj studiji ističu da je čak u 75% slučajeva mjesto opstrukcije krikofaringealni mišić, odnosno prvo suženje.⁵ Damghani i suradnici kao najčešće mjesto opstrukcije u svom istraživanju navode područje hipofarinksa ikrikofaringealnog mišića.¹⁷ Pudar i suradnici također kao najčešće mjesto opstrukcije ističu prvo suženje.¹⁵ Iz navedenoga je vidljivo da su rezultati našeg istraživanja usporedivi sa svjetskim podacima, te da je prvo suženje jednjaka najčešće mjesto opstrukcije stranim tijelom.

Kod 559 slučajeva ezofagoskopije krutim ezofagoskopom učinjene radi sumnje na strano tijelo, zabilježena je svega jedna komplikacija u obliku aspiracije stranog tijela. Kao komplikacije zahvata praćene su aspiracija stranog tijela i perforacije jednjaka. Erozijske, laceracijske i oskudna krvarenja sluznice nisu se posebno evidentirala. Stubington i suradnici ističu kako je perforacija jednjaka prisutna u samo 0,25-2% bolesnika.¹⁸ Sličan postotak perforacija su zabilježili Tsao i suradnici.¹⁹ Za razliku od perforacije jednjaka, podaci o aspiraciji stranog tijela kao komplikaciji ezofagoskopije su oskudni. S obzirom na to, aspiraciju stranog tijela možemo smatrati izrazito rijetkom komplikacijom.

Wu i suradnici u svojoj studiji ističu da je 19,9% bolesnika prethodno imalo neke gastrointestinalne probleme, a kao najčešće izdvajaju karcinom jednjaka i strikture.¹¹ Također ističu da su takva stanja bila češća u ljudi sa stranim tijelom u obliku bolusa hrane koja bi u zdravih ljudi bila uredno pasirana.¹¹ Sperry i suradnici strikturu jednjaka su zabilježili u 12% ispitanika, a malignu tvorbu u 2% ispitanika.¹⁴ U našem istraživanju je ta brojka nešto manja. Naime, kod svega 2% ispitanika uočena je stenoza jednjaka, dok je u 1% postavljena sumnja na zloćudnu leziju. Do ovakvih podataka došli su u svome istraživanju i drugi autori.¹⁵

Naše istraživanje zaostalih stranih tijela u jednjaku, tijekom razdoblja od 21 godine, pokazuje postupni pad broja ezofagoskopija učinjenih krutim ezofagoskopom. Nasuprot tome, u zadnjih šest godina stalan je broj EGDS učinjenih fleksibilnim endoskopom. Razlika u broju učinjenih endoskopija između ove dvije metode je statistički značajna tijekom posljednjih šest godina ovoga istraživanja i ukazuje na promjenu trenda u liječenju bolesnika sa stranim tijelom jednjaka.

Zaključak

Gutanje je automatizirana motorička radnja koju izvršavamo nebrojeno puta u danu, te stoga ne iznenađuje da su strana tijela jednjaka relativno česta.

Slično kao i u stranoj literaturi ovo je istraživanje pokazalo da su strana tijela jednjaka najčešća među pedijatrijskom populacijom i osobama starije životne dobi, s većom prevalencijom kod muškaraca. Kao najčešće mjesto opstrukcije pokazalo se prvo suženje jednjaka, dok je najčešća vrsta zaostalog stranog tijela biobolus hrane. Važno je za istaknuti pad broja ezofagoskopija krutim ezofagoskopom tijekom zadnjih šest godina istraživanja, uz konstantan broj fleksibilnih EGDS. Taj podatak možemo objasniti složenošću zahvata ezofagoskopije krutim ezofagoskopom i potrebom za uvođenjem bolesnika u opću anesteziju. Isto tako, razvojem medicine i tehnologije, instrumenti za izvođenje fleksibilne EGDS su svakim danom sve napredniji i precizniji, što dodatno olakšava sam endoskopski zahvat. Stoga je EGDS sve češće metoda izbora kod odstranjenja stranog tijela iz jednjaka.

Literatura

1. Birk M, Bauerfeind P, Deprez PH, Häfner M, Hartmann D, Hassan C, i sur. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*2016;48:489–96.
2. Aiolfi A, Ferrari D, Riva CG, Toti F, Bonitta G, Bonavina L. Esophageal foreign bodies in adults: systematic review of the literature. *Scand J Gastroenterol*2018;53:1171–8.
3. Shuja A, Winston DM, Rahman AU, Mitty RD, Jaber BL, Keo T. Esophageal food impaction during cultural holidays and national athletic events. *Gastroenterol Rep (Oxf)*2017;5:43–6.
4. Vrdoljak FV, Poljak NKP. Traheobronhologija i ezofagologija. U: Drviš PD. *Otorinolaringologija s kirurgijom glave i vrata*. Prvo izdanje. Split: Redak; 2019. str. 197-212.
5. Long B, Koyfman A, Gottlieb M. Esophageal foreign bodies and obstruction in the emergency department setting: An evidence-based review. *J Emerg Med*2019;56:499–511.
6. Connolly AA, Birchall M, Walsh-Waring GP, Moore-Gillon V. Ingested foreign bodies: patient-guided localization is a useful clinical tool. *Clin Otolaryngol Allied Sci*1992;17:520–4.
7. Yamada T, Sato H, Seki M, Kitagawa S, Nakagawa M, Shimazaki H. Successful salvage of aorto-esophageal fistula caused by a fish bone. *Ann Thorac Surg*1996;61:1843–5.
8. ASGE Standards of Practice Committee, Ikenberry SO, Jue TL, Anderson MA, Appalaneni V, Banerjee S, i sur. Management of ingested foreign bodies and food impactions. *Gastrointest Endosc*2011;73:1085–91.
9. Nimmo SS, Nimmo A, Chin GA. Ingestion of a unilateral removable partial denture causing serious complications. *Oral Surg Oral Med Oral Pathol*

- 1988;66(1):24–6.
10. Stiles BM, Wilson WH, Bridges MA et al. Denture esophageal impaction refractory to endoscopic removal in a psychiatric patient. *Emerg Med* 2000;18:323–6.
 11. Lee JB, Ahmad S, Gale CP. Detection of coins ingested by children using a handheld metal detector: a systematic review. *Emerg Med J* 2005;22:839–44.
 12. Pinto A, Lanza C, Pinto F, Grassi R, Romano L, Brunese L, i sur. Role of plain radiography in the assessment of ingested foreign bodies in the pediatric patients. *Semin Ultrasound CT MR* 2015;36:21–7.
 13. Muensterer OJ, Joppich I. Identification and topographic localization of metallic foreign bodies by metal detector. *J Pediatr Surg* 2004;39:1245–8.
 14. Nation J, Jiang W. The utility of a handheld metal detector in detection and localization of pediatric metallic foreign body ingestion. *Int J Pediatr Otorhinolaryngol* 2017;92:1–6.
 15. Singleton J, Schafer JM, Hinson JS, Kane EM, Wright S, Hoffmann B. Bedside sonography for the diagnosis of esophageal food impaction. *Am J Emerg Med* 2017;35:720–4.
 16. Ahn JH, Sohn Y. Application of point-of-care ultrasound for different types of esophageal foreign bodies: three case reports: A CARE-compliant article. *Medicine (Baltimore)* 2020;99:e18893.
 17. Mori T, Ihara T, Hagiwara Y. Pediatric food impaction detected through point-of-care ultrasonography. *Clin Exp Emerg Med* 2018;5:135–7.
 18. Khayyat YM. Pharmacological management of esophageal food bolus impaction. *Emerg Med Int* 2013;2013:924015.
 19. Wu W-T, Chiu C-T, Kuo C-J, Lin C-J, Chu Y-Y, Tsou Y-K, i sur. Endoscopic management of suspected esophageal foreign body in adults: Esophageal foreign body. *Dis Esophagus* 2011;24:131–7.
 20. Centers for Disease Control and Prevention (CDC). Gastrointestinal injuries from magnet ingestion in children--United States, 2003-2006. *MMWR Morb Mortal Wkly Rep* 2006;55:1296–300.
 21. Zhao-Shen L, Zhen-Xing S, Duo-Wu Z, Guo-Ming X, Ren-Pei W, Zhuan L. Endoscopic management of foreign bodies in the upper-GI tract: experience with 1088 cases in China. *Gastrointest Endosc* 2006;64:485–92.
 22. Sperry SLW, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. *Gastrointest Endosc* 2011;74:985–91.
 23. Pudar G, Vlaski L. Esophageal foreign bodies: retrospective study in 203 cases. *Med Pregl* 2010;63:254–7.
 24. Athanassiadi K, Gerazounis M, Metaxas E, Kalantzi N. Management of esophageal foreign bodies: a retrospective review of 400 cases. *Eur J Cardiothorac Surg* 2002;21:653–6.
 25. Damghani M, Halavati N, Motamedi N. Foreign body in the upper airway and oesophagus: a seven years study from Iran. *J Pak Med Assoc* 2011;61:859–62.
 26. Longstreth GF, Longstreth KJ, Yao JF. Esophageal food impaction: epidemiology and therapy. A retrospective, observational study. *Gastrointest Endosc* 2001;53:193–8.
 27. Stubington TJ, Kamani T. Food bolus and oesophageal foreign body: a summary of the evidence and proposed management process. *Eur Arch Otorhinolaryngol* 2021;278:3613–23.
 28. Tsao GJ, Damrose EJ. Complications of esophagoscopy in an academic training program. *Otolaryngol Head Neck Surg* 2010;142:500–4.

Emerging Management of Chronic Subdural Hematoma (CSDH) in High-Income Country (HIC) and Low-Income Country (LIC): A Review

Novo liječenje kroničnog subduralnog hematoma (CSDH) u zemlji s visokim (HIC) i u zemlji s niskim prihodima (LIC): pregled

Tommy Nazwar Alfandy, Farhad Bal'afif, Donny Wisnu Wardhana, Mustofa Mustofa*

Summary

Chronic Subdural Hematoma (CSDH) is a common neurosurgical condition that affects individuals worldwide. However, the management of CSDH varies significantly between high-income and low-income countries due to disparities in healthcare resources, infrastructure, and access to advanced medical technologies. In this literature review, we aim to compare and contrast the management approaches of CSDH in high-income and low-income countries. By adopting a global health perspective, we highlight the challenges faced by healthcare systems in both settings and offer insights and recommendations for improving the management of CSDH in low-income countries. This topic is unique and important as it sheds light on the ethical dilemmas posed by the differences in healthcare access and outcomes between high-income and low-income countries and emphasizes the importance of equitable healthcare distribution.

Keywords: Hematoma, subdural, chronic, low-Income Country, management, care, neurosurgical procedures, recommendations

Sažetak

Kronični subduralni hematom (CSDH) uobičajeno je neurokirurško stanje koje pogađa pojedince diljem svijeta. Međutim, upravljanje CSDH značajno se razlikuje između zemalja s visokim i niskim dohotkom zbog razlika u zdravstvenim resursima, infrastrukturi i pristupu naprednim medicinskim tehnologijama. U ovom pregledu literature, cilj nam je usporediti i suprotstaviti pristupe upravljanja CSDH u zemljama s visokim i niskim prihodima. Usvajanjem globalne zdravstvene perspektive, ističemo izazove s kojima se zdravstveni sustavi suočavaju u oba okruženja i nudimo uvide i preporuke za poboljšanje upravljanja CSDH u zemljama s niskim prihodima. Ova je tema jedinstvena i važna jer rasvjetljava etičke dileme koje postavljaju razlike u pristupu zdravstvenoj skrbi i rezultatima između zemalja s visokim i niskim prihodima, te naglašava važnost pravedne raspodjele zdravstvene skrbi.

Ključne riječi: kronični subduralni hematom, zemlja s niskim prihodima, upravljanje njegovom, pregled

Med Jad 2023;53(3):181-198

Introduction

In the realm of healthcare, the global landscape is marked by significant variations in resources, disease

burden, and treatment capabilities across different regions. As emerging statistics reveal, traumatic brain injuries (TBIs) continue to exert a substantial toll on global health, affecting approximately 69 million

* Division of neurosurgery, Department of Neurosurgery Brawijaya University/Saiful Anwar Hospital Malang East Java Indonesia (Tommy Nazwar Alfandy, MD; Farhad Bal'afif, MD; Donny Wisnu Wardhana, MD; Mustofa B., M. biomed.)

Corresponding address / *Corresponding address:* Dr. Farhad Bal'afif, Jl. Jaksa Agung Suprpto no.2, Klojen, Kec. Klojen, Kota Malang, Jawa Timur 65112 E-mail: nsubtommy@gmail.com

Received/*Primljeno* 2023-07-04; Revised/*Ispravljeno* 2023-08-21; Accepted/*Prihvaćeno* 2023-10-18

individuals annually. These injuries span a wide spectrum of severity, with mild and moderate cases comprising the majority. Strikingly, it is in low-income countries (LIC) that the healthcare systems bear the brunt of this burden, grappling with nearly triple the number of TBIs compared to their counterparts in high-income countries (HIC).¹

The glaring disparities in healthcare resources and disease management between regions with contrasting socio-economic profiles call for a concerted focus on addressing this imbalance. One area that stands out amidst this complex web of challenges is the global landscape of surgical interventions for emergent pathological conditions. A staggering 11% of all surgical procedures worldwide are attributed to addressing pathological disorders and emergency illnesses². Within this context, the occurrence of subdural hematoma, characterized by the accumulation of blood beneath the protective dura mater surrounding the brain tissue, emerges as a critical pathological entity.³ The onset of subdural hematoma often results from the rupture of bridging veins due to opposing forces, leading to a range of clinical presentations.³⁻⁶

One significant dimension of subdural hematoma management that demands urgent attention is the divergent treatment strategies employed by surgeons, particularly within the context of chronic subdural hematoma (CSDH). Despite aggressive medical interventions, traumatic acute subdural hematoma remains associated with a notable fatality rate. Notably, CSDH exhibits a propensity for affecting males and is commonly observed in individuals aged 70 years or older. This demographic profile, coupled with the observed lack of uniformity in treatment approaches, underscores the need for tailored interventions.⁷

Interestingly, the discrepancies in healthcare provision and outcomes extend to the field of neurosurgery, further exacerbating the challenges associated with subdural hematoma management. A survey conducted among young neurosurgeons by the World Federation of Neurosurgical Societies revealed an acute shortage of neurosurgeons globally, with a particularly pronounced deficit in LIC and low- to middle-income countries (LMIC). This deficiency in resources for research and specialized training highlights the urgent need for increased attention to bolster educational initiatives and support service programs within the realm of neurosurgery.⁸

Addressing the nuanced intricacies of subdural hematoma management within such diverse healthcare settings demands comprehensive research efforts that transcend geographic boundaries. A key point of focus is the exploration of nascent

technologies and methodologies that can alleviate the challenges posed by resource constraints. Such initiatives hold the potential to revolutionize the care provided to subdural hematoma patients in both HIC and LIC contexts, providing hope for improved outcomes and reduced mortality. In light of these considerations, this literature review embarks on a comprehensive examination of the utilization of emerging technologies and innovative approaches in the management of subdural hematoma. By shedding light on the distinctive challenges faced by different income strata, this review aims to contribute to the ongoing discourse on enhancing subdural hematoma management across the global healthcare spectrum.

Obstacles in diagnosing CSDH in low-resource settings

Diagnosing chronic subdural hematoma (CSDH) in low-resource settings presents several challenges due to limited medical infrastructure, resources, and access to specialized care. Delayed presentation and diagnosis due to, amongst other reasons, postponed imaging resulted in a prolonged time to definitive treatment and a high mortality rate compared to other regions of the world.⁹ Here are some specific obstacles that contribute to difficulties in diagnosing CSDH in such settings:

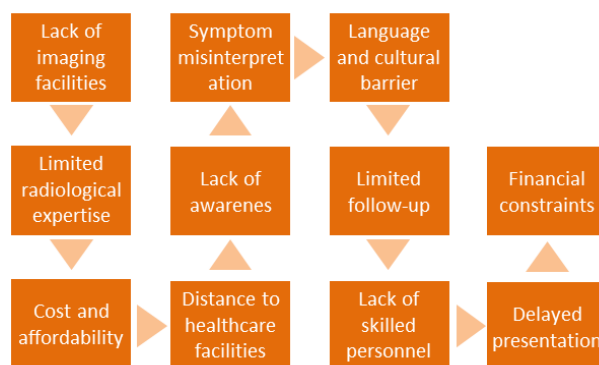


Figure 1 Diagnostic obstacles in low settings resource countries

Slika 1. Dijagnostičke prepreke u zemljama s niskim postavkama resursa

1) Lack of Imaging Facilities: Low-resource settings often lack advanced imaging technologies like computed tomography (CT) scanners and magnetic resonance imaging (MRI) machines, which are crucial for accurately diagnosing CSDH and assessing its severity. Imaging is proven clinically useful in high-income nations and should be deployed and upscaled in LMICs. In an unprecedented situation, digitalization and recent technological

advances are allowing LMICs to deploy imaging at a large scale and lower costs than before. Prerequisites are to carefully evaluate population needs and organize and fund imaging implementation locally using a holistic approach that accounts for all LMIC complexities and promotes collaboration with other medical specialties to strengthen healthcare systems.¹⁰

2) Limited Radiological Expertise: Even if imaging facilities are available, there might be a shortage of trained radiologists or healthcare professionals who can interpret imaging results accurately, leading to potential misdiagnosis or delayed diagnosis. Despite MRI's emergence as a long-term diagnostic tool, a large gap has emerged in population coverage: most people in low- and middle-income countries lack access to this vital imaging tool. Inadequate infrastructure and the lack of a specialized crew are two important factors in the observed shortage of MRI in LMICs.¹¹

3) Cost and Affordability: Diagnostic imaging procedures, such as CT scans and MRIs, can be expensive. Patients in low-resource settings might be unable to afford these tests, leading to delayed or incomplete diagnosis. Many low-income countries don't prioritize surgical care due to its perceived high expenses. Basic surgical care is unavailable to 2 billion individuals. Without surgical care, common, treatable diseases become debilitating and deadly. Low- and middle-income countries (LMICs) lack essential facilities and equipment for processes. Indeed, inadequate infrastructure and medical professional training hinder worldwide surgical services.¹²

4) Distance to Healthcare Facilities: Rural and remote areas often lack access to healthcare facilities equipped with diagnostic tools. Patients may need to travel long distances to reach a medical center, leading to delays in diagnosis and treatment. Currently, a significant proportion of low- and middle-income countries (LMICs) face considerable challenges in delivering sufficient neurosurgical services. There are notable obstacles that impede access to adequate healthcare services, such as the scarcity of qualified medical, nursing, and allied health professionals, insufficiency of essential medical equipment, and the absence of reasonably accessible and affordable healthcare facilities for patients.¹³

5) Lack of Awareness: Both healthcare providers and patients may have limited awareness of CSDH, its symptoms, and the importance of early diagnosis. This lack of awareness can result in delayed medical attention. Limited awareness of chronic subdural hematoma (CSDH) and its symptoms among

healthcare providers and patients can lead to delayed medical attention. This delay can result in complications and increased morbidity.¹⁴

6) Symptom Misinterpretation: Symptoms of CSDH, such as headaches, confusion, and balance problems, can be mistakenly attributed to other common conditions, leading to misdiagnosis or underdiagnosis. Symptoms of chronic subdural hematoma (CSDH), such as headaches, confusion, and balance problems, can be mistakenly attributed to other common conditions, leading to misdiagnosis or underdiagnosis. This is particularly true in the elderly population, where cognitive impairments associated with CSDH may be misinterpreted as dementia.¹⁵

7) Language and Cultural Barriers: Effective communication between patients and healthcare providers is essential for accurate diagnosis. Language barriers and cultural differences can hinder the proper exchange of information. There is a scarcity of scholarly articles in the indexed literature that articulate the viewpoints and experiences of neurosurgeons from low- and middle-income countries (LMICs), indicating a prevailing dearth of engagement within the global neurosurgery research community. One potential factor contributing to the problem can be attributed to the inherent nature of modern surgical discourse, which places significant emphasis on technical advancements and ideology originating from high-income countries (HIC). Therefore, all surgeons in LIC encounter several impediments and challenges while endeavoring to provide a critical comment regarding their experiences pertaining to nearly any facet of surgical care.¹⁶

8) Limited Follow-up: Diagnosing CSDH might require follow-up appointments for monitoring the progression of the condition. However, limited resources and accessibility can prevent patients from receiving necessary follow-up care. A follow-up appointment helps patients understand their postoperative or nonoperative care, identify issues, offer further operative management, and coach the patient and family to improve outcomes.¹⁷ Uninsured patients and Medicaid patients are associated with a greater incidence of complications and poor outcomes. The relationship between insurance status and loss to follow-up, is an indirect reflection of socioeconomic factors, literacy, and education.¹⁷

The protective effect of clinic follow-up on readmission varies by the cause of readmission. Early follow-up within 10–14 days provides an opportunity to diagnose wound-related complications, deep venous thrombosis, pulmonary embolism, and postoperative systemic infections. Later follow-up within four weeks postoperatively provides an

opportunity to detect complications associated with the recurrence of CSDH. Regardless, ≥ 1 follow-up visit, preferably with a neurosurgical or primary care provider, could assist in reducing the need for readmission.¹⁷

9) Lack of Skilled Personnel: Skilled neurologists, neurosurgeons, and other specialists experienced in diagnosing and treating CSDH might be scarce in low-resource settings. The cost of neurosurgery training is also an important consideration for graduates and aspiring trainees from LMICs. Frequently, these prohibitive costs may limit aspiring neurosurgeons from continuing the pursuit of neurosurgery, whether in-country or elsewhere. In addition, the absence of a reliable and sufficient salary for neurosurgical trainees in LMICs can often lead to the need to find other part-time jobs unrelated to neurosurgery, hindering their ability to focus on their training. After training, they may seek employment in the private healthcare sector, where salaries can be higher, to compensate for these increased costs. This, in turn, leads to inequitable patient care access as the public health sector suffers.¹⁸

10) Inadequate Training: Healthcare providers in these settings might lack proper training in recognizing and managing neurological conditions like CSDH, contributing to diagnostic challenges. Cost is an important barrier that can not only limit the capacity to train neurosurgeons but can also perpetuate inequitable access to training. Additional investment by governments and other stakeholders can help develop a sufficient workforce and reduce inequality for the next generation of neurosurgeons worldwide.¹⁸ Even in the United States, the average cost for applying to neurosurgical residency is USD 10,300 - higher than that of other surgical specialties. The largest component of this cost is interviews, averaging USD 7,180 for applicants.¹⁸

11) Delayed Presentation: Due to socioeconomic factors and limited healthcare access, patients might delay seeking medical care for their symptoms, leading to more advanced and severe cases by the time they are diagnosed. This delay in seeking medical care can have serious consequences, particularly for conditions that require early intervention. For example, chronic pain is a common reason for patients to seek care in the emergency department. Still, it is often undertreated, leading to dissatisfaction with medical care, hostility toward the physician, and, potentially, an increased risk of litigation.¹⁹

12) Financial Constraints: Surgical interventions are often necessary to treat CSDH effectively. However, patients may not have the financial means

to undergo surgery, leading to inadequate treatment. Financial constraints can be a significant barrier to receiving adequate treatment for chronic subdural hematoma (CSDH).²⁰ In resource-challenged environments, the standard treatment of CSDH in the theater may be delayed due to financial constraints and logistic problems, which can negatively impact the outcome.²⁰ However, there are options available for patients who cannot afford standard surgical treatment. For example, a bedside single burr hole craniostomy drainage of the hematoma under local anesthesia at the accident and emergency unit may be a useful option in resource-challenged settings.²⁰ This procedure can be lifesaving in patients with CSDH who present in extreme neurological condition but in whom prompt standard surgical treatment in the theater is not feasible.²⁰ In a study by Oyemolade, three patients with CSDH who presented at the service in poor neurological condition underwent bedside single frontal burr hole craniostomy drainage of the hematoma under local anesthesia at the accident and emergency unit of the hospital. Surgery was done within 1 hour of review by the neurosurgical team in all cases, and the outcome was good in all cases. Therefore, while financial constraints can be a significant barrier to receiving adequate treatment for CSDH, options such as bedside single burr hole craniostomy drainage may be a useful alternative in resource-challenged settings.²⁰

To address these obstacles and improve the diagnosis of CSDH in low-resource settings, efforts should focus on increasing awareness, providing training for healthcare workers, implementing telemedicine solutions for remote consultation, improving access to affordable diagnostic tools, and establishing referral systems to connect patients in remote areas with specialized care centers. Collaboration between international organizations, governments, and local healthcare providers is crucial to overcome these challenges and ensure timely and accurate diagnosis of CSDH in low-resource settings.

Risk factors of CSDH

Chronic Subdural Hematoma (CSDH) is a medical condition characterized by the accumulation of blood between the brain's surface and its outermost covering, the dura mater. While the risk factors for CSDH recurrence are generally consistent regardless of the setting, there are specific challenges and considerations in low-resource settings and low-income countries that can influence the recurrence rates and management of this condition. According to Sim YW, various factors were considered to be risk factors of CSDH, such as head trauma, chronic

alcoholism, epilepsy, previous shunt surgery, underlying disease having bleeding tendency, and medications with ACs/APs such as warfarin, aspirin, clopidogrel, or triflusal.²¹ Risk factors for CSDH recurrence include:

1) **Advanced Age:** Elderly individuals are more prone to CSDH due to age-related brain atrophy and fragile blood vessels. In low-resource settings, where access to quality healthcare and early intervention might be limited, the aging population can contribute to higher recurrence rates. Chronic subdural hematoma (CSDH) is a condition that occurs more frequently in elderly patients due to age-related brain atrophy and fragile blood vessels.^{22,23} Elderly patients with CSDH may experience symptoms of cognitive change, memory disturbance, urinary incontinence, and decreased activity, as well as disturbance of consciousness at admission.²² In low-resource settings where access to quality healthcare and early intervention might be limited, the aging population can contribute to higher recurrence rates of CSDH.²² The recurrence rate of CSDH has not decreased over recent decades and ranges from 0.36% to 33.3%.²² Outcomes in patients over 75 years old are significantly worse than those younger than 75, and long-term outcomes for elderly patients with CSDH are poor.²² However, burr hole surgery with drainage under local anesthesia is the most common surgical procedure, even in elderly patients.²² Some studies suggest using atorvastatin after surgery in elderly patients with CSDH may reduce hematoma volume and improve neurological outcomes.²⁴ Middle meningeal artery embolization (MMAE) for CSDH in selected high-risk elderly patients and relapsed patients might also be effective.²⁵

2) **Trauma:** Head injuries, even minor ones, are a significant risk factor for CSDH development and recurrence. In regions with poor infrastructure, inadequate safety measures, and limited access to timely medical care, the likelihood of head injuries could be higher, consequently increasing the risk of CSDH recurrence—factors contributing to the development and recurrence of CSDH including Traumatic Subdural Effusion (TSDE). TSDE is one of the etiological factors for developing CSDH, especially in the elderly. The evolution of TSDE into CSDH is initially a hidden process and may present with nonspecific signs and symptoms.²⁶ Multiple pathways have been proposed for developing Subdural hygroma (SDG) after traumatic brain injury. The fluid collection might result from damaged vascular effusion and dura-arachnoid interface separation at the dural border cell layer.²⁷

3) **Coagulopathy and Anticoagulant Use:** Conditions that affect blood clotting and the use of

anticoagulant medications increase the risk of CSDH. In low-resource settings, where access to regular medical check-ups and monitoring may be limited, individuals with coagulopathies or those on anticoagulants might be at higher risk of recurrence due to inadequate management. In low-resource settings where access to regular medical check-ups and monitoring may be limited, individuals with coagulopathies or those on anticoagulants might be at higher risk of recurrence due to inadequate management.²⁸

4) **Alcohol Abuse:** Chronic alcohol abuse can lead to cerebral atrophy and increase the risk of CSDH. In some low-income countries, alcohol consumption patterns and limited awareness of its health risks may contribute to higher recurrence rates. Chronic alcohol abuse can lead to cerebral atrophy and increase the risk of chronic subdural hematoma (CSDH). In some low-income countries, alcohol consumption patterns and limited awareness of its health risks may contribute to higher recurrence rates.²⁹

5) **Hypertension:** Uncontrolled hypertension can weaken blood vessels and increase the risk of bleeding into the subdural space. Lack of access to regular medical care and medication in low-resource settings could exacerbate this risk factor. Uncontrolled hypertension can weaken blood vessels and increase the risk of bleeding into the subdural space.³⁰

6) **Diabetes:** Diabetes is associated with vascular changes that can make blood vessels more susceptible to rupture. In settings with limited diabetes management and education, this could contribute to recurrent CSDH cases. Vascular changes associated with diabetes can make blood vessels more susceptible to rupture, which could contribute to recurrent chronic subdural hematoma (CSDH) cases in settings with limited diabetes management and education.³¹

7) **Surgical Factors:** The surgical technique used to evacuate the hematoma can influence recurrence rates. Suboptimal surgical procedures due to lack of resources, infrastructure, or trained personnel in low-resource settings might contribute to higher recurrence rates. In low-resource settings, suboptimal surgical procedures due to a lack of resources, infrastructure, or trained personnel might contribute to higher recurrence rates.³²

8) **Nutrition and Health Access:** Malnutrition and poor overall health can weaken the body's ability to heal, potentially impacting the recurrence of CSDH. Limited access to nutritious food and healthcare in low-income countries can exacerbate this risk. The intricate relationship between health status, nutrition, and the healing process holds a pivotal role in the

recurrence of chronic subdural hematoma (CSDH). Malnutrition and compromised overall health can substantially undermine the body's inherent capacity to recover effectively, thereby influencing the likelihood of CSDH recurrence. This concern assumes heightened significance within the context of low-income countries, where access to both nutritious sustenance and quality healthcare services is often severely constrained.

9) Patient Compliance and Follow-up: Successful management of CSDH often requires regular follow-up appointments and compliance with medication. Economic constraints, transportation challenges, and lack of awareness can all contribute to reduced patient compliance in low-resource settings, leading to higher recurrence rates. It is important for healthcare providers to consider these factors and work with patients to develop strategies to overcome them. For example, telemedicine may be a useful tool for follow-up.

10) Limited Access to Neurosurgical Care: Timely and appropriate surgical intervention is crucial in treating CSDH and preventing recurrence. In low-resource settings, there might be a lack of specialized neurosurgical care, leading to delays in treatment or suboptimal surgical outcomes. However, there may be a lack of specialized neurosurgical care in low-resource settings, leading to delays in treatment or suboptimal surgical outcomes.³³

Addressing these risk factors in low-resource settings and low-income countries requires a comprehensive approach, including improving healthcare infrastructure, increasing awareness of CSDH and its risk factors, providing proper training for medical personnel, ensuring access to essential medications, and promoting safety measures to prevent head injuries.

Surgical Treatment of Chronic Subdural Hematoma Controversies

The literature study on the management of subdural hematoma by Solou et al. reviewed points including indications for surgery, timing of surgery, method of surgery, number of burr holes, irrigation, drainage insertion, drainage location, drainage duration, membranectomy, and MMA embolization.³⁴ In addition, Solou used the American Academy of Neurology protocol for strength recommendations from the papers selected.³⁴

1) Indications for surgery are determined by clinical and radiologic presentation; no studies compare surgical vs. conservative management. However, there is clinical consensus that hematomas greater than 1 cm in thickness, or equal to or

exceeding the thickness of the skull, should be evacuated. In general, conservative treatment is usually reserved for patients with mild symptoms.

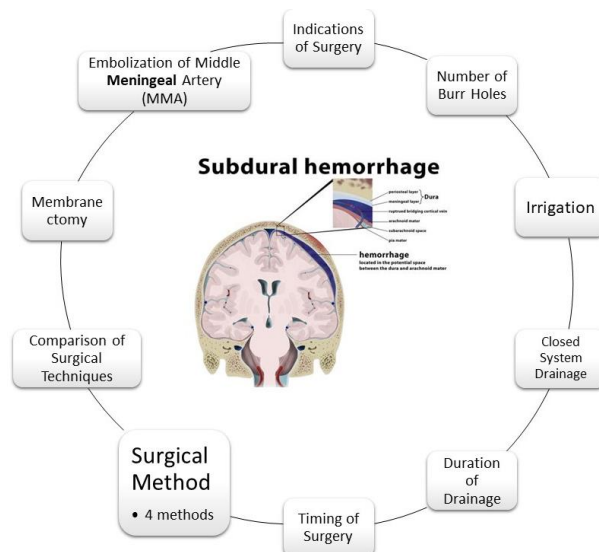


Figure 2 The management of subdural hematoma by Solou et al. reviewed points

Slika 2. Liječenje subduralnog hematoma prema Solou i sur. pregledane točke

2) The timing of surgery in managing subdural hematoma is not too many studies that discuss this subject. Still, according to Venturini, it is better if the above CSDH cases with surgery are less than seven days.³⁵ But once upon a time, there were occasions when patients had to pause surgery. The European Heart Rhythm Association (EHRA) recommends pausing in patients who are given oral anticoagulants before surgery.

3) Common methods for CSDH management are twist drill craniostomy (TDC), burr hole craniostomy (BHC), craniotomy, and endoscopic evacuation. Although burr hole craniostomy is an option for CSDH treatment, there are still many controversies regarding its operation that remain unanswered.

4) BHC, TDC, and craniotomy are effective in treating CSDH. BHC is considered the first level of treatment and seems to offer a good cure ratio and low complications. TDC is recommended in high-risk surgical patients. TDC tends to be associated with a higher risk of recurrence rate than BHC and is recommended in high-risk surgical patients. For recurrent CSDH, it is reasonable to perform BHC or craniotomy. Craniotomy offers comparable results to BHC but with a higher complication rate. Craniotomy is recommended in patients with significant or recurrent amniotic membranes. Endoscopic-assisted evacuation is safe and effective.

5) The variable number of thorn holes did not

affect recurrence rates when comparing single versus double burr holes. That there was no significant difference between one and two burr holes in terms of recurrence risk. It was concluded that no difference was seen between one and two burr holes, which falls under the issue of surgeon preference.

6) Intraoperative irrigation in subdural hematoma aims to clear the hematoma elements and reduce the risk of recurrence. The selected summary by Solou et al. explains that there is a controversy between using and not using inflow and outflow irrigation in the use of burr hole craniostomy (BHC) and Twist Drill Craniostomy (TDC) is associated with less recurrence rate.³⁴ However, it was also concluded that irrigation at BHC for CSDH treatment did not lead to further healing and was associated with short-term complications such as pneumocephalus.

7) The variable closed drainage system concluded that the placement of a continuous drainage system was favorable. However, the complications of acute hemorrhage from the neomembrane, parenchymal injury, tension pneumocephalus, meningitis, subdural empyema, complications associated with prolonged immobility, and seizures need to be considered. In conclusion, subperiosteal or subgaleal drainage placement appears to be as effective as subdural placement, with comparable recurrence rates and potentially lower complication rates (Grade A recommendation).

8) The duration of drainage after surgery is also involved in managing subdural hematoma. According to Solou et al., controversy exists in studies that state there is a significant difference in drainage time affecting the risk of recurrence or the possibility of infection. On the other hand, studies examining the duration of drainage within a few days reduced the risk of recurrence.

9) Membranectomy protocol when craniotomy is used, concurrent membranectomy may reduce recurrence.

10) The application of MMA embolization as a major standalone treatment of primary treatment in recurrent CSDH or as prophylaxis after surgery for CSDH is a safe and efficient method with a low recurrence rate.

Conservative approach on CSDH in low-resource settings

Upon performing a categorization of the data based on countries, it was noted that the management of CSDH in LIC entailed using diverse surgical techniques such as single burr hole, double burr hole, with or without drainage system, flap craniotomy, and craniotomy. The scientific investigation of the

administration of steroids during the perioperative phase for CSDH) has been conducted. As per extant literature, the administration of steroids has been linked to a reduced incidence of CSDH recurrence³⁶. Additionally, corticosteroids have been posited to hold potential benefits in the management of CSDH³⁷. The administration of dexamethasone significantly improved the functional outcome of patients suffering from symptomatic CSDH at the 6-month follow-up period.³⁸

Chan et al.³⁹ conducted a randomized controlled trial to examine dexamethasone's effectiveness when combined with surgical drainage in reducing the recurrence of reoperation. The research findings revealed that the application of steroids did not result in a statistically noteworthy decrease in the frequency of recurrence.

The successful attainment of clinical and radiological resolution in patients with CSDH necessitates the implementation of multi-technique management approaches. Recent studies have demonstrated the efficacy of steroid administration⁴⁰ and the use of subdural drains in conjunction with burr hole drainage in reducing recurrence rates. Furthermore, surgical treatments utilizing these techniques have been found to have comparable risks of morbidity.⁴¹ Nevertheless, an evidence-based approach that opposes the conventional practice proposes that the customary insertion of a subdural drain may not be essential to perform a burr hole evacuation procedure for chronic and subacute subdural hematoma.⁴² The efficacy of subdural drainage in the treatment of CSDH remains a topic of ongoing discussion. The selection of a management strategy is contingent upon the clinical presentation, surgeon's preference, and recurrence rate following previous interventions.

The use of anti-inflammatory drugs

Inflammation plays a role in the development and progression of CSDH. The inflammatory response can contribute to the formation of new blood vessels (neovascularization) within the hematoma capsule, leading to continued bleeding and expansion of the hematoma. Anti-inflammatory drugs are thought to counteract this process and potentially promote hematoma resolution.

Anti-inflammatory drugs like corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are often used to reduce inflammation, which could potentially help resolve the hematoma and improve clinical outcomes. However, the evidence regarding their impact on mortality in surgically treated patients with CSDH is not entirely consistent.

According to Vychopen⁴³, anti-inflammatory therapy seems to be associated with increased mortality in surgically treated patients with chronic subdural hematoma. However, anti-inflammatory drug treatment seems to reduce the risk of recurrence or the probability of a switch to surgical treatment if it is administered as an adjuvant treatment to surgery or in the case of a conservative regimen.⁴³

The utilization of anti-inflammatory medication therapy has shown a notable decrease in the occurrence and expansion of chronic subdural hematoma (CSDH) in patients who underwent surgical or conservative treatment for CSDH. The administration of corticosteroid therapy was found to have a notable impact on mortality rates among patients who underwent surgical treatment. Conversely, the use of anti-inflammatory therapy, specifically atorvastatin or corticosteroid therapy, did not result in an increase in mortality rates among patients who received conservative treatment for chronic subdural hematoma (CSDH).⁴³

Vychopen and colleagues⁴³ summarized as follows:

- 1) Anti-inflammatory medication was observed to increase mortality in surgically treated CSDH patients but not in conservatively treated ones.
- 2) Anti-inflammatory drug treatment as an adjunct to surgery or a conservative regimen reduces the risk of recurrence or surgical switch. Anti-inflammatory medication did not affect neurological prognosis in surgically or conservatively treated CSDH patients.
- 3) Anti-inflammatory medication did not affect neurological prognosis in surgically or conservatively treated CSDH patients.
- 4) Corticosteroid therapy significantly reduced the recurrence of surgically treated CSDHs, but curiously, only a cumulative low-dose regimen was related to death.

In low-resource settings, limited access to timely surgical intervention and postoperative care might influence the effectiveness of any adjunct therapies, including anti-inflammatory drugs. The use of anti-inflammatory drugs in the treatment of CSDH has been studied through clinical trials and observational studies. However, the quality and consistency of the evidence vary. Some studies suggest that anti-inflammatory drugs can reduce recurrence rates and improve outcomes, while others do not find a significant impact on mortality.

Treatment decisions for patients with CSDH should be based on a variety of factors, including the patient's overall health, the size and severity of the hematoma, the presence of neurological symptoms, and the available medical resources. In some cases, anti-inflammatory drugs might be considered part of

a comprehensive treatment plan.

Surgical method regarding the surgical treatment of chronic subdural hematoma (CSDH)

An individual's socioeconomic status may impact their ability to obtain neurosurgical intervention for the management of CSDH. A comparative study conducted by Laeke et al.⁴⁴ examined the demographics, treatment, and outcome of patients with CSDH in low-income (Ethiopia) and high-income (Norway) countries. According to Mekaj's⁴⁵ findings, the preferred technique for burr hole trepanation involved the utilization of a closed drainage system due to its ease and low risk.

A recent study done in the United States from 2016 to 2020 found that inpatient care for CSDH led to higher in-hospital death rates, complication rates, length of stay, and total costs for the surgical group than for the medical group.⁴⁶ While this investigation did not explicitly examine the influence of socioeconomic status on the availability of neurosurgical intervention for CSDH, it implies that the modality of treatment administered could have implications for both clinical outcomes and financial burden.

Moreover, a recent investigation in Ethiopia has demonstrated that using single burr hole craniostomy constitutes a facile, secure, and efficacious approach for managing CSDH.⁴⁷ The preponderant surgical modality employed for CSDH in low-resource settings is burr hole drainage. The predominant surgical approach employed in Japan involves the utilization of singular burr holes. The predominant therapeutic approach employed in Saudi Arabia is conservative management. In Korea and Germany, a variety of techniques are employed for the treatment of intracranial pathologies via a single burr hole [Table 1 and 2]. These techniques include burr hole trepanation with subdural drain placement and scheduled computed tomography (CT) scans to monitor patient progress. The surgical technique of burr hole craniostomy was predominantly employed in China, while Ireland used this method as well. The United Kingdom, on the other hand, used a different version of this method called burr hole craniostomy with or without drainage. The Belgian medical community has posited that the burr hole technique may be superior to alternative methodologies. The Austria burr hole craniostomy is a surgical procedure used in neurosurgery to create a small opening in the skull to access the brain. The implementation of burr hole craniostomy (BHC) in conjunction with subdural irrigation and closed drainage is also observed in Italy [Table 1 and 2].

Table 1: Subdural hematoma in low-income countries
 Tablica 1. Subduralni hematom u zemljama s niskim dohotkom

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
Gauteng- South Africa <i>Južna Afrika</i>	128	Mosadi 2019	43.6 ± 26.5	N/A	Chronic Subdural hematoma <i>Kronični subduralni hematom</i>	55% of the surgeries involved burr holes with or without a subdural drain or craniotomy, and 45% did not have steroids given before or after the surgery. <i>55% operacija uključivalo je rupice sa ili bez subduralnog drena ili kraniotomije, a 45% nije imalo steroide prije ili poslije operacije.</i>	Good Outcome <i>Dobar ishod</i>
Benin- West Africa <i>Zapadna Afrika</i>	104	Hode 2015	49.66±14.46	83.65% and 17 women 17 <i>žena</i> 16.35%	N/A	52% of the patients had a single burr hole trephination, 47% had a double burr hole trephination, and 1% had a five-hole bone flap. <i>52% pacijenata imalo je trefinaciju s jednom rupom, 47% imalo je trefinaciju s dvostrukom rupom, a 1% je imalo režanj kosti s pet rupica.</i>	Good Outcome <i>Dobar ishod</i>
Multan- Pakistan	60	Khan 2019	62±14 (range 38-94)	40 (66.7) men and <i>muškarci i</i> 20(33.3) women <i>žene</i>	Right hematoma 29 (48.3%), <i>Desni hematom</i> Left hematoma 24 <i>Lijeve hematom</i> (40.0%), Bilateral hematoma 7 (11.7%) <i>Bilateralni hematom</i>	Single bur hole 30 and double bur hole 30 (50% each) <i>Jednostruka rupa za svrdlo 30 i dvostruka rupa za svrdlo 30 (50% svaka)</i>	N/A
Khatmandu- Nepal	53	Bidur, 2022	61.87 ± 17.35	male 83%) and female 17 <i>muškarci i</i> <i>žene</i>	Hematoma: right 19 (35.8%), <i>Desni hematom</i> left 27 (50.9% - <i>lijevi</i> and Bilateral 7 (13.2%) bilateralni	35 patients (66%) had a single burr hole, and 18 patients (34%) had a double burr hole. <i>35 pacijenata (66%) imalo je jednostruku rupu, a 18 pacijenata (34%) dvostruku rupu</i>	N/A
Mumbai-India	267	Kansal 2010	3-78 (48)	165 males <i>muškaraca</i> and 102 females <i>žena</i>	N/A	single burr hole 195, double burr hole 72 <i>jednostruka rupa za svrdlo 195, dupla rupa za svrdlo 72</i>	N/A

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
Sierra Leone	23	Russel 2021	65.8 years (ranging from 54-78) <i>65,8 godina (od 54-78)</i>	male: female ratio of 3: 2: 1. <i>Omjer muško- žensko</i>	right side in 17 patients (73.9%), desna strana kod 17 pacijenta and the left side in 6 patients (22.1%) lijeva strana kod 6 pcijenta.	Flap craniotomy under general anesthesia with subdural drainage left in situ (100%) was done for all patients. <i>Svim je bolesnicima učinjena kraniotomija režnja u općoj anesteziji sa subduralnom drenažom ostavljenom in situ (100%).</i>	Good Outcome <i>Dobar ishod</i>
Uganda	205	Kitya 2018	63 years (range 11–95). <i>63 godina (omjer 11-95)</i>	Male <i>muškarci</i> (72.8%, 147/202)	No. (%) SDH laterality <i>SDH lateralmost</i> Rt 77 (42.3%) Lt 66 (36.3%) 39% Bilat	burr holes, drain, and 22.4% (46/205) rupe za brušenje, drenaža i 22,4% (46/205)	Good Outcome <i>Dobar ishod</i>
Brazil	117	Silva 2012	69 years <i>69 godina</i>	male/female ratio of 102/23 <i>muško/žensko omjer</i>	64 lt, 42 rt. Bilat 19 cases (15.2%) 19 slučajeva	Drainage systems were used in 93.6% of the cases. <i>Sustavi drenaže korišteni su u 93,6% slučajeva.</i>	Good Outcome <i>Dobar ishod</i>
Malaysia <i>Malezija</i>	82	Zakaraia 2008	60 years or younger <i>60 godina ili mlađi</i>	Men 76.0%, <i>Muškarci</i> and women 24.0% <i>žene</i>	persistent subdural hematomas (30.5%), <i>perzistentni subduralni hematomi</i> 22 trabecular (26.8%), <i>trabekularni</i> 20 separated (24.4%) <i>odvojeni,</i> and 15 laminar <i>laminarin</i> (18.3%). Bilateral lesions: 1 <i>Bilateralne lezije</i> homogeneous -homogene, 3 laminar,- <i>laminarne</i> 2 separated- <i>odvojene,</i> and 4 <i>trabecular-tabekularne.</i>	Burr hole drainage with or without irrigation reduces midline shift significantly. 52 (71.2%) of 73 midline shift patients got resolution. <i>Drenaža rupice sa ili bez navodnjavanja značajno smanjuje pomak središnje crte. 52 (71,2%) od 73 pacijenta s pomakom središnje crte dobilo je povlačenje</i>	Good Outcome <i>Dobar ishod</i>
Kenya <i>Kenija</i>	259	Githinj 2010	41.1 years + 19.659	223 (86.1%) men <i>muškarci</i>	N/A	functional recovery (47.3%) and a lower mortality (17.6%)	Good Outcome <i>Dobar ishod</i>

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
				while 36 (13.9%) women <i>žene</i>			

GCS = Glasgow Coma Scale Glasgow Com skala, ICU = intensive care unit – jedinica intenzivne njege, CSDH = Chronic Subdural Hematoma kronični subduralni hematoma, N/A= not available – nije dostupno

Table 2: Subdural hematoma in high-income countries
Tablica 2. Subduralni hematom u zemljama visokim dohotkom

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
Japan Japan	63,358	Toi H 2018	76.0 ± 12	(68.4%) male, <i>muškarci</i> (31.6%) female, <i>žene</i>	N/A	(57,345 patients (90.5%) used a single burr hole, 926 patients (1.5%) underwent craniotomy <i>(57 345 pacijenata (90,5%) koristilo je jednu rupu za brušenje, 926 pacijenata (1,5%) podvrgnuto je kraniotomiji)</i>	Good Outcome <i>Dobar ishod</i>
Saudi Arabia Saudijska Arabija	171	Alghamdi F 2021	Median age 31 <i>Medijan starost 31</i>	151 (88.3%) males, <i>muškarci</i> and 20 (11.7%) females, <i>I 20 žena</i>	Thoracic cases (43, 25.1%) and subdural hematoma (47, 27.4%), then spine (40, 23.4%) <i>Torakalni slučajevi (43, 25,1%) i subduralni hematom (47, 27,4%), zatim kralježnica (40, 23,4%)</i>	(15.20%) got neurosurgical treatment, whereas (78.4%) received conservative care. 134 (78.4%) are conservative; 37 (21.6%) are active. <i>Neurokirurško je liječeno (15,20%), a konzervativno (78,4%). 134 (78,4%) su konzervativni; Aktivno ih je 37 (21,6%).</i>	N/A <i>Nije dostupno</i>
Republic of Korea Republika Koreja	293	Jin Oh H 2021	75 (22–95)	208 (71.0) males <i>muškarci</i> i and 85 (29.0) females <i>žena</i>	77.5% had unilateral hematomas and 46.1% had homogeneous hematoma types. <i>77,5% imalo je jednostrane hematome, a 46,1% imalo je homogene tipove hematoma.</i>	70% had general anesthesia, and 74.7% had single burr hole craniostomy surgery <i>70% imalo je opću anesteziju, a 74,7% imalo je operaciju kraniostomije s jednom rupom.</i>	Good Outcome <i>Dobar ishod</i>
German Njemačka	131	Bronkikel 2013	median of 131, ranging from 32-92	89 (68%) male <i>muškarci</i> and	40 (31%), 60 (46%), and 31 (24%).	Enlarged burr hole trepanation and subdural drain implantation, recommended postoperative CT-imaging following drain removal.	N/A <i>Nije dostupno</i>

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
			<i>medijan od 131, u rasponu od 32-92</i>	42 (32%) female <i>žena</i>		<i>Trepanacija proširene rupe i implantacija subduralnog drena, preporučeno postoperativno CT snimanje nakon uklanjanja drena.</i>	
China Kina	1453	Huang J 2019	60 and 80	85.01% male <i>muškarci</i> and 51.91% female <i>žena</i>	Headache (58.55%), dyskinesia (36.92%), and dizziness (33.96%) were hospital admission symptoms. Hematoma spread 1001 (78.14%) unilateral hematoma 280 (21.86%) bilateral hematoma <i>Glavobolja (58,55%), diskinezija (36,92%) i vrtoglavica (33,96%) bili su simptomi prijema u bolnicu. Širenje hematoma 1001 (78,14%) jednostrani hematom 280 (21,86%) bilateralni hematom</i>	Burr hole craniostomy 1132 (88.37%), Conservative 87 (6.79%), Craniotomy 62 (4.84%). <i>Kraniostomija s burr hole 1132 (88,37%), konzervativna 87 (6,79%), kraniotomija 62 (4,84%).</i>	Good Outcome <i>Dobar ishod</i>
Republic of Ireland Republika Irska	50	Kaliaperumal 2012	17 to 91 years <i>Od 17 do 91 godine</i>	33 (male) <i>muško</i> , 17 (female) <i>žensko</i>	The SDD group had 9 left-sided, 12 right-sided, and 4 bilateral CSDHs, while the SPD group had 11 left-sided, 10 right-sided, and 4 bilateral SDHs. Fifty-two individuals received surgery for 60 symptomatic CSDHs. <i>Grupa SDD imala je 9 lijevih, 12 desnih i 4 bilateralna CSDH, dok je grupa SPD imala 11 lijevih, 10 desnih i 4 bilateralna SDH. Pedeset dvije osobe operirane su zbog 60 simptomatskih CSDH</i>	Subperiosteal and subdural drains after burr hole craniostomy. <i>Subperiostalni i subduralni dreni nakon kraniostomije s rupom</i>	Good outcome <i>Dobar ishod</i>
UK Uj Kralj	269	Santarius 2009	18 years and older <i>18 godina i starije</i>	N/A <i>Nije dostupno</i>	symptomatic chronic subdural hematoma with CT-proven burr hole drainage was eligible.	burrhole drainage and without drainage <i>drenaža s bušilicom i bez drenaže</i>	Good Outcome <i>Dobar ishod</i>

Country <i>Zemlja</i>	Population <i>Stanovništvo</i>	Study <i>Rad</i>	Age <i>Starost</i>	Gender <i>Spol</i>	Profile <i>Profil</i>	Management <i>Upravljanje</i>	Output <i>Učinak</i>
					simptomatski kronični subduralni hematom s CT-om dokazanom drenažom kroz rupicu bio je prihvatljiv.		
Belgium Belgija	245	Duerinck 2018	19 years and older <i>19 godina ili stariji</i>	86 female, 159 male <i>žena 159 muškaraca</i>	Surgery-required CSDH without contraindication <i>CSDH potreban kirurški zahvat bez kontraindikacija</i>	burr hole craniostomy (BHC), minicraniotomy (MC), and twist drill craniostomy (TDC) <i>kraniostomija s bušilicom (BHC), minikraniotomija (MC) i kraniostomija sa spiralnom bušilicom (TDC)</i>	Good Outcome <i>Dobar ishod</i>
Austria Austrija	52	unterhofer2016	72 years (range, 48-89 years) <i>72 godine (omjer 48-89)</i>	The male/female ratio was 3:1	CT/MRI confirms CSDH. <i>CT/MRI potvrđuje CSDH.</i>	were prospectively randomized to either partial opening of the inner hematoma membrane (group A) or not (group B) after enlarged burr hole craniotomy and hematoma evacuation <i>bili su prospektivno randomizirani na djelomično otvaranje unutarnje membrane hematoma (skupina A) ili ne (skupina B) nakon kraniotomije s proširenom rupom i evakuacije hematoma</i>	Good Outcome <i>Dobar ishod</i>
Italy Italija	47	Muzii 2005	N/A <i>Nije dostupno</i>	N/A <i>Nije dostupno</i>	randomized 47 patients to BHC, TDC, or vacuum drainage. <i>randomizirano je 47 pacijenata na BHC, TDC ili vakuumsku drenažu</i>	14 men, 8 women, and a mean age of 78.7 years underwent TDC with closed-system drainage and suction reservoir. 24 more patients had BHC with subdural irrigation and closed drainage (16 men, 8 women, mean age 76.3 years). <i>14 muškaraca, 8 žena i prosječne dobi od 78,7 godina podvrgnuto je TDC-u sa zatvorenim sustavom drenaže i usisnog spremnika. Još 24 bolesnika imalo je BHC sa subduralnom irigacijom i zatvorenom drenažom (16 muškaraca, 8 žena, prosječna dob 76,3 godine).</i>	Good Outcome <i>Dobar ishod</i>

GCS = Glasgow Coma Scale Glasgow Com skala, ICU = intensive care unit – jedinica intenzivne njege, CSDH = Chronic Subdural Hematoma kronični subduralni TDC = twist drill craniostomy, kraniostomija spiralnom bušilicom BHC = Burr Hole Craniostomy, kraniostomija s bušilicom mRS = modified Rankin Scale, modificirana Rankin Skala, CT = Computed Tomography, Kompjuterizirana tomografija N/A= not available, nije dostupno

The data from several studies conducted in high-income countries show that burr hole craniostomy is commonly used and is non-invasive, and in addition, this method is used in traumatic or non-traumatic recurrence conditions. CSDH and acute subdural hematoma (ASDH) with subdural drainage irrigation. This technique has been found to be both effective and safe, as evidenced by research conducted by Wang in 2016. The burr hole craniostomy is a surgical intervention that entails the creation of a small aperture in the cranium to gain entry to the cerebral tissue and excise the hematoma. The technique in question represents a less intrusive approach compared to craniotomy, which entails the excision of a segment of the cranial bone to gain access to the cerebral tissue.³¹

The burr hole craniostomy is the preferred surgical approach in HIC due to its comparatively lower risk of complications, shorter hospitalization periods, and faster recuperation times when compared to craniotomy. Furthermore, the burr hole craniostomy procedure can be executed utilizing local anesthesia, thereby reducing the potential risks associated with general anesthesia.⁴⁸ Burr hole craniostomy represents a cost-effective alternative for managing CSDH and acute subdural hematoma (ASDH), both of which are prevalent neurological disorders necessitating surgical intervention.

Burr hole craniostomy is a frequently employed surgical intervention in the field of neurosurgery. However, it is not exempt from potential hazards and adverse outcomes. Adverse outcomes that may arise subsequent to burr hole craniostomy for subdural lesions encompass acute intracranial hemorrhagic complications, misplacement of the drainage catheter within the brain parenchyma, contralateral surgical intervention, de novo seizure activity, non-surgical complications such as pulmonary and urinary complications, psychological sequelae, and cognitive deficits.⁴⁹

The frequency of complications following burr hole craniostomy and drainage for subdural lesions is greater than previously estimated. These complications include severe events such as acute intracranial hematomas and errors in surgical or management procedures, which cannot be overlooked and may result in legal issues. Lee⁴⁹ emphasizes the importance of exercising caution during surgery and the postoperative period. Additionally, Lee suggests that complications should be included in the informed consent form prior to surgery. An adequately positioned solitary burr hole can effectively accommodate small to moderately large craniotomies, while larger craniotomies can be achieved with minimal burr holes, resulting in

favorable cosmetic outcomes and preventing bone flap depression.⁵⁰ Burr hole surgery utilizing urokinase is a minimally invasive surgical approach for managing acute subdural hematoma. This technique has been found to be as efficacious as craniotomy while also being a safer and less complex alternative.⁵¹

Importance of Postoperative Treatment in Low-Income Countries

Postoperative treatment is a critical phase of patient care following surgical procedures, including chronic subdural hematoma (CSDH). It plays a crucial role in ensuring the success of the surgery, preventing complications, and promoting patient recovery. In low-income countries (LIC), where healthcare resources and infrastructure might be limited, the importance of effective postoperative treatment becomes even more significant due to the potential challenges and constraints faced by both healthcare providers and patients. Implementing effective postoperative treatment in low-income countries presents unique challenges due to limited resources, inadequate infrastructure, and socioeconomic constraints. Reintegrating patients into their communities after surgery is crucial for their overall well-being and the success of postoperative treatment. In low-income conditions, where social support networks might be limited, the process of patient reintegration faces additional challenges:

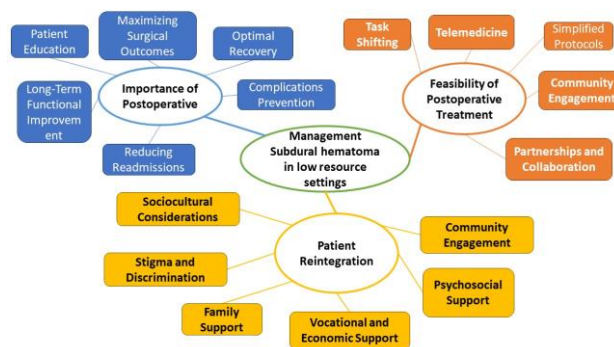


Figure 3 Management importance of postoperative treatment and its feasibility in low-income countries
Slika 3. Važnost upravljanja postoperativnim liječenjem i njegova izvedivost u zemljama s niskim dohotkom

Proper postoperative care helps prevent complications arising after surgery, such as infections, bleeding, and wound breakdown. In LIC, where resources for managing complications might be scarce, prevention becomes paramount. Complications may be caused by coagulation

abnormalities, arterial and venous pressure imbalance, intracranial displacement during surgery, uncontrolled fluid drainage, and intracranial hypotension.

Coagulopathies, blood pressure, and medicines must be corrected to avoid such consequences. According to the study by Rusconi et al., careful and gradual drainage of the subdural hematoma without considerable head movement is recommended during surgery to avoid fast intracranial content shift. Use drains without Hoover bulbs at the end of the process. Additional post-operative monitoring of drainage quantities and characteristics, neurologic evaluation, and radiological examination are required.^{33,52}

Adequate postoperative care enhances patient recovery by facilitating wound healing, reducing pain, and promoting overall well-being. This can lead to shorter hospital stays and lower healthcare costs, which is particularly crucial in resource-constrained settings.

Surgical procedures, including those for CSDH, can have better outcomes when followed by appropriate postoperative care. This involves monitoring patients for signs of complications and adjusting treatment plans accordingly.

Postoperative care provides an opportunity to educate patients and their families about wound care, medication management, and recognizing warning signs. In LIC, where health literacy might be lower, effective patient education can significantly impact recovery. Postoperative rehabilitation, including physical therapy and cognitive interventions, can improve long-term functional outcomes for patients. This is especially relevant for CSDH cases, as patients might experience cognitive and neurological deficits. Comprehensive postoperative care can help prevent readmissions due to complications, reducing the burden on already strained healthcare systems in LIC. Empower healthcare workers with various levels of training, such as nurses and community health workers, to provide basic postoperative care, freeing up skilled clinicians for more complex cases. Utilize telemedicine and mobile health technologies to provide remote guidance and follow-up care, especially for patients in remote or underserved areas.

Develop streamlined postoperative care protocols tailored to the resources available in LIC, focusing on essential interventions that can be effectively carried out.

Involve communities in the care process by educating them about postoperative care, recognizing complications, and seeking help when needed. Foster partnerships with international organizations, non-governmental organizations, and academic institutions to provide training, resources, and

expertise in postoperative care. Understanding and respecting the sociocultural norms of the community is important to ensure that patients are accepted and supported upon reintegration. Patients might face stigma and discrimination due to their medical condition. Community awareness campaigns can help reduce these negative attitudes.

In LIC, family plays a significant role in patient care and reintegration. Providing families with the necessary education and resources can enhance the patient's reintegration process. Providing vocational training and economic support to patients who experience functional limitations can empower them to contribute to their households and communities. Offering psychosocial support through counseling and support groups can help patients cope with the emotional and psychological challenges of reintegration. Involving local leaders, community organizations, and religious institutions can facilitate a smoother reintegration process by building a supportive patient environment.

Postoperative treatment and patient reintegration in low-income countries are complex endeavors that require innovative strategies, community engagement, and collaborative efforts. Despite the challenges, focusing on patient-centered care and utilizing available resources can improve outcomes and successfully reintegrate patients into their communities.

In low-middle income countries, developing cost-effective treatment options can help ensure patients access appropriate care. Additionally, improving access to care can help ensure patients receive timely treatment. It is also important to ask and learn from mentors who are aligned with international standards, and one of the organizations that provide this platform is WFNS and EANS.⁸ However, it is important to understand how these resources can be accessed to overcome difficulties in low-income countries. Some of the steps can be attributed to relevant organizations.

Accessing Resources in Low-Income Countries:

1. **International Collaborations:** Establish partnerships with universities, hospitals, and medical organizations from high-income countries to facilitate knowledge exchange, training programs, and resource sharing.
2. **Telemedicine and E-Learning:** Leverage telemedicine platforms and e-learning resources to provide remote training and consultations, enabling healthcare workers in low-income countries to access expert advice and guidance.
3. **Medical Equipment Donation:** Partner with

charitable organizations and medical equipment manufacturers to donate essential surgical and postoperative care equipment to low-income countries.

4. **Grants and Funding:** Seek grants from international organizations, foundations, and philanthropic individuals to support infrastructure development, training programs, and patient care initiatives.
5. **Local Capacity Building:** Focus on training local healthcare workers to perform surgeries, manage postoperative care, and provide rehabilitation services.

Role of WFNS and EANS

1. The World Federation of Neurosurgical Societies (WFNS) and the European Association of Neurosurgical Societies (EANS) are prominent international organizations dedicated to advancing neurosurgery and promoting collaboration among neurosurgeons worldwide. While their primary roles are education, research, and professional development, they also play a significant part in assisting low-income countries:
2. **Training Programs:** WFNS and EANS could develop training programs specifically tailored to the needs of neurosurgeons and healthcare workers in low-income countries. These programs might include workshops, webinars, and hands-on training sessions
3. **Scholarships and Fellowships:** Offer scholarships and fellowships allowing neurosurgeons from low-income countries to train in well-established centers of excellence in high-income countries, gaining valuable skills and knowledge to return home.
4. **Guidelines and Protocols:** Develop guidelines and protocols for managing conditions like chronic subdural hematoma in resource-constrained settings, taking into account the available resources and expertise.
5. **Advocacy and Support:** Advocate for increased funding and resources for neurosurgical services in low-income countries on a global scale, collaborating with international health organizations and policymakers.
6. **Collaborative Projects:** Initiate collaborative research projects that address neurosurgical challenges specific to low-income countries and develop practical solutions.
7. **Resource Sharing:** Facilitate the donation of medical equipment, textbooks, and educational materials to institutions in low-income countries

through partnerships with manufacturers and organizations.

8. **Capacity Building Workshops:** Organize workshops that focus on building the capacity of healthcare systems in low-income countries to manage neurosurgical cases, including postoperative care effectively.
9. **Networking and Exchange:** Foster a network of neurosurgeons from diverse backgrounds, encouraging knowledge exchange and collaboration between high-income and low-income countries.

Conclusion and highlights

Comparing and contrasting the management approaches of chronic subdural hematoma in high-income and low-income countries would adopt a global health perspective, focusing on the challenges faced by healthcare systems in both high-income and low-income countries, discuss the differences in available resources, healthcare policies, and patient outcomes, explore how epidemiological differences impact the disease's presentation and management strategies, discuss disparities influence the accuracy and timeliness of diagnosis, management approaches could differ due to the availability of neurosurgical expertise, equipment, and facilities, explore the financial burden of managing CSDH in both settings, due to advanced treatments, while low-income countries might struggle with affordability and resource allocation, explore availability of intensive care units, postoperative care facilities, and rehabilitation services could vary, discuss differences impact patient outcomes and recovery. In contrast, low-income countries might need to adapt their management approaches due to limited resources. The paper could explore how these variations affect patient care. High-income countries may have more resources for medical research and innovation, leading to the development of novel treatment approaches. Explore the potential for collaboration between countries to address healthcare disparities. Understanding the differences can delve into the ethical dilemmas posed by the differences in healthcare access and outcomes between high-income and low-income countries. It could discuss the importance of equitable healthcare distribution and offer insights and recommendations for improving the management of CSDH in low-income countries. This might include strategies for resource allocation, capacity building, and international collaborations.

References

1. Dewan, MC, Rattani A, Gupta S et al. Estimating the global incidence of traumatic brain injury. *J. Neurosurg* 2018; 130:1080–1097.
2. Ologunde R, Maruthappu M., Shanmugarajah K, Shalhoub J. Surgical care in low and middle-income countries: Burden and barriers. *Int. J. Surg* 2014;12: 858–863.
3. Pierre, L, Kondamudi NP. Subdural Hematoma. In: *StatPearls* (StatPearls Publishing, 2023).
4. Mehta V, Harward SC, Sankey E.W, Nayar G, Codd P J. Evidence based diagnosis and management of chronic subdural hematoma: A review of the literature. *J Clin Neurosci* 2018;50:7–15.
5. Yadav Y.R, Parihar V, Namdev H, Bajaj, J. Chronic subdural hematoma. *Asian J. Neurosurg* 11, 330–342.
6. AbdelFatah, MAR. Prognosis of acute subdural hematoma greater than 10 mm in thickness in head injury patients with an extension or no motor response to pain after resuscitation. *Egypt J Neurosurg* 2019; 34:9.
7. Suleman M, Tendai J, Lodhia J. Burr hole as a management for extra axial hematomas in a low-resource setting. *Int. J. Surg. Case Rep* 2023;105:108125.
8. Robertson FC, Gnanakumar S, Karekezi C et al. The World Federation of Neurosurgical Societies Young Neurosurgeons Survey (Part II): Barriers to Professional Development and Service Delivery in Neurosurgery. *World Neurosurg* 2020; 8:100084
9. Rashid, SM, Deliran SS, Dekker MC. Howlett W P. Chronic subdural hematomas: a case series from the medical ward of a north Tanzanian referral hospital. *Egypt. J Neurosurg* ;2019; 34:29.
10. Frija G, Blažić I, Frush DP et al..How to improve access to medical imaging in low- and middle-income countries ? *EClinicalMedicine*. 2021; 38:101034.
11. Jalloul M, Miranda-Schaebinger M, Noor AM et al.MRI scarcity in low- and middle-income countries. *NMR Biomed*. 2023 Aug 13:e5022.
12. Liang KE, Bernstein I, Kato Y, Kawase T, Hodaie M. Enhancing Neurosurgical Education in Low- and Middle-income Countries: Current Methods and New Advances. *Neurol Med Chir (Tokyo)*. 2016;56:709-715.
13. Punchak, M, Mukhopadhyay S, Sachdev S. Neurosurgical Care: Availability and Access in Low-Income and Middle-Income Countries. *World Neurosurg* 2018;112:e240-e254.
14. Dimopoulou A, Yfanti A, Argyropoulos T et al. Time between onset of symptoms and definitive treatment in children with acute appendicitis: How it affects length of hospital stay? *Afr J Paediatr Surg*. 2022;19:245-250.
15. Ye HH, Kim JH, Kim YS, Cho C W, Kim, D. J. Cognitive Impairment in the Elderly with Chronic Subdural Hematoma. *J. Korean Neurotraumatol. Soc* 2008; 4:66.
16. Ashfaq A. Lazareff J. Language and style: A barrier to neurosurgical research and advancement in Latin America. *Surg. Neurol. Int* 2017;8:308.
17. Tang AR, Lan M, Kelly KA et al. Predicting for Lost to Follow-up in Surgical Management of Patients with Chronic Subdural Hematoma. *World Neurosurg* 2021; 148:e294-e300.
18. Garba DL, Fadalla T, Sarpong K et al.Access to training in neurosurgery (Part 2): The costs of pursuing neurosurgical training. *Brain Spine* 2022; 2: 100927
19. Todd KH. Chronic Pain and Aberrant Drug-Related Behavior in the Emergency Department. *J. Law. Med. Ethics* 2005;33:761–769.
20. Oyemolade TA, Adeolu AA.Bedside single burr hole craniostomy drainage of chronic subdural hematoma in the emergency room: A useful option in resource challenged settings. *Surg Neurol Int* 2020;11:349.
21. Sim, Y.-W., Min, K.-S., Lee, M.-S., Kim, Y.-G. & Kim, D.-H. Recent Changes in Risk Factors of Chronic Subdural Hematoma. *J. Korean Neurosurg Soc* 2012; 52:234-9..
22. Uno M, Toi H, Hirai S. Chronic Subdural Hematoma in Elderly Patients: Is This Disease Benign? *Neurol Med Chir (Tokyo)*. 2017;57:402-409
23. Suzuki MTM, Moura MC. Casulari L.A. Comparative Epidemiological Profile of Elderly and Non-elderly Patients Operated on Chronic Subdural Hematoma. *JBNC - J Bras Neurocir* 2020;31:191–200.
24. Sun T, Yuan YK, Wu K, You C, Guan JW. Effects of postoperative atorvastatin use in elderly patients with chronic subdural hematoma. *Eur Rev Med Pharmacol Sci* 2021;25: 7211–7217.
25. Seok JH, Kim, JH, Kwon T H, Byun J, Yoon WK. Middle meningeal artery embolization for chronic subdural hematoma in elderly patients at high risk of surgical treatment. *J Cerebrovasc Endovasc Neurosurg* 2023;25: 28–35.
26. Richard SA., Wu M., Lin D. Traumatic Subdural Effusion Evolving into Chronic Subdural Hematoma. *Open J Mod Neurosurg* 2015;5:12–22.
27. Ahn JH, Jun HS, Kim JH, Oh JK, Song JH, Chang IB Analysis of Risk Factor for the Development of Chronic Subdural Hematoma in Patients with Traumatic Subdural Hygroma. *J Korean Neurosurg Soc* 2016;59:622-627.
28. Suarez JI, Kapinos G.Thromboembolism prevention after chronic subdural hematoma in the elderly: A leap in the dark. *Neurology* 2017; 88:1880–1881.
29. Savage C. Alcohol and Tobacco Related Health Inequity: A Population Health Perspective. *J Addict Nurs* 2012; 23:72–74.
30. Xu K, Chan NC. The conundrum of resuming anticoagulant therapy after intracerebral bleeding: In whom, when, and how? *Vasc. Med* 2020;25:60–62.
31. Liu H, Yan R, Xie F., Richard SA. Hematoma cavity separation and neomembrane thickness are potential triggers of recurrence of chronic subdural hematoma. *BMC Sur* 2022;22: 236.
32. Opsenak R, Hanko M, Benco M, Snopko P,

- Ritcherova B, Kolarovszki B. Non-acute subdural hematoma: estimation of recurrence using CT-volumetric measurements. *Bratisl Lek Listy* 2023; 124: 3–11.
33. Chang CL, Connolly Jr ES. Predictors of Chronic Subdural Hematoma Recurrence Following Surgical Intervention: A Review of the Recent Literature? *Arch Neurol Neurosci* 2020; 6:1-3.
 34. Solou, M, Ydreos I, Gavra M et al. Controversies in the Surgical Treatment of Chronic Subdural Hematoma: A Systematic Scoping Review. *Diagnostic* 2022;12:2060.
 35. Venturini S, Fountain DM, Glancz LJ et al. Time to surgery following chronic subdural hematoma: post hoc analysis of a prospective cohort study. *BMJ Surg Interv Health Technol* 2019; 1: e000012.
 36. Shrestha, DB, Budhathokoki P, Sedhai YR et al. Steroid in Chronic Subdural Hematoma: An Updated Systematic Review and Meta-Analysis Post DEX-CSDH Trial. *World Neurosurg* 2022; 158:84-99.
 37. Blaauw, J. et al. Neurosurgical and Perioperative Management of Chronic Subdural Hematoma. *Front Neurol* 2020;11:550.
 38. Hutchinson, P. J. et al. Trial of Dexamethasone for Chronic Subdural Hematoma. *N Engl J Med* 2020;383:2616–2627.
 39. Chan, D. Y. C., Sun, T. F. D. & Poon, W. S. Steroid for chronic subdural hematoma? A prospective phase IIB pilot randomized controlled trial on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation. *Chin Neurosurg J*; 2015; 1: 2.
 40. Olobatoke T, Ekwegbara S, Ayantayo T et al. Multi-Technique Management of Chronic Subdural Hematoma in a Single Patient: A Case Report. *Int J Med Stud* 2022; 10: (S211): 1787.
 41. Tailor J, Fernando D, Sidhu Z, Foley R, Abeysinghe KD, Walsh DC. Clinical audit effectively bridges the evidence-practice gap in chronic subdural haematoma management. *Acta Neurochir (Wien)* 2017;159:627–631.
 42. Sivaraju L, Moorthy RK, Jeyaseelan V, Rajshekhar V. Routine placement of subdural drain after burr hole evacuation of chronic and subacute subdural hematoma: a contrarian evidence based approach. *Neurosurg Rev* 2018; 41: 165–171.
 43. Vychopen M, Güresir E, Wach J. Anti-Inflammatory Drug Therapy in Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis of Prospective Randomized, Double-Blind and Placebo-Controlled Trials. *Int J Mol Sci* 2022, 23: 16198.
 44. Laeke T, Kalleklev L, Tirsit A, Moen BE, Lund-Johansen M, Sundstrøm T. Surgical treatment and outcome of chronic subdural hematoma: a comparative study between Ethiopia and Norway. *Acta Neurochir (Wien)*; 2023;165: 49–59.
 45. Mekaj AY, Morina AA, Mekaj YH. et al. Surgical treatment of 137 cases with chronic subdural hematoma at the university clinical center of Kosovo during the period 2008-2012. *J Neurosci Rural Pract* 2015; 6:186–190.
 46. Hendrix P, Goren O, Dalal S et al. In-hospital mortality rates, complication rates, length of stay, and total costs of >14,000 chronic subdural hematomas treated in the U.S. between 2016 and 2020: Query of the premier health-care database. *Surg Neurol Int* 2022;13:364.
 47. Mersha A, Abat S, Temesgen T, Nebyou A. Outcome of Chronic Subdural Hematoma Treated with Single Burr Hole Under Local Anesthesia. *Ethiop J Health Sci* 2020; 30: 101–106.
 48. Wang QF, Cheng C, You, CA. New Modified Twist Drill Craniostomy Using a Novel Device to Evacuate Chronic Subdural Hematoma. *Medicine (Baltimore)* 2016; 95: e3036.
 49. Lee HS, Song SW, Chun Yi et al. Complications Following Burr Hole Craniostomy and Closed-System Drainage for Subdural Lesions. *Korean J Neurotrauma* 2018; 14: 68–75.
 50. Rai SKR, Dandpat SK, Jadhav D, Ranjan S, Shah A, Goel AH. Optimizing Burr Hole Placement for Craniotomy: A Technical Note. *J Neurosci Rural Pract* 2019; 10: 413–416.
 51. Miyazaki A, Nakagawa T, Matsuura J, Takesue Y, Otsuka, T. Surgical safety criteria for burr hole surgery with urokinase in patients with acute subdural hematoma: Retrospective comparison between burr hole surgery and craniotomy. *Surg Neurol Int* 2021; 12: 574.
 52. Rusconi A, Sangiorgi S, Bifone L, Balbi S. Infrequent Hemorrhagic Complications Following Surgical Drainage of Chronic Subdural Hematomas. *J Korean Neurosurg Soc* 2015; 57:379.

Oftalmolog Albrecht von Graefe (1828.-1870.) i njegovi asistenti i učenici

Ophthalmologist Albrecht von Graefe (1828-1870) and his assistants and pupils

Milan Ivanišević*

Sažetak

Albrecht von Graefe (1828. – 1870.) bio je glasoviti njemački oftalmolog koji je živio i radio u Berlinu. Udario je temelje modernoj i znanstvenoj oftalmologiji i prvi je specijalist koji se bavio isključivo oftalmologijom. Smatra ga se jednim od najvažnijih oftalmologa 19. stoljeća. Bio je svestran, ali najviše ga se pamti po tome što je prvi napravio iridektomiju u liječenju akutnog glaukoma. Izumio je nož za operacije katarakti koji se koristio stotinu godina, prvi se koristio Helmholtzovim oftalmoskopom i osnovao je prvo oftalmološko društvo na svijetu.

Osnovao je poznatu privatnu očnu kliniku u Berlinu u kojoj je poučavao mnogobrojne studente i liječnike iz cijelog svijeta, od kojih su poslije mnogi postali poznatim oftalmolozima. Imao je oko 130 asistenata i učenika, a među poznatijima su bili Douglas Argyll Robertson, Johann Friedrich Horner, Theodor Leber, Richard Leibreich, Louis de Wecker, Albert Mooren, Edmund Landolt, Louis Émile Javal, Julius Hirschberg. Osim toga, mnogi su liječnici dolazili posjetiti von Graefe i vidjeti njegovu čuvenu očnu kliniku. Iako je umro od plućne tuberkuloze u 42. godini, a oftalmologijom se bavio samo dvadeset godina, ostavio je veliki trag u svjetskoj oftalmologiji.

Njegovi učenici prenosili su njegovo znanje i vještine, a svojim radom i inventivnošću uvelike su doprinijeli razvoju oftalmologije kao samostalne struke. Cilj ovoga rada jest prikazati von Graefeove asistente i učenike i njihov utjecaj na razvoj oftalmologije.

Ključne riječi: Albrecht von Graefe, oftalmologija, asistenti, učenici, povijest

Summary

Albrecht von Graefe (1828–1870) was a famous German ophthalmologist who lived and worked in Berlin. He was the founder of modern and scientific ophthalmology and the first specialist to deal only with ophthalmology. He is considered to be one of the most important ophthalmologists of the 19th century. Graefe was a versatile person, but he is mostly remembered for making the first iridectomy for the treatment of acute glaucoma. He invented a knife for cataract surgery which has been used for a hundred years, and he was the first to use the Helmholtz ophthalmoscope and established the world's first ophthalmological society.

He founded a well-known private eye clinic in Berlin where he trained many students and doctors from all over the world, who later became ophthalmologists. There were around 130 assistants and pupils, the most well-known among them included Douglas Argyll Robertson, Johann Friedrich Horner, Theodor Leber, Richard Leibreich, Louis de Wecker, Albert Mooren, Edmund Landolt, Louis Émile Javal, Julius Hirschberg. In addition to these, many doctors came to visit Graefe and see his famous eye clinic. Although he died of pulmonary tuberculosis at the age of 42 and practiced ophthalmology for only 20 years, his work has left a large impact on the world of ophthalmology.

His pupils passed on his knowledge and skills, and through their work and inventiveness, they made a major contribution to the development of ophthalmology as an independent profession. The aim of this paper is to give an account on Graefe's assistants and pupils, and what impact they have had on the development of ophthalmology.

Key words: Albrecht von Graefe, ophthalmology, assistants, pupils, history

Med Jad 2023;53(3):199-206

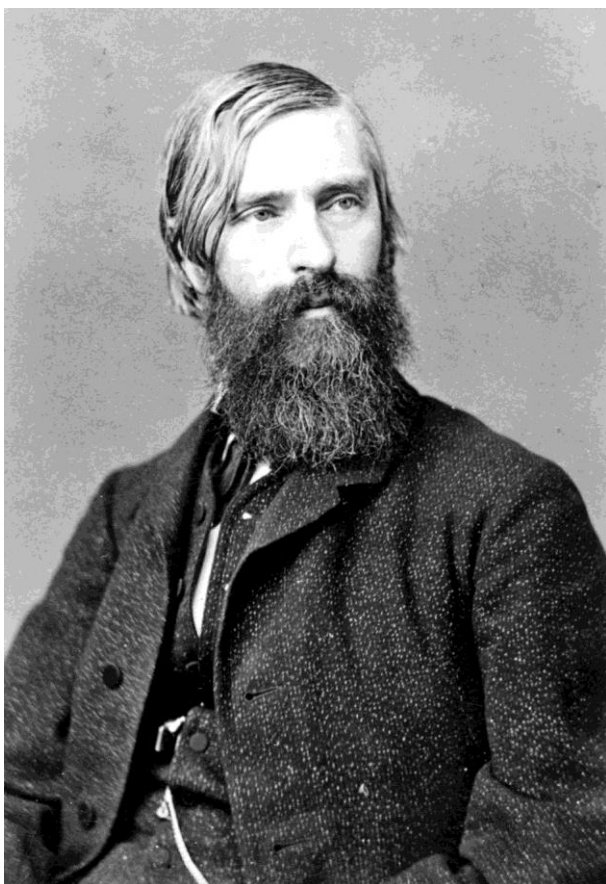
* Sveučilište u Splitu, Medicinski fakultet Split (prof.emer.dr.sc. Milan Ivanišević, dr.med.)

Adresa za dopisivanje / *Corresponding address:* Milan Ivanišević, Sveučilište u Splitu, Medicinski fakultet, Šoltanska 2, 21 000 Split E-mail: milan.ivanisevic@mefst.hr

Primljeno/Received 2023-05-09; Ispravljeno/Revised 2023-07-05; Prihvaćeno/Accepted 2023-07-20

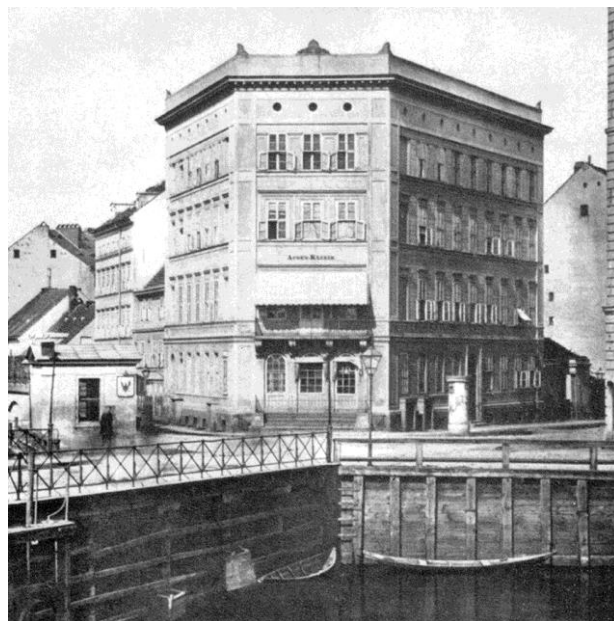
Uvod

Albrecht von Graefe (1828.–1870.) bio je glasoviti njemački oftalmolog koji je živio i radio u Berlinu. Udario je temelje modernoj i znanstvenoj oftalmologiji i prvi je specijalist koji se bavio isključivo oftalmologijom. Imao je brojne asistente i učenike koje je educirao i koji su poslije širili svoje oftalmološko znanje po svijetu, te tako unaprijedili oftalmološku struku. Von Graefe je u svojoj karijeri liječio više od 100.000 domaćih i stranih bolesnika (Slika 1.).



Slika 1. Albrecht von Graefe (1828. – 1870.), u dobi od oko 38 godina (Foto: Ernst Milster, Berlin)
Figure 1 Albrecht von Graefe (1828 – 1870), aged around 38 (Photo: Ernst Milster, Berlin)

Od 1. studenoga 1850. radio je u Berlinu, u maloj očnoj klinici u Behrenstrasse 52, a operirao u Johannisstrasse 12.¹ Krajem 1852. godine otvorio je veliku privatnu očnu kliniku na tri kata u Karlstrasse 46, a koja je postala jednom od najpoznatijih na svijetu (Slika 2.). U njoj je predavanjima i operacijama poučavao mnoge studente i liječnike, od kojih su mnogi poslije postali poznati oftalmolozi.² Tako je samo tijekom 1858. godine bilo 300 studenata.³ Imao je oko 130 asistenata i učenika.



Slika 2. Von Graefeova poznata privatna očna klinika u Karlstrasse 46 u Berlinu (prije 1870.)
Figure 2 Von Graefe's well-known private eye clinic at 46 Karlstrasse in Berlin (before 1870)

Učenici koji su se kasnije preorijentali u druge specijalnosti

Bilo je i onih liječnika koji su se kasnije preorijentali na kirurgiju, poput Theodora Billrotha, na otologiju poput, Antona von Trötscha ili na anatomiju, kao Heinrich Müller.

T. Billroth (1829. – 1894.) nekoliko je mjeseci tijekom 1853. godine boravio u von Graefeovoj očnoj klinici. Kasnije je u Beču prvi operirao rak želuca 1881. godine i postao „ocem moderne abdominalne kirurgije“.⁴ A. von Trötsch (1829.–1890.) obrazovao se kod A. von Graefa 1854. godine. Kasnije je ipak postao „pionir modernog otologije“, te popularizirao čeno zrcalo za otoskopiju 1855./1856. godine.⁵ H. Müller (1820.–1864.) asistirao je von Graefeu tri mjeseca tijekom 1854. godine. Kasnije je postao profesorom patološke anatomije. Po njemu su dobili ime eponimi Müllerov cilijarni, tarzalni i orbitalni mišić, te Müllerove potporne stanice retine. Dao je naziv družu 1856., a 1851. godine otkrio je i rodopsin.⁶

Asistenti koji su dulje vrijeme pomagali u cjelokupnom radu klinike

Neki od učenika postali su mu asistentima. Među važnije njegove asistente koji su dulje vrijeme radili s njim i pomagali u cjelokupnom radu klinike ubrajaju se Richard Liebreich, od 1854. do 1862.,

njegov rođak Alfred Karl Graefe, od 1855. do 1858., Karl Ernst Theodor Schweigger, od 1857. do 1864., potom Rudolf Schelske, od 1864. do 1867. i Theodor Leber, od 1867. do 1870. R. Leibreich (1830. – 1917.) napravio je prvi oftalmoskopski atlas i objavio ga 1863. godine. Uspješno je operirao svekrvu cara Napoleona III. (groficu Montijo) zbog bilateralnog glaukoma.⁷ A. K. Graefe (1830. – 1899.) bio je pionir asepse u oftalmološkoj kirurgiji. Bio je i liječnik skladatelja Franza Liszta.^{8,9} Th. Leber (1840. – 1917.) opisao je kongenitalnu amaurozu 1869. i hereditarnu optičku neuropatiju 1871. godine, a koje su po njemu dobile naziv. Zvali su ga „ocem eksperimentalne oftalmologije“ jer je proučavao očnu cirkulaciju.¹⁰

Privatni asistenti

Von Graefe je imao i tzv. privatne asistente koji su mu bili stari prijatelji iz djetinjstva i iz sveučilišnih dana, a prema kojima je A. von Graefe imao određene obveze. To su bili Julius Arendt (1825.–1870.) i Eduard Michaelis (1824. – 1891.), njegovi prijatelji iz djetinjstva i također članovi povjerenstva na obrani Graefeovog diplomskog rada na medicini 1847. godine, te Adolf Schuft-Waldau (1822.–1895.) i Hermann Ewers (1829.–1873.), prijatelji iz studentskih dana. E. Michaelis radio je s von Graefom od 1851. do 1862. Godine 1877. napisao je von Graefeovu biografiju pod nazivom „*Albrecht von Graefe – Sein Leben und Wirken*“. A. Schuft-Waldau radio je u von Graefeovoj očnoj klinici od 1851. do 1869. i bio mu je često „desna ruka“. Svoje prezime Schuft promijenio je u Waldau 1860. godine. Prvi je izradio oftalmo-fantoma za vježbanje očnih operacija mladih oftalmologa. Godine 1871. operirao je glaukom princu Albrechtu, bratu cara Wilhelma I.¹¹

Prvi asistenti

Među prvim poznatijim asistentima i učenicima koji su započeli obrazovanje kod von Graefea u vremenu od 1852. do 1854. bili su Andreas Anagnostakis, Albert Mooren, Elkanah Williams, Adolf Weber, Alexander Pagenstecher, Johann Friedrich Horner, Julius Jacobson, Robert Ritter Welz.

A. Anagnostakis (1826.–1897.) bio je grčki oftalmolog koji je učio oftalmoskopiju u von Graefeovoj klinici 1852., a 1867. i ekstrakciju katarakte po von Graefeu. Godine 1854. postao je šefom očne klinike u Ateni i profesorom oftalmologije.¹² Amerikanac E. Williams (1822.–1888.) drugu polovinu 1854. godine proveo je kod A. von Graefea učeći oftalmoskopiju, koju je prvi donio u Sjedinjene Američke Države 1855. godine. Također

je prvi odvojio oftalmologiju kao posebnu specijalnost u SAD-u. Bio je prvi profesor oftalmologije u SAD-u.^{13,14} A. Mooren (1828.–1899.) bio je njemački očni kirurg koji je bio pod utjecajem A. von Graefea od 1852. do 1855. godine. Definirao je 1863. godine klinički entitet Moorenov ulkus – perifernu rožničku ulceraciju. Prakticirao je preliminarnu iridektomiju tijekom operacije katarakte.¹⁵ A. Weber (1829.–1915.) slušao je von Graefeova predavanja u zimu 1854./1855. Uveo je pilokarpin u oftalmološku praksu 1876. godine.¹⁶ A. Pagenstecher (1828. – 1879.) posjetio je 1853. godine von Graefea u Berlinu. Godine 1862. napravio je žuti živin oksid nazvan Pagenstecherova mast za liječenje fliktenuloznog keratokonjunktivitisa koji je u to vrijeme bio jako proširen. Godine 1866. uveo je u kiruršku praksu intrakapsularnu operaciju katarakte.^{17,18} J. F. Horner (1831.–1886.) bio je von Graefeov asistent, počevši od listopada 1854. do svibnja 1855. godine. Postao je prvim profesorom oftalmologije u Švicarskoj. Poznat je po eponimu Hornerov sindrom, koji je opisao 1869. godine. Na sveučilišnoj očnoj klinici i svojoj privatnoj očnoj klinici *Hottingerhof* u Zürichu poučavao je i prve oftalmologinje u svijetu.^{19,20} J. Jacobson (1828.–1889.) educirao se kod svog obožavanog idola Graefea 3-4 mjeseca 1853./54. godine. Najstariji Jacobsonov učenik bio je Arthur von Hippel. Godine 1873. postao je redoviti profesor oftalmologije na Sveučilištu u Königsbergu, te nakon toga direktor očne klinike (1877.).²¹ R. R. Welz (1814.–1878.), izumitelj je prvih inhalatora za etersku anesteziju (1847.) i bio je prvi profesor oftalmologije u Würzburgu. Upoznao je Graefea 1849. u Parizu, a bio mu je asistent 1854./55. godine. Osnovao je privatnu očnu kliniku u Würzburgu 1857. A. v. Graefe ga je redovito posjećivao u Würzburgu u slobodno vrijeme i napravio bi nekoliko operacija (pogotovo kompliciranih) u njegovom institutu.²²

Posljednji klinički asistenti

Neki od posljednjih kliničkih asistenata bili su Louis Casper (1841.–1918.), Jacob Katz (1839.–1920.), Jacob Tachau (oko 1840.–1895.) i Julius Hirschberg (1843.–1925.). Dr. J. Tachau bio je nekoliko godina asistent, a potom je 1869. godine otišao u Egipat liječiti trahomske bolesnike. Imao je izvrsne kirurške rezultate, pa su ga zvali „Bog od očiju“.^{23,24} J. Hirschberg bio je asistent od 1866. do 1868. godine. Prvi se koristio elektromagnetom za vađenje metalnih stranih tijela iz oka 1879. i uveo je skopolamin u oftalmološku praksu 1881. godine. Poznat je po eponimu Hirschbergov test za ispitivanje strabizma (1886.). Napisao je opsežnu povijest

oftalmologije u vremenu od 1899. do 1918. godine.²⁵ Posljednje tri godine u von Graefeovoj klinici obrazovali su se i Sir Henry Rosborough Swanzy, Hermann Pagenstecher, Vilmos Schulek, Louis Émile Javal, Edmund Landolt i Marc Dufour. H. R. Swanzy (1843.–1913.) bio je irski oftalmolog iz Dublina. Godine 1868. postao je asistentom A. von Graefeu. U razdoblju od 1897. do 1899. bio je predsjednik Oftalmološkog društva Ujedinjenog Kraljevstva. Od 1906. do 1908. bio je predsjednik Kraljevskog koledža kirurga Irske.²⁶ H. Pagenstecher (1844.–1932.) učio je oftalmologiju kod A. von Graefea od 1868. do 1870. godine. Zajedno s Carlom Philipom Genthom 1875. godine prvi je opisao i ilustrirao disciformnu senilnu makularnu degeneraciju i nazvao je *chorioretinitis in regione maculae luteae*. Kraljica Viktorija tražila je njegovo (sekundarno) mišljenje glede njezine katarakte 1899. godine.^{27,28} V. Schulek (1843.–1905.) bio je mađarski oftalmolog koji je 1869. godine šest mjeseci slušao predavanja A. von Graefea. Postao je profesorom i šefom na Očnoj klinici u Budimpešti.²⁹ L. É. Javal (1839. – 1907.) bio je francuski oftalmolog koji se obrazovao kod A. von Graefea od 1868. do 1870. godine. Zvali su ga „ocem ortoptike“. Izumio je 1881. godine Javalov oftalmometar.³⁰ E. Landolt (1846. – 1926.) bio je švicarski oftalmolog i von Grafeov učenik 1869. godine. Izradio je Landoltove prstene za optotipe. Bio je oftalmolog slikara Edgara Degasa i Mary Casatt.^{31,32,33} Marc Dufour (1843.–1910.) švicarski oftalmolog, radio je u Berlinu kao učenik A. v. Graefea 1868. Bio je profesor oftalmologije na Sveučilištu u Lausannei (rektor 1894.). Od 1896. Dufourov asistent bio je Jules Gonin (1870.–1935.) koji je nominiran za Nobelovu nagradu.³⁴

Neki od poznatijih Graefeovih učenika i asistenata

Među ostalim učenicima važni su sljedeći oftalmolozi: Douglas Argyll Robertson, Rudolf Berlin, Louis de Wecker, Carl Wilhelm von Zehender, Frank-Francis Buller, Ludwig Laqueur, Robert Blessig, John Graf Magawly, August von Rothmund, Hermann Jakob Knapp, Edwin Theodor Saemisch, Heinrich Sellerbeck, Edmund Hansen Grut, Heinrich Schiess-Gemuseus i Hilário de Gouvêa.

Douglas Argyll Robertson (1837.–1909.) bio je škotski oftalmolog iz Edinburgha koji se obrazovao kod A. von Graefea dvije godine, tj. od 1859. do 1861. godine. Vezan je za pojam Argyll Robertsonova zjenica – simptom neurosifilisa, koji je opisao 1869. godine. Prvi je opisao rezultate operacije glaukoma trepanom 1876. godine. Neko vrijeme bio je počasni liječnik kraljice Viktorije i kralja Edwarda

VII.³⁵ R. Berlin (1833.–1897.) bio je kod von Graefea oko 1857. godine. Po njemu je dobio ime eponim Berlinov edem – traumatski edem retine, koji je opisao 1873. Pojam disleksija – „sljepoća govora“ definirao je 1887. godine. Napravio je i popularizirao prvu modernu dakriocistektomiju 1868. godine.³⁶ L. de Wecker (1832. – 1906.) dobio je 1860. godine von Grafeovu potvrdu da može obavljati oftalmološku praksu. Izradio je škarice koje se po njemu zovu „Weckerove škarice“ za intraokularnu kirurgiju šarenice i lećne kapsule.³⁷ W. von Zehender (1819. – 1916.) bio je asistent od 1854. do 1856. godine. Prvi je oftalmolog koji je uspješno operirao koristeći se mikroskopskim povećanjem 1887. godine, te je nazvan „ocem očne mikrokirurgije“. Osnivač je i oftalmološkog časopisa *Klinische Monatsblätter für Augenheilkunde* 1863. godine.³⁸ F. F. Buller (1844. – 1905.) učio je oftalmologiju u Berlinu kod A. von Graefea 1869. godine. Osnivač je moderne oftalmologije u Kanadi i dao joj je neovisan status.³⁹ L. Laqueur (1839.–1905.) studirao je u Berlinu kod A. von Graefea od 1861. do 1862. godine. Uveo je prvo medikamentno liječenje glaukoma fizostigminom (ezerinom) 1876. godine. Testirao ga je na sebi jer je imao glaukom.⁴⁰ R. Blessig (1830. – 1878.) i J. G. Magawly (1831. – 1904.) utemeljitelji su moderne ruske oftalmologije. Blessig je bio von Grafeov učenik 1857. godine. Opisao je periferne retinalne ciste 1855. godine.⁴¹ J. G. Magawly posjećivao je von Graefea od 1856. do 1859. godine. Bio je okulist ruskog cara Nikole II.⁴² A. von Rothmund (1830. – 1906.) stekao je oftalmološko obrazovanje 1853./1854. Uveo je subkonjunktivalne injekcije 1866. godine.⁴³ H. J. Knapp (1832. – 1911.) bio je von Grafeov student i asistent od 1854. do 1856. godine. Osnivač je moderne američke oftalmologije. Pukotine u Bruchovoj membrani nazvao je *angioid streaks* 1892. godine. Izradio je i pincetu za liječenje trahoma.^{44,45,46} E. T. Saemisch (1833.–1909.) obrazovao se kod A. von Graefea 1859. više od godinu dana. 1876. godine opisao je vernalni konjunktivitis i *ulcus serpens corneae*.⁴⁷ H. Sellerbeck (1842. – 1918.) učenik je A. von Graefea. Prvi je presadio rožnicu s čovjeka na čovjeka 1878. godine.⁴⁸ E. H. Grut (1831.–1907.) bio je entuzijastički von Grafeov učenik gotovo cijelu 1862. godinu, te drugi put između 1857. i 1863. godine. Profesora Gruta smatraju „ocem moderne danske oftalmologije“. Godine 1884. imenovao je „dendritički ulkus“. Njegov asistent bio je Jannik Petersen Bjerrum.^{49,50} H. Schiess-Gemuseus (1833. – 1914.) Imao je 4 mjeseca praktične obuke s Grafeom u Berlinu 1858., ali kasnije i u Heidenu u hotelu Freihof (asistirao Grafeu). Bio je zainteresiran za oftalmologiju zbog visokog stupnja miopije u

njegovoj obitelji. Osljepio je na desno oko zbog katarakte koju je operirao, ali je bio zahvaćen i očni živac, a na lijevo oko zbog visoke miopije i ablacije retine. Osnivač je prve očne klinike u Bazelu 1864. Postao je izv. profesor oftalmologije 1867., a redoviti od 1876. Specijalizirao je očnu patologiju. Bio je očni doktor Friedrichu Nietzscheu koji je imao visoku miopiju, strabizam, centralni korioretinitis i anisocoriu.⁵¹ H. de Gouvêa (1843. – 1923.) obrazovao se iz oftalmologije u klinici kod A. von Graefa 1867. godine. Jedan je od pionira brazilske oftalmologije. Prvi je dokumentirao familijarni retinoblastom 1872. godine.⁵²

Prema navodima iz razne literature Albrecht von Graefe imao je oko 130 asistenata i učenika od osnivanja prve očne klinike 1850. do svoje smrti 1870. godine. Najviše ih je bilo iz Njemačke (63), Rusije (17), SAD-a (16), Švicarske (12), Turske (3), iz Austrije, Italije, Francuske i Danske po dvoje, te iz ostalih dijelova Europe i Amerike (Škotska, Irska, Engleska, Mađarska, Rumunjska, Grčka, Poljska, Švedska, Norveška, Finska, Kanada, Brazil i Venezuela). Učenika židovskog podrijetla bilo je sedamnaest. Profesorima je postalo 65 von Graefeovih učenika, a 55 direktorima, šefovima ili osnivačima očnih odjela i klinika.^{53,54,55} Među asistentima i učenicima nije bila ni jedna žena koja je učila i specijalizirala oftalmologiju. Profesor Johann Friedrich Horner, bivši asistent Albrechta von Graefa, vodio je u Zürichu očnu kliniku u kojoj su među prvima u svijetu oftalmologiju mogle studirati i žene.^{19,20}

Godine 1851. i 1852., dok je von Graefe radio u Behrenstrasse 52 i Johannisstrasse 12, imao je samo nekoliko asistenata i učenika. Najviše asistenata i učenika dobio je nakon formiranja klinike u Karlstrasse 46 i uvođenja nastave (1854. i 1855.), potom u godini popularizacije iridektomije i oftalmoskopije (1857.), te nakon što je uveo „linearan nož“ za operaciju katarakte i postao redovitim profesorom (1867.–1869.) (Slika 3.). Najmanje asistenata i učenika imao je nakon što se razbolio od tuberkuloze pluća (1861.–1863.) i, razumljivo, u godini svoje smrti (1870.).

Dvanaest učenika boravilo je u njegovoj klinici tri godine, dva učenika četiri godine, a više od četiri godine boravilo je njih šest. Najdulje su s njim proveli Adolf Schuft-Waldau i Julius Arendt – osamnaest godina, prvi od 1851. do 1869., a drugi od 1852. do 1870. godine.

Prvi školovani hrvatski oftalmolog, dr. Vinko Lušić-Matković (Vrbanj, otok Hvar, 1861. – Zagreb, 1931.) obrazovao se 1891. godine kod dvojice von Graefeovih učenika. Prvi je bio K. E. T. Schweigger, direktor i profesor na sveučilišnoj očnoj klinici u

Ziegelstrasse u Berlinu, a drugi Louis de Wecker, koji je imao svoju oftalmološku kliniku u Rue du Cherche-Midi 55 u Parizu.⁵⁶ Tako je V. Lušić-Matković bio Graefeov „oftalmološki unuk“.



Slika 3. Profesor Albrecht von Graefe za vrijeme operacije (Dr. H. R. Swanzy daje bolesniku kloroform), 1869. (časopis "Über Land und Meer", crtao Carl Koch)
Figure 3 Professor Albrecht von Graefe during an operation (Dr H R Swanzy administering chloroform), 1869 (journal "Über Land und Meer", drawn by Carl Koch)

Posjetiooci

Mnogi liječnici dolazili su posjetiti von Graefa i vidjeti njegovu kliniku u Berlinu. Njegov učitelj i prijatelj profesor F. von Arlt (1812.–1887.) prvi put je posjetio Graefa u Berlinu 1853. godine. Nakon toga posjetio ga je o Uskrsu 1857., kako bi nazočio njegovoj operaciji glaukoma. Godine 1867. operirao je glaukom na lijevom oku svojoj ženi i tako joj sačuvao vid.⁵⁷ F. C. Donderes (1818.–1889.), njegov prijatelj i kolega, posjetio ga je u Berlinu 1854. i sredinom 60-ih godina 19. stoljeća.⁵⁸ Sin Juliusa Sichel, Arthur (1839.–1895.) posjećivao je von Graefevu kliniku 1867. godine.⁵⁹ Danski oftalmolog Nathan Gerson Melchior (1811.–1872.) bio je kod von Graefa 1862. godine.⁶⁰ Također ga je posjetio i švedski oftalmolog i kirurg Carl Jakob Rossander (1828.–1901.).⁶⁰ Engleski kirurg Charles Roberts došao je vidjeti von Graefevu kliniku.⁶¹ Često ga je posjećivao i liječnik i novinar Max Ring (1817.–1901.).⁶² Kirurg Ernst von Bergmann (1836.–1907.) bio je na von Graefevu seminaru 1865. godine. Za

Graefea je rekao da „operira po strogim pravilima i uvijek vrlo pažljivo“.⁶³

Rasprava i zaključak

Albrecht von Graefe tri godine obrazovao se kod poznatih europskih oftalmologa (od 1848. do 1851.) u Pragu, Beču, Parizu, Londonu, Glasgowu i Dublinu. Osnovao je 1852. godine poznatu privatnu očnu kliniku u Berlinu.^{64,65}

Bio je veliki radoholičar, te inteligentan, vješt i inventivan operater. Iznimno je doprinio svjetskoj oftalmologiji. Udario je temelje modernoj i znanstvenoj oftalmologiji i prvi je specijalist koji se bavio isključivo oftalmologijom. Smatra ga se jednim od najvažnijih oftalmologa 19. stoljeća. Bio je svestran, ali najviše ga se pamti po tome što je prvi uveo iridektomiju u liječenje akutnog glaukoma (1856.). 1865. godine izumio je nož za operacije katarakti, koji se koristio još stotinu godina. Prvi se koristio Helmholtzovim oftalmoskopom (1851.) i osnovao je prvo oftalmološko društvo na svijetu (1857.).

Njegova očna klinika bila je magnet koji je privlačio, ne samo oboljele, već i studente, asistente, liječnike i mlade oftalmologe iz gotovo cijeloga svijeta. Njegovi učenici postali su vrlo cijenjene osobe u oftalmologiji. Oni su prenosili oftalmološka znanja diljem Europe i svijeta, što je imalo veliki utjecaj na daljnji razvoj oftalmologije.⁶⁶ Von Graefeovi kontakti, dopisivanje i sastanci na oftalmološkim kongresima s njegovim učiteljima, asistentima i kolegama, također su pridonijeli međunarodnoj suradnji i internacionalizaciji u oftalmologiji.

Literatura

1. Snyder C. Dr. Albrecht von Graefe in Behrenstrasse will treat free of charge the eye diseases of the poor. *Arch Ophthalmol* 1965;74:545-8.
2. Kazimirski J. Albrecht von Graefe Augenlinik. *Ophthalm-Chirurgie* 1995;7:171-9.
3. Lebensohn JE. The legacy of Albrecht von Graefe. *Am J Ophthalmol* 1970;69:1088-90.
4. Kazi RA, Peter RE. Christian Albert Theodor Billroth: Master of surgery. *J Postgrad Med* 2004;50:82-3.
5. Pappas DG. Anton Friedrich von Trölsch (1829-1890). The beginning of otology in Germany. *Ear Nose Throat J* 1996;75:650-1.
6. Kaden R. Heinrich Müller (1820-1864). In memory of his 150th birthday. *Klin Monbl Augenheilkd* 1971;158:607-9.
7. Ravin JG, Kenyon C. From von Graefe's clinic to the Ecole des Beaux-Arts. The meteoric career of Richard Liebreich. *Surv Ophthalmol* 1992;37:221-8.
8. Snyder C. Alfred Carl Graefe. *Arch Ophthalmol* 1964;72:858-61.
9. Tost M. Alfred Graefe (1830-1899)-Leben und Wirken. In: Hartmann C. Ed. Albrecht von Graefe. Berlin 1828 bis 1870. Germering: Verlag für Medizin und Naturwissenschaften, 1996;93-101.
10. Jaeger W. The foundation of experimental ophthalmology by Theodor Leber. *Doc Ophthalmol* 1988;68:71-7.
11. Hirschberg J. Geschichte der Augenheilkunde. Die Reform der Augenheilkunde, 2. Teil. In: Graefe A, Saemisch T. Eds. *Handbuch der gesamten Augenheilkunde*, 2. Aufl. 15. Bd. Berlin: Julius Springer, 1918;5-7.
12. Schett A, Keeler CR. The ophthalmoscope. Andreas Anagnostakis (1826-1897). Ostende: J.-P. Wayenborgh, 1996;128-9.
13. Asbury T. A condensed history of ophthalmology in Cincinnati (1827-1899). *Surv Ophthalmol* 2000;44:442-9.
14. Atkinson WB. The physicians and surgeons of the United States. Philadelphia: Charles Robson, 1878;7-8.
15. Hoß J. Albert Mooren-Ein Augenarzt im 19. Jahrhundert [Dissertation]. Düsseldorf: Tritsch Verlag Düsseldorf, 1980;87.
16. Engelmayr W, Krieglstein GK. Adolf Weber: attempt at a life portrait. *Hist Ophthalm Intern* 1985;3:335-46.
17. Hosford GN, McKenny JP. Ointment of yellow mercuric oxide (Pagenstecher's ointment). Its use and abuse. *JAMA* 1933;100:17-9.
18. Wormer EJ. Pagenstecher, Alexander. *Neue Deutsche Biographie (NDB)*. Band 20. Berlin: Duncker & Humblot, 2001;2.
19. Roper-Hall G. Historical Vignette: Johann Friedrich Horner (1831-1886): Swiss ophthalmologist, scientific contributor, and accomplished academic. *Am Orthopt J* 2016;66:126-34.
20. Bonner TN. Rendezvous in Zurich. Seven who made a revolution in women's medical education, 1864-1874. *J Hist Med Allied Sci* 1989;44:7-27.
21. Herde J. Julius Jacobson und die Überwindung des „Nothstandes im Cultus Preussen“. In: Krogmann F. Ed. *Mitteilungen der Julius-Hirschberg-Gesellschaft zur Geschichte der Augenheilkunde*. Band 10. Würzburg: Königshausen & Neumann, 2008;53-85.
22. Robert von Welz. Dostupno na adresi: https://wuerzburgwiki.de/wiki/Robert_von_Welz Datum pristupa: 27.02.2023.
23. Schneck P. Die Privatklinik Albrecht von Graefes in Berlin. In: Hartmann C. Ed. Albrecht von Graefe. Berlin 1828 bis 1870. Germering: Verlag für Medizin und Naturwissenschaften, 1996;49-61.
24. McCallan AF. The history of ophthalmology in Egypt. *Br J Ophthalmol* 1927;11:602-9.
25. Koelbing HM. Julius Hirschberg (1843-1925) ophthalmologist and medical historian. *Klin Monbl Augenheilkd* 1976;168:103-8.
26. Fitzgerald CE. Sir Henry Rosborough Swanzy. *Dublin J Med Sci* 1913;135:408-13.
27. Scheffels O. Hermann Pagenstecher, M.D. 1844-1932. *Arch Ophthalmol* 1932;8:903.

28. Ravin JG. Queen Victoria, her physicians, and her cataract. *Surv Ophthalmol* 1994;38:474-82.
29. Zajác M. *Ophthalmology in Hungary*. Debrecin: SOE '97, 1997;36-43.
30. Roper-Hall G. Historical vignette: Louis Émile Javal (1839-1907): the father of orthoptics. *Am Orthopt J* 2007;57:131-6.
31. Edmund Landolt. Dostupno na adresi: [//en.wikipedia.org/wiki/Edmund_Landolt](https://en.wikipedia.org/wiki/Edmund_Landolt) Datum pristupa: 15.3.2023.
32. Ivanišević P, Ivanišević M. The influence of retinal eye diseases on painting. *Coll Antropol* 2015;39:243-6.
33. Ravin JG. Cataracts, diabetes, and radium. The case of Cassatt. In: Marmor MF, Ravin JG. Eds. *The eye of the artist*. St. Louis: Mosby, 1997;181-6.
34. Streiff EB. The genealogy of ophthalmic teaching in Switzerland. *Hist Ophthalm Intern* 1982;2:407-30.
35. Timoney PJ, Breathnach CS. Douglas Argyll Robertson (1837-1909) and his pupil. *Ir J Med Sci* 2010;179:119-21.
36. Pagel J. *Biographisches Lexikon, hervorragender Ärzte des neunzehnten Jahrhunderts*. Berlin: Urban & Schwarzenberg, 1901;146-7.
37. Laios K, Moschos MM, Androustos GC. Louis de Wecker (1832-1906) and his innovations in ocular surgery. *Surg Innov* 2016;23:640-1.
38. Stave J, Guthoff R, Draeger J. Prof. Carl Wilhelm Zehender (1819-1916) Mitbegründer der Deutschen Ophthalmologischen Gesellschaft, Erfinder des ersten Spaltlampenmikroskops. *Spektr Augenheilkd* 2004;18:5-7.
39. Murphy SB. *Portraits of ophthalmology at McGill University 1876-1990*. Montreal: McGill University, 2005;7-24.
40. Snyder C. Ludwig Laqueur, MD (1839-1905). *Arch Ophthalmol* 1964;72:111-3.
41. Bezkorovainy A. *Science and medicine in imperial Russia*. Raleigh: Lulu Enterprises Inc., 2018;162.
42. Fischer M. *Russische Karrieren: Leibärzte im 19. Jahrhundert*. Aachen: Shaker Verlag, 2010;150-2.
43. Shroff AA. An eye in number. A ready reckoner in ophthalmology. Mumbai: PostScript Media Pvt.Ltd., 2011;234.
44. Honegger H, Hessler B. Jacob Hermann Knapp in Heidelberg, 1860-1868. *Ber Zusammenkunft Dtsch Ophthalmol Ges* 1970;70:602-5.
45. Blodi FC. The influence of some ophthalmologists of German origin on the development of American ophthalmology. *Klin Monbl Augenheilkd* 1992;201:3-8.
46. Truhlsen SM. The Knapps. *Arch Ophthalmol* 2005;123:676-80.
47. Hammann K. *Edwin Theodor Saemisch: eine historische Studie [Dissertation]*. Bonn: Rheinische Friedrich-Wilhelms Universität, 1969;65.
48. Sellerbeck H. Über Keratoplastik. *Albrecht von Graefe Archiv für Ophthalmologie* 1878;24:1-46.
49. Dreyer V, Edmund J, Møller PM. The first Danish chairs of ophthalmology. *Doc Ophthalmol* 1992;81:87-96.
50. Andersen SR. The history of the Ophthalmological Society of Copenhagen 1900-50. *Acta Ophthalmol Scand Suppl* 2002;234:6-17.
51. Rintelen F. Centennial of the Basle Eye Hospital and its founder Heinrich Schiess. *Klin Monbl Augenheilkd* 1978;172:638-41.
52. Monteiro ANA, Waizbord R. The accidental cancer genetics: Hilário de Gouvêa and hereditary retinoblastoma. *Cancer Biol Ther* 2007;6:811-3.
53. Hirschberg J. *History of Ophthalmology. The Reform of Ophthalmology. vol. 11, part 1b* (F. C. Blodi, transl.). Bonn: Wayenborgh J-P, 1992;1-125.
54. Rohrbach JM, Leitritz MA. Albrecht von Graefe und die Internationalität. *Ophthalmologe* 2017;114:775-80.
55. Münchow W. *Geschichte der Augenheilkunde*. Stuttgart: Ferdinand Enke, 1984;594-603.
56. Dorn V. Vinko Lušić-Matković—prvi hrvatski školovani oftalmolog. *Liječ Vjesn* 1971;93:781-6.
57. Ullman EV. Albrecht von Graefe: The man in his time. *Am J Ophthalmol* 1954;38:695-711.
58. Horner JF. Ein Lebensbild, geschrieben von ihm selbst, ergänzt von E. Landolt. *Frauenfeld: J. Huber's Verlag*, 1887;44.
59. Hirschberg J. *History of Ophthalmology. The Reform of Ophthalmology. vol. 11, part 1a* (F. C. Blodi, transl.). Bonn: Wayenborgh J-P, 1992;222.
60. Lebensohn JE. The legacy of Albrecht von Graefe. *Am J Ophthalmol* 1970;69:1088-90.
61. Roberts C. Von Graefe's opinion of Sir William Bowman. *BJ* 1883;2:1261.
62. Ring M. Gräfe und die Augenklinik. *Gartenlaube. Illustriertes Familienblatt. Heft 14*. Leipzig: Ernst Keil Verlag, 1857;188-92.
63. Hoffmann-Axthelm W. Die Familie von Graefe und ihre Villa Finkenherd im Berliner Tiergarten. *Ber Zusammenkunft Dtsch Ophthalmol Ges* 1969;69:685-706.
64. Michaelis E. Albrecht von Graefe. Sein Leben und Wirken. Berlin: G. Reimer, 1877;12-34.
65. Heynold von Graefe B. Albrecht von Graefe: Mensch und Umwelt. Berlin: Stapp Verlag, 1991;40-1.
66. Remky H. Albrecht von Graefe facets of his work. On occasion of the 125th anniversary of his death (20 July 1870). *Graefes Arch Clin Exp Ophthalmol* 1995;233:537-48.

Utjecaj COVID-19 pandemije na bolesnike s novootkrivenim kolorektalnim karcinomom u Općoj bolnici Zadar

The impact of the COVID-19 pandemic on patients with newly diagnosed colorectal cancer in Zadar General Hospital

Ivo Dilber, Sara Bilić Knežević, Mirisa Tokić, Jakov Mihanović, Josipa Jović Zlatović*

Sažetak

Kolorektalni karcinom je jedna od najučestalijih zloćudnih bolesti u Republici Hrvatskoj.¹ Ako se otkrije u ranom, odnosno lokaliziranom stadiju bolesti, petogodišnje preživljenje iznosi oko 90%.⁵ Iznimno je važno dijagnosticirati bolest u što ranijem stadiju radi boljeg ishoda liječenja. Stoga je odlukom Vlade Republike Hrvatske 2007. godine usvojen Nacionalni program ranog otkrivanja raka debelog crijeva.¹ Pojava pandemije koronavirusne bolesti dovela je do izazova u funkcioniranju zdravstvenog sustava diljem svijeta, pa tako i programa ranog otkrivanja raka debelog crijeva.³ Za vrijeme Covid-19 pandemije zabilježen je smanjen broj obavljenih kolonoskopija i odaziv na program ranog otkrivanja raka debelog crijeva. Cilj ovog istraživanja je retrospektivno otvrditi utjecaj COVID-19 pandemije na bolesnike s novootkrivenim kolorektalnim karcinomom u razdoblju od 01.04.2020. do 30.09.2021. (za vrijeme COVID-19 pandemije) u odnosu na razdoblje od 01.04.2018. do 30.09.2019. (vrijeme prije COVID-19 pandemije) u Općoj bolnici Zadar. Glavni cilj istraživanja bio je odrediti vrstu operacije primarnog tumora (elektivne i hitne operacije) prije i za vrijeme COVID-19 pandemije. U našem istraživanju uspjeli smo dokazati hipotezu da će u COVID-19 pandemiji biti povećan udio hitnih operacijskih zahvata u odnosu na elektivne, što se može povezati sa smanjenim brojem preventivnih pregleda u sekundarnim zdravstvenim ustanovama, odnosno smanjenim odazivom na program za rano otkrivanje raka debelog crijeva.

Ključne riječi: kolorektalni karcinom, pandemija COVID-19, nacionalni screening, kolonoskopija, kemoterapija, kirurško liječenje.

Summary

Colorectal cancer is one of the most common malignant diseases in the Republic of Croatia.¹ If colorectal cancer is detected in the early, or localized stage of the disease, the five-year survival is about 90%.⁵ It is extremely important to diagnose colorectal cancer at the earliest possible stage of the disease for a better treatment outcome. Therefore, the National Colon Cancer Early Detection Program was adopted by the Decision of the Government of the Republic of Croatia in 2007.¹ The emergence of the coronavirus disease pandemic has led to challenges in the functioning of the health system around the world, including the program of early colon detection.³ During the Covid-19 pandemic, the number of colonoscopies performed and the response to the colon cancer early detection program decreased. The aim of this research is to retrospectively evaluate the impact of the COVID-19 pandemic on patients with newly diagnosed colorectal cancer in the period from April 1, 2020 until September 30, 2021 (during the Covid-19 pandemic) compared to the period from April 1, 2018 until September 30, 2019 (period prior to the COVID-19

* **Opća bolnica Zadar, Odjel za onkologiju i nuklearnu medicinu** (Ivo Dilber, dr.med., Sara Bilić Knežević, dr.med., Mirisa Tokić, dr.med.); **Opća bolnica Zadar, Služba za kirurgiju** (doc.dr.sc. Jakov Mihanović, dr.med.); **Sveučilište u Zadru, Odjel za zdravstvene studije** (doc.dr.sc. Jakov Mihanović, dr.med.); **Opća bolnica Šibenik, Odjel za internu medicinu** (Josipa Jović Zlatović, dr.med.)

Adresa za dopisivanje/*Correspondence address:* Ivo Dilber, dr.med., Opća bolnica Zadar, Odjel za onkologiju i nuklearnu medicinu, Bože Peričića 5, 23 000 Zadar E-mail: ivodilber81@gmail.com

Primljeno/*Received* 2023-06-13; Ispravljeno/*Revised* 2023-09-25; Prihvaćeno/*Accepted* 2023-09-26

pandemic) in Zadar GH. The main goal of the research was to determine the type of primary tumor surgery (elective and emergency surgery) before and during the COVID-19 pandemic). In our research, we were able to prove the hypothesis that during the COVID-19 pandemic, there was an increased share of emergency surgical procedures compared to elective ones, which can be connected to a reduced number of preventive examinations in secondary health institutions, a reduced response to the program for the early detection of colon cancer respectively.

Key words: colorectal cancer, COVID-19 pandemic, national screening, colonoscopy, chemotherapy, surgical treatment.

Med Jad 2023;53(3):207-212

Uvod

Kolorektalni karcinom je jedna od najučestalijih zloćudnih bolesti u Republici Hrvatskoj.¹ Godišnje od te bolesti prosječno oboli oko 3600 osoba, od čega 60% muškaraca.¹ Po smrtnosti od zloćudnih bolesti kolorektalni karcinom je na drugom mjestu, iza raka pluća.¹ Stoga je iznimno važno dijagnosticirati kolorektalni karcinom u što ranijem stadiju bolesti radi boljeg ishoda liječenja. Odlukom Vlade Republike Hrvatske 2007. godine usvojen je Nacionalni program ranog otkrivanja raka debelog crijeva.¹ Program je namjenjen osobama od 50 do 74 godine života s ciljem smanjenja smrtnost od ovog oblika raka za 15% u razdoblju od 10 godina.¹ Za navedeni plan smanjenja smrtnosti potreban odaziv na program bio bi 45%, a željeni 65% od pozvanih na testiranje.¹ Udio testiranih osoba u Republici Hrvatskoj iznosi svega 25%, te za sada nije dostatan za polučiti ciljeve Nacionalnog programa.¹ Krajem 2019. godine novi soj koronavirusa (SARS-CoV-2) pojavio se u Kini, u gradu Wuhan i vrlo brzo izazvao pažnju cijeloga svijeta zbog uzrokovanja neobične virusne upale pluća.² Utvrđeno je da je nova bolest, nazvana COVID-19 (engl. Coronavirus disease 2019), jedna od vrlo zaraznih i smrtonosnih bolesti, a zbog takvih karakteristika širila se velikom brzinom u različite dijelove svijeta.² Pojava pandemije koronavirusne bolesti dovela je do izazova u funkcioniranju zdravstvenog sustava diljem svijeta, pa tako i programa ranog otkrivanja raka debelog crijeva.³ Za vrijeme Covid-19 pandemije zabilježen je smanjen broj obavljenih kolonoskopija i odaziv na program ranog otkrivanja raka debelog crijeva. U Republici Hrvatskoj su tako 2020. godine napravljene 15443 kolonoskopije, dok je u istom razdoblju 2019. godine napravljeno 22638 kolonoskopija.³ Preporuke Europskog društva za internističku onkologiju (ESMO) za liječenje hematoloških i onkoloških bolesnika za vrijeme COVID-19 pandemije bile su zamjena intravenskog pripravka peroralnim ili subkutanim oblikom, odnosno smanjenje intenziteta

liječenja, u svrhu smanjenja izloženosti bolesnika i medicinskog osoblja virusu SARS-CoV-2.⁴

Ispitanici i metode

Ispitanici su svi bolesnici s postavljenom dijagnozom kolorektalnog karcinoma u razdoblju od 01.04.2020. do 30.09.2021. (za vrijeme COVID-19 pandemije) u odnosu na razdoblje od 01.04.2018. do 30.09.2019. (vrijeme prije COVID-19 pandemije) u OB Zadar.

Kriteriji uključenja: odrasli bolesnici oba spola s novootkrivenim kolorektalnim karcinomom.

Kriteriji isključenja: 1. bolesnici koji nisu imali potpunu dokumentaciju, 2. bolesnici kojima patohistološkom analizom nije potvrđena dijagnoza kolorektalnog karcinoma.

Istraživanje je provedeno u OB Zadar, a podaci su prikupljeni pretragom bolničkog informatičkog sustava.

Cilj ovoga istraživanja je retrospektivno evaluirati utjecaj COVID-19 pandemije na bolesnike s novootkrivenim kolorektalnim karcinomom u razdoblju od 01.04.2020. do 30.09.2021. (za vrijeme Covid-19 pandemije) u odnosu na razdoblje od 01.04.2018. do 30.09.2019. (vrijeme prije COVID-19 pandemije) u OB Zadar. Istraživanje je uključilo 216 bolesnika kojima je kolorektalni karcinom dijagnosticiran u OB Zadar. Glavni cilj istraživanja bio je odrediti vrstu operacije primarnog tumora (elektivne i hitne operacije) prije i za vrijeme COVID-19 pandemije. Dodatno smo uspoređivali broj i opće stanje bolesnika, dob, stadij bolesti, te izbor terapijskog liječenja. Od analiziranih 216 bolesnika, 103 bolesnika u razdoblju prije COVID-19 pandemije, te 113 bolesnika za vrijeme COVID-19 pandemije.

Hipoteza: 1.: Zbog COVID-19 pandemije smanjen je udio elektivnih kirurških operacija kolorektalnog karcinoma, a povećan udio hitnih kirurških operacija kolorektalnog karcinoma.

2. Zbog COVID-19 pandemije dijagnosticiran je veći broj bolesnika u višem stadiju bolesti za vrijeme COVID-19 pandemije.

Rezultati

U razdoblju prije COVID-19 pandemije dijagnosticirano je nešto manje oboljenja u žena, a više u muškaraca, nego za vrijeme COVID-19 pandemije (tablica 1). Prosječna dob bolesnika prije COVID-19 pandemije bila je 69,8 godina, a za vrijeme COVID-19 pandemije 69,1 godina. Većina bolesnika bilo je ECOG (Eastern Cooperative Oncology Group) statusa 0 i 1 (tablica 1). Nije bilo statistički značajne razlike u stadijima bolesti prije COVID-19 pandemije i za vrijeme COVID-19 pandemije (tablica 1). Podjednak je bio broj bolesnika koji nisu dobili kemoterapiju nakon operativnog zahvata, kao i broj bolesnika koji su liječeni kapecitabinom i Capeox protokolom (oksalipatina + kapecitabin) s bevacizumabom (tablica 1). Međutim, zabilježen je veći broj bolesnika koji je liječen Capeox protokolom za vrijeme COVID-19 pandemije u odnosu na vrijeme prije COVID-19 pandemije, ali nije bilo statistički značajne razlike. Isti broj bolesnika proveo je neoadjuvatnu kemoradioterapiju za lokalno uznapredovali karcinom rektuma prije COVID-19 pandemije i za vrijeme COVID-19 pandemije. Zabilježena je statistički značajna razlika u broju hitnih kirurških operacija u odnosu na elektivne kirurške zahvate za vrijeme COVID-19 pandemije u usporedbi s vremenom prije COVID-19 pandemije (slika 1, tablica 1).

Rasprava

Po incidenciji kolorektalnog karcinoma u Europskoj uniji, Republika Hrvatska nalazi se na 9. mjestu, dok se po smrtnosti od navedene bolesti nalazi na visokom drugom mjestu.⁵ Godišnje u Republici Hrvatskoj prosječno oboli oko 3600 osoba. Ako se kolorektalni karcinom otkrije u ranom, odnosno lokaliziranom stadiju, petogodišnje preživljenje iznosi oko 90%.⁵ Da bi se kolorektalni karcinom otkrio u što ranijem stadiju bolesti, odnosno polučio cilj Nacionalnog program za rano otkrivanje raka debelog crijeva, potreban odaziv na program bio bi 45%, a željeni 65% od pozvanih na testiranje.¹ Udio testiranih osoba u Republici Hrvatskoj iznosi svega 25%, te za sada nije dostatan za polučiti ciljeve Nacionalnog programa za smanjenje smrtnosti od ovog oblika karcinoma za 15% u razdoblju od 10 godina.¹ Pridržavajući se općih mjera prevencije, uz adekvatan odaziv na Nacionalni program, te slijedeći primjere zemalja sjeverne i zapadne Europe, bilo bi moguće smanjiti incidenciju i smrtnost od kolorektalnog karcinoma u Republici Hrvatskoj.⁵ Dobar primjer uspješnosti Nacionalnog programa za

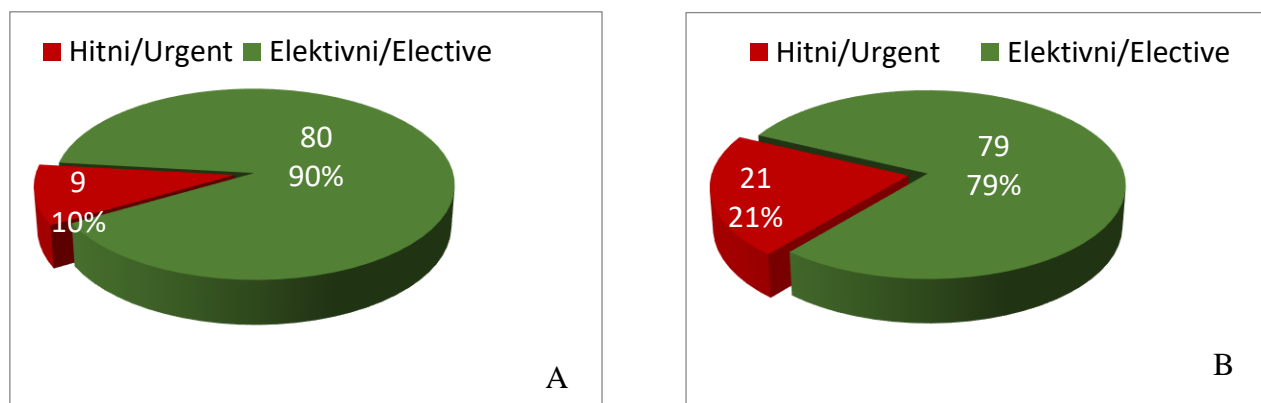
rano otkrivanje kolorektalnog karcinoma zabilježen je u Republici Sloveniji gdje je u posljednjih 5 godina postignuto smanjenje incidencije kolorektalnog karcinoma za 21%.⁶ Naime, po incidenciji kolorektalnog karcinoma u Europskoj uniji, Republika Slovenija nalazi se na visokom 6. mjestu, dok se po smrtnosti nalazi značajno ispod prosjeka Europske unije, što se tumači izvrsnim odazivom za pregled stolice na okultno krvarenje.^{6,7} Odaziv na preventivni Svit program (“Nacionalni program provjere i ranog otkrivanja prekancerozne promjene i raka debelog crijeva”) u Republici Sloveniji 2022. godine bio je 63.4%.⁸ Smatramo da je odaziv na Nacionalni program u Republici Hrvatskoj slab dijelom zbog neinformiranosti građana o važnosti preventivnih pregleda, kao i strahom od neugodnog kolonoskopskog pregleda. Stoga smo mišljenja da je potrebna dodatna medijska kampanja i dodatni angažman zdravstvenih djelatnika i stručnih društava radi osvješćivanja građana o važnosti obavljanja preventivnih pregleda i povećanja odaziva na Nacionalni program za rano otkrivanje raka debelog crijeva. Slijedeći primjer brojnih europskih i svjetskih organizacija, odlukom Vlade i Sabora Republike Hrvatske i naša se zemlja pridružila odluci da se mjesec ožujak posveti borbi protiv raka debelog crijeva.⁹ Funkcioniranje zdravstvenog sustava diljem svijeta, pa tako i programa ranog otkrivanja raka debelog crijeva, naišlo je na velike izazove pojavom pandemije koronavirusne bolesti.^{2,3,10}

Dosadašnja istraživanja pokazuju da je u vrijeme COVID-19 pandemije značajno smanjen odaziv na kontrolne i preventivne preglede u sklopu nacionalnih programa za rano otkrivanje raka.³ U Republici Hrvatskoj za vrijeme COVID-19 pandemije zabilježen je smanjen broj obavljenih kolonoskopija, kao i odaziv na program ranog otkrivanja raka debelog crijeva.³ Odbađanje ili otkazivanje preventivnih pregleda može dovesti do odgode liječenja i dijagnosticiranja zloćudne bolesti u višim stadijima bolesti.¹¹ U našem istraživanju uspjeli smo dokazati hipotezu da će u COVID-19 pandemiji biti povećan udio hitnih operacijskih zahvata u odnosu na elektivne, što se može povezati sa smanjenim brojem preventivnih pregleda u sekundarnim zdravstvenim ustanovama, odnosno smanjenim odazivom na program za rano otkrivanje raka debelog crijeva. Naši su rezultati u skladu rezultatima studije koju je objavio Jian Cui i njegovi suradnici. Oni su naime uspjeli dokazati da je postojao pad u broju elektivnih zahvata za vrijeme COVID-19 pandemije, a kao glavne razloge navode smanjenje broja fizikalnih pregleda, te odgađanje putovanja iz udaljenih mjesta u kliničke bolničke centre zbog COVID-19 pandemije.¹²

Tablica 1. Karakteristike bolesnika s novootkrivenim kolorektalnim rakom
 Table 1 Characteristics of patients with newly colorectal cancer

Karakteristika <i>Characteristics</i>	Prije COVID-19 pandemije N=103 <i>Prior to COVID-19 pandemic N=103</i>	ZA vrijeme COVID-19 pandemije N=113 <i>During the COVID-19 pandemic N=113</i>	P Vrijednost/ value
DOB/Age (godine/years)	69.8	69.1	
Spol /Gender			
Ž/F (%)	36 (35%)	53 (47%)	0.747
M	67 (65%)	60 (53%)	
Broj operiranih bolesnika <i>Number of operated patients</i>	89	100	
Broj hitnih operacija <i>Number of urgent operations</i>	9 (10%)	21 (21%)	0.014
Broj elektivnih operacija <i>Number of elective operations</i>	80 (90%)	79 (79%)	
ECOG status			
1	80 (77.6%)	74 (65.5%)	0.461
2	17 (16.6%)	24 (21.2%)	
3	4 (3.8%)	10 (8.8%)	
4	2 (2%)	5 (4.5%)	
Stadij bolesti <i>Stage of the disease</i>			
I	19 (18,4%)	15 (13,3%)	0.555
II	25 (24,3%)	33 (29,2%)	
III	32 (31%)	28 (24,8%)	
IV	27 (26,3%)	37 (32,7%)	
Terapija/therapy			
Kliničko praćenje (bez terapije) <i>clinical follow up (without therapy)</i>	37 (36%)	32 (28,3%)	0.539
Kapecitabin	21 (20,2%)	19 (16,8%)	
Capeox (oksalipatina+kapecitabin)	18 (17,5%)	30 (26,5%)	
Capeox+bevacizumab	14 (13,6%)	19 (17%)	
Neadjuvantna kemoradioterapija <i>chemoradiotherapy</i>	13 (12,7%)	13 (11,4%)	

ECOG, Eastern Cooperative Oncology Group



Slika 1. Raspodjela bolesnika prema vrsti operativnog zahvata:
 A) prije pandemije COVID-19, B) za vrijeme pandemije COVID-19
 Figure 1 Distribution of patients according to the type of surgical procedure:
 A) before COVID-19 pandemic B) during COVID-19 pandemic

U svom radu Feier i njegovi suradnici pretražujući literaturu navode podatke o značajno manjem broju elektivnih kirurških operacija kolorektalnog raka u vrijeme početka COVID-19 pandemije, što povezuju s karantenom, te preporukama o ograničavanju posjeta bolesnika bolnicama, kao i samom strahu bolesnika od zaraze koronavirusom.¹³ U diplomskom radu Antonije Muslim o utjecaju COVID-19 pandemije na kirurško liječenje kolorektalnog raka u Kliničkom bolničkom centru Split nije potvrđena hipoteza da će zbog COVID-19 pandemije u navadenoj ustanovi biti povećan udio hitnih operativnih zahvata u odnosu na elektivne.¹⁴ U svom zaključku, kao potencijalni razlog o statistički neznajčajnom smanjenju udjela elektivnih operacija tijekom pandemije, navode da bolesnici koji bi se inače odlučili na liječenje izvan svoga mjesta boravka, sada to, zbog ograničenog kretanja, nisu mogli učiniti.¹⁴ Drugi dio hipoteze o dijagnosticiranju većeg broja bolesnika u višem stadiju bolesti za vrijeme COVID-19 pandemije nismo uspjeli dokazati. Naši rezultati se razlikuju od rezultata koji su objavili Aguiar S i njegovi suradnici, koji su uspjeli dokazati da je statistički značajno više bolesnika klinički dijagnosticirano u uznapredovalijem stadiju bolesti (klinički T4 bolest – tumor zahvaća pridruženi organ ili peritoneum, klinički pozitivni limfni čvorovi, metastatska bolest) za vrijeme COVID-19 pandemije.¹⁵ Kao što je vidljivo iz tablice 1, većina naših bolesnika zahtjevala je primjenu kemoterapije, njih 63% prije COVID-19 pandemije, a 71,7% za vrijeme COVID-19 pandemije. Adjuvantna i palijativna kemoterapija u liječenju kolorektalnog karcinoma uvelike su poboljšali prognozu bolesnika s kolorektalnim karcinomom. Imunosupresivni učinci kemoterapije, pak, učinili su njihovu upotrebu tijekom COVID-19 pandemije kontroverznom.¹⁶ Većina preporuka za vrijeme COVID-19 pandemije bila je da se adjuvantna kemoterapija ne treba odgađati ili prekidati obzirom na važnost iste u cilju potpunog izlječenja.^{3,16} Intravenski oblik kemoterapije može se zamijeniti s jednako učinkovitim peroralnim pripravkom. Liječenje pojedinih stadija kolorektalnog karcinoma zahtijevaju hospitalizaciju ili ugradnju centralnog venskog katetera radi kontinuirane primjene kemoterapije kroz 46 sati. Kako Odjel za onkologiju i nuklearnu medicinu OB Zadar nema Odjel za stacionarnu djelatnost, te nismo u mogućnosti svim bolesnicima ugraditi centralni venski kateter, gotovo sve naše bolesnike koji su zahtijevali primjenu dvojne kemoterapije liječili smo kombinacijom oksaliplatine i kapecitabina (peroralni pripravak), a ne kombinacijom oksaliplatine i 5-fluorouracila (intravenski pripravak), što je za

vrijeme COVID-19 pandemije i bila preporuka ESMO-a.³

Zaključak

Odgadanje ili otkazivanje preventivnih pregleda može dovesti do odgode liječenja i dijagnosticiranja zloćudne bolesti u višim stadijima bolesti. Ovo istraživanje pokazalo je da je COVID-19 pandemija imala značajan utjecaj na vrstu operativnog zahvata, što se može povezati sa smanjenim brojem preventivnih pregleda u sekundarnim zdravstvenim ustanovama, odnosno smanjenim odazivom na program za rano otkrivanje raka debelog crijeva. Mišljenja smo da je potrebna dodatna medijska kampanja i dodatni angažman zdravstvenih djelatnika i stručnih društava radi osvješćivanja građana o važnosti obavljanja preventivnih pregleda i povećanja odaziva na Nacionalni program za rano otkrivanje raka debelog crijeva.

Literatura

1. HZJZ - Rano otkrivanje raka debelog crijeva. Datum pristupa: 2023.05.10. Dostupno na: <https://www.hzjz.hr/nacionalni-programi/rano-otkrivanje-raka-debelog-crijeva/>
2. Islam KU, Iqbal J. An update on molecular diagnostics for COVID-19. *Front Cell Infect Microbiol* 2020;10:560616.
3. Franjić D, Marijanović I. Prevencija i rano otkrivanje karcinoma debelog crijeva u vrijeme pandemije covid-19. *Zdravstveni glasnik*. 2020;6:96-104.
4. ESMO - management and treatment adapted recommendations in the COVID-19 era: Colorectal cancer. Datum pristupa: 2023.05.10. Dostupno na: <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gastrointestinal-cancers-colorectal-cancer-crc-in-the-covid-19-era>
5. Epidemiologija raka debelog crijeva u Hrvatskoj [Internet]. Zagreb: Hrvatski zavod za javno zdravstvo; 2023. [Pristupljeno 2023. travanj 9]. Dostupno na: <https://www.hzjz.hr/sluzba-epidemiologija-prevencija-nezaraznih-bolesti/epidemiologija-raka-debelog-crijeva-u-hrvatskoj/>
6. Mjesec svjesnosti o raku debelog crijeva [Internet]. Zagreb: Hrvatski zavod za javno zdravstvo; 2023. [Pristupljeno 2023. travanj 9]. Dostupno na: <https://www.hzjz.hr/aktualnosti/mjesec-svjesnosti-o-raku-debelog-crijeva/>
7. Colorectal cancer statistics [Internet]. London: World cancer research fund international; 2023. [Pristupljeno: 2023. svibanj 05]. Dostupno na: <https://www.wcrf.org/cancer-trends/colorectal-cancer-statistics/>
8. Letno poročilo o delovanju Programa Svit za obdobje od 1. 1. do 31. 12. 2022 [Internet]. Ljubljana:

- Nacionalni institut za javno zdravlje; 2023 [Pristupljeno 2023. svibanj 04.]. Dostupno na: <https://www.program-svit.si/wp-content/uploads/2023/03/Letno-porocilo-o-delovanju-Programa-Svit-za-obdobje-od-1.1.-do-31.12.2022.pdf>
9. Rano otkrivanje raka debelog crijeva [Internet]. Zagreb: Hrvatski zavod za javno zdravstvo; 2023. [Pristupljeno 2023. travanj 9]. Dostupno na: <https://www.hzjz.hr/nacionalni-programi/rano-otkrivanje-raka-debelog-crijeva/>
 10. Morris EJA, Goldacre R, Spata E. et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. *Lancet Gastroenterol Hepatol* 2021;6:199 – 208.
 11. Choi JY, Park IJ, Lee HG et al. Impact of the COVID-19 Pandemic on Surgical Treatment Patterns for Colorectal Cancer in a Tertiary Medical Facility in Korea. *Cancers (Basel)* 2021;13:2221.
 12. Cui J, Li Z, An Q, Xiao G. Impact of the COVID-19 pandemic on elective surgery for colorectal cancer. *J Gastrointest Cancer* 2023;53:403-409.
 13. Feier CVI, Bardan R, Muntean C, Olariu A, Olariu S. Impact of the COVID-19 Pandemic on the Elective Surgery for Colorectal Cancer: Lessons to Be Learned. *Medicina (Kaunas)* 2022;58:1322.
 14. Ana Muslim. Utjecaj COVID-19 pandemije na kirurško liječenje kolorektalnog karcinoma u Kliničkom bolničkom centru Split (diplomski rad). Medicinski fakultet, Sveučilište u Splitu. 2021.
 15. Aguiar S, Riechelmann RP, de Mello CAL et al. Impact of COVID-19 on colorectal cancer presentation. *Br J Surg* 2021;108:e81-e82.
 16. Xu Y, Huang ZH, Zheng CZ et al. The impact of COVID-19 pandemic on colorectal cancer patients: a single-center retrospective study. *BMC Gastroenterol* 2021;21:185.

Karcinom paratiroidne žlijezde – prikaz bolesnice

Parathyroid gland carcinoma – a case report

Ivan Vučković, Ivana Pajić Matić, Tomislav Stojadinović, Damir Sauerborn,
Karolina Veselski, Antonija Mišković, Josip Samardžić*

Sažetak

Uvod: S prevalencijom od 0,005% svih karcinoma, karcinom paratiroidne žlijezde jedna je od najrjeđih malignih bolesti koja zahvaća oko 1% bolesnika s primarnim hiperparatiroidizmom. Pojavljuje se sporadično ili u sklopu genetskog sindroma. Više od 90% karcinoma paratiroidne žlijezde su hormonski funkcionalni i dovode do hipersekrecije parathormona, što uzrokuje izrazitu hiperkalcijemiju. Zbog sličnih simptoma s benignim uzrocima hiperparatiroidoze otežano je preoperativno dijagnosticiranje karcinoma paratiroidne žlijezde. Ultrazvuk vrata i scintigrafija s Tc-99m MIBI mogu pomoći u lokalizaciji bolesti, dok se citopunkcija prije primarne operacije ne preporučuje. Primarni modalitet liječenja je potpuna kirurška resekcija s mikroskopski negativnim rubovima i nudi najbolju šansu za izlječenje. Do sada ne postoje dokazi o učinkovitosti kemoterapijskog ili radioterapijskog pristupa. U više od 50% bolesnika dolazi do razvoja recidiva bolesti, kada je ponovna kirurška resekcija najbolji način liječenja koje tada, rijetko kurativno, služi u svrhu ublažavanja metaboličkih poremećaja i komplikacija hiperkalcijemije koje su glavni uzrok letaliteta.

Prikaz bolesnice: Šezdesetogodišnja žena s nizom komorbiditeta upućena je od strane nefrologa sa sumnjom na adenom paratiroidne žlijezde. Po učinjenoj ultrazvučnoj i citološkoj obradi ekstirpira se desna donja paratiroidna žlijezda, te se patohistološkom analizom postavi dijagnoza karcinoma paratiroidne žlijezde, što posljedično indicira reoperaciju. Prije reoperacije učinjena je scintigrafija koja ukazuje na hiperfunkcijsko paratiroidno tkivo, te se u sklopu reoperacije učini desnostrana lobektomija štitnjače i ekstirpacija desne gornje uvećane paratiroidne žlijezde s disekcijom regije VI. Patohistološkom obradom izolira se uredno tkivo štitnjače, adenom paratiroidne žlijezde i jedan hormonski aktivni metastatski limfni čvor iz regije VI. Karcinom paratiroidne žlijezde je izrazito rijedak entitet koji zahtijeva operativnu intervenciju i cjeloživotno praćenje vrijednosti serumskog kalcija i parathormona. Kako bi se unaprijedilo i standardiziralo liječenje bolesnika s karcinomom paratiroidne žlijezde, potrebne su daljnje multicentrične studije.

Ključne riječi: karcinom, paratiroidna žlijezda, hiperparatiroidizam

Summary

Introduction: With a prevalence of 0.005% of all cancers, parathyroid carcinoma is one of the rarest malignancies affecting approximately 1% of patients with primary hyperparathyroidism. It can occur sporadically or as part of a genetic syndrome. More than 90% of parathyroid carcinomas are hormonally functional and lead to hyper secretion of parathyroid hormone, which causes marked hypercalcemia. Due to similar symptoms with benign causes of hyperparathyroidism, preoperative diagnosis of parathyroid gland cancer is difficult. Neck ultrasound and Tc-99m MIBI scintigraphy can help localize the disease,

* **Opća bolnica „Dr. Josip Benčević“ Slavonski Brod, Odjel za otorinolaringologiju** (Ivan Vučković, dr.med., izv.prof.dr.sc. Ivana Pajić Matić, dr.med.; Tomislav Stojadinović, dr.med.; dr.sc. Damir Sauerborn, dr.med.; Karolina Veselski, dr.med., Antonija Mišković, dr.med.) **Opća bolnica „Dr. Josip Benčević“ Slavonski Brod, Služba za kirurške djelatnosti, Odjel za abdominalnu i torakalnu kirurgiju** (doc.prim.dr.sc. Josip Samardžić, dr.med.)

Adresa za dopisivanje/ *Correspondence address:* Ivan Vučković, dr.med.; Opća bolnica „Dr. Josip Benčević“ Slavonski Brod, Odjel za otorinolaringologiju, Andrije Štampara 42, 35000 Slavonski Brod, Hrvatska E-mail: vucko.ivan@hotmail.com

Primljeno/Received 2022-08-30; Ispravljeno/Revised 2023-05-10; Prihvaćeno/Accepted 2023-07-17

while fine needle aspiration before primary surgery is not recommended. The primary treatment modality is complete surgical resection with microscopically negative margins and offers the best chance for recovery. So far, there is no evidence of the effectiveness of chemotherapy or radiotherapy. In more than 50% of cases the disease relapses and surgical resection is the best way of treatment, which is then rarely curative and serves the purpose of mitigating metabolic disorders and complications of hypercalcemia, which are the main cause of mortality.

Case report: A 60-year-old woman with a number of comorbidities was referred by a nephrologist with suspicion of parathyroid adenoma. After ultrasound and cytological processing, the right lower parathyroid gland was extirpated, and the pathohistological analysis established the diagnosis of carcinoma of the parathyroid gland, which consequently indicated reoperation. Before the reoperation, a scintigraphy was performed, which indicated hyperfunctioning parathyroid tissue, and as part of the reoperation, a right-sided thyroid lobectomy and extirpation of the right upper enlarged parathyroid gland with dissection of region VI were performed. Pathohistological processing isolated normal thyroid tissue, adenoma of the parathyroid gland and one hormonally active metastatic lymph node from region VI. Carcinoma of the parathyroid gland is an extremely rare entity that requires operative intervention and lifelong monitoring of serum calcium and PTH values. Further multicenter studies are needed to improve and standardize the treatment of patients with parathyroid carcinoma.

Key words: cancer, parathyroid gland, hyperparathyroidism

Med Jad 2023;53(3):213-218

Uvod

Karzinom paratiroidne žlijezde jedna je od najrjeđih malignih bolesti. Predstavlja manje od 0,005% svih karzinoma i manje od 1% paratiroidnih poremećaja.¹ Prvi put opisao ga je Quervain prije više od 100 godina, točnije 1909. godine, te je od tada u literaturi prijavljeno manje od 1000 slučajeva.² Većina karzinoma paratiroidne žlijezde pojavljuje se sporadično, iako se može susresti i u sklopu genetskog sindroma.³ Više od 90% karzinoma paratiroidne žlijezde su hormonski funkcionalni i dovode do hipersekrecije parathormona (PTH), što uzrokuje izrazitu hiperkalcijemiju. Nefunkcionalni ili nesekretirajući oblik karzinoma paratiroidne žlijezde je puno rjeđi, te je zbog izostanka specifičnih simptoma izuzetno teško postaviti dijagnozu u stadiju dok je još izlječiv. Godine 2017. Američki združeni odbor za karzinome izdao je 8. izdanje TNM klasifikacije u koje je uvršten i karzinom paratiroidne žlijezde. Zbog rijetkosti ove maligne bolesti ona i dalje nije univerzalno prihvaćena. Tijek bolesti karzinoma paratiroidne žlijezde je indolentan, ali progresivan.

Prikaz bolesnice

Šezdesetogodišnja žena s nizom komorbiditeta upućena je od strane nefrologa sa sumnjom na adenom paratiroidne žlijezde. Anamnestički se uočavaju dugogodišnje tegobe povezane s bubrezima, gušteračom i koštanim sustavom. Prije 40 godina liječena je zbog nefrolitijaze, a zadnjih 20 godina, po nefrologu kontrolirala je kroničnu bubrežnu insuficijenciju. U više navrata hospitalizirana je zbog liječenja kroničnog pankreatitisa, te donosi nalaze

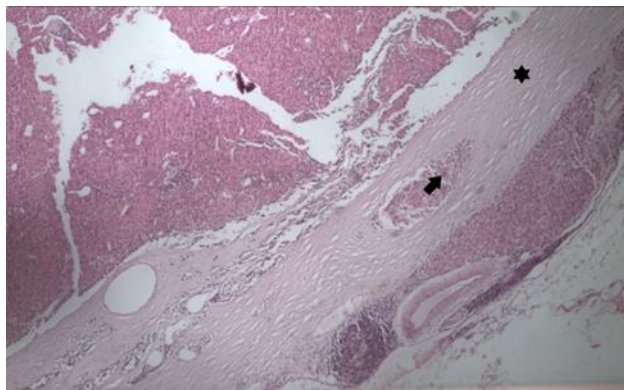
scintigrafije skeleta. Nalazi upućuju na promjene u sklopu renalne osteoartropatije. Zadnjih nekoliko godina zbog terminalnog stadija bubrežne insuficijencije provodi se liječenje hemodijalizom.

U osobnoj anamnezi ističe se operacija pseudociste gušterače, operacija desne dojke i provedena adjuvantna kemoterapija zbog adenokarcinoma.

Prije više od 10-ak godina operirala je adenom paratiroidne žlijezde u vanjskoj ustanovi, te donosi nalaze na kojima se jasno uočava da je operirana lijeva gornja paratiroidna žlijezda. Intraoperativni patohistološki nalaz govori u prilog adenoma paratiroidne žlijezde. Otpuštena je urednog nalaza kalcija, te je 6 mjeseci postoperativno učinjena scintigrafija štitnih žlijezda, koja je uredna, kao i nalaz serumskog kalcija.

Po postavljenoj sumnji na adenom paratiroidne žlijezde, učinjena je ultrazvučna (UZV) obrada na kojoj se uočava hipoehogena zona ispod srednje trećine desnog režnja štitnjače. Tvorba je punktirana, a citološki nalaz upućuje na tumor folikularne morfologije, neodređenog malignog potencijala, mogućeg porijekla paratiroidne žlijezde. Učinjena je i scintigrafija, gdje se uočavaju znakovi hiperfunkcijskog paratiroidnog tkiva u području srednje trećine desnog režnja štitnjače. Pregledom otorinolaringologa ne uoči se patologija u području glave i vrata koji je palpatorno bio bez osobitosti, pa se pristupi ekstirpaciji desne donje paratiroidne žlijezde u endotrahealnoj anesteziji. Tijekom hospitalizacije vrijednosti kalcija su unutar granica referentnih vrijednosti, što je rezultat redovitih hemodijaliza. Vrijednosti PTH izrazito su visoke, 2631.00 pg/ml, što je više od 40 puta više od gornje granice referentnih vrijednosti. Po odstranjenju

tumora, usprkos intraoperativnoj patohistološkoj potvrdi da se radi o traženoj paratiroidnoj žlijezdi, nije došlo do značajnijeg pada vrijednosti PTH (manje od 3% vrijednosti prije operacije). Patohistološkom obradom postavi se dijagnoza karcinoma paratiroidne žlijezde veličine 2×1,5cm, što indicira reoperaciju (Slika 1.).



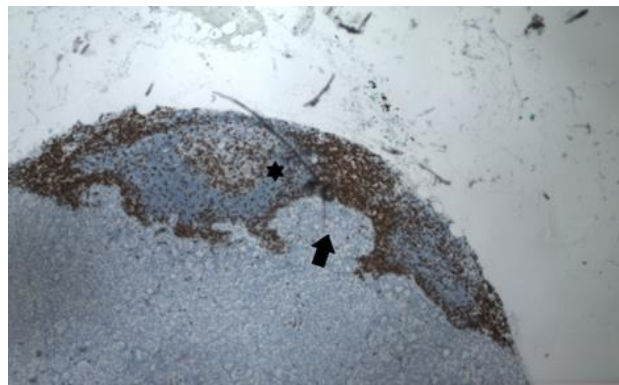
Slika 1. Karcinom paratiroidne žlijezde s debelom vezivnom kapsulom i suspektom invazijom krvne žile (HE staklo). Zvezdicom je označena kapsula, a strelicom invazija krvne žile.

Figure 1 Parathyroid gland carcinoma with a thick connective capsule and suspected blood vessel invasion (HE glass). The capsule is marked with an asterisk, and the invasion of a blood vessel with an arrow

U konzultaciji s onkologom, preoperativno se napravi scintigrafija paratiroidnih žlijezda s Tc-99m MIBI, uoči se postojanje hiperfunkcijskog paratiroidnog tkiva u projekciji donjeg pola desnog reznja štitnjače. U sklopu reoperacije učini se lobektomija desnog reznja štitnjače i istmektomija, ekstirpacija desne gornje paratiroidne žlijezde i disekcija vrata regije VI s eksploracijom vrata regija III i IV desno. Patohistološkom obradom potvrđeno je da je u sklopu reoperacije uklonjeno uredno tkivo štitnjače, adenom gornje paratiroidne žlijezde i jedan limfni čvor u regiji VI koji je zauzet tumorskim tkivom koje odgovara metastatskom karcinomu paratiroidne žlijezde (Slika 2.). U regijama vrata III i IV desno izolirano je 11 limfnih čvorova koji nisu infiltrirani tumorom. Nakon operacije zabilježen je pad vrijednosti PTH od 99,7% vrijednosti PTH prije operacije, na razinu koja je unutar referentnih vrijednosti, te autori smatraju da je za izrazito visoke vrijednosti PTH bila odgovorna hormonski aktivna metastaza u regiji VI koja se prikazivala na scintigrafiji kao hiperfunkcijsko paratiroidno tkivo.

U sklopu postoperativnih kontrola, četiri mjeseca nakon operacije, vrijednosti kalcija su ispod donje granice referentnih vrijednosti, kao i vrijednosti PTH, što možemo smatrati uspjehom. U daljnjem praćenju,

uz redovite kontrole serumskog kalcija i PTH, planirana je i scintigrafija paratiroidnih žlijezda.



Slika 2. Metastaza karcinoma paratiroidne žlijezde u limfni čvor (imunohistokemijskom analizom sa CD3 obojano je limfatično tkivo limfnog čvora). Zvezdicom je označen limfni čvor, a strelicom metastaza karcinoma.
Figure 2 Metastasis of parathyroid gland cancer to the lymph node (lymphatic tissue of the lymph node was stained by immunohistochemical analysis with CD3). An asterisk indicates a lymph node, and an arrow indicates cancer metastasis.

Rasprava

Karcinom paratiroidne žlijezde najčešće je sporadičan, ali može se javiti i u sklopu genetskog sindroma, najčešće sindroma hiperparatiroidizma s tumorom čeljusti (HPT-JT), gdje je incidencija karcinoma paratiroidne žlijezde čak 15%. Osim HPT-JT i sindrom multiple endokrine neoplazije (MEN) tip 1 i tip 2A, kao i izolirani obiteljski hiperparatiroidizam, povezani su s povećanom incidencijom karcinoma paratiroidne žlijezde.³ U podlozi sindroma HPT-JT, ali i u većini sporadičnih karcinoma, mutacije su u tumor supresorskom genu HRPT2, a koje se pojavljuju u više od 75% potvrđenih karcinoma paratiroidne žlijezde.⁴ Osim njega i tradicionalni regulatori staničnog ciklusa, npr. ciklin D1, retinoblastom, BRCA2, p53 i gen paratiroidne adenomatoze-1, mogu igrati ulogu u patogenezi karcinoma paratiroidne žlijezde.^{4,5,6} Karcinomi paratiroidne žlijezde javljaju se 10 godina ranije od tipične dobi za pojavu benignog oblika primarnog hiperparatiroidizma koji se javlja u 50-ima. Ne iskazuju spolnu preferenciju, što se razlikuje od benignih neoplazmi paratiroidne žlijezde, koje više pogađaju žene i to u omjeru 3-4:1 u odnosu na muškarce.⁷ Hormonski funkcionalni karcinomi paratiroidne žlijezde uzrokuju hipersekreciju PTH, što dovodi do hiperkalcijemije, pa su i simptomi vrlo slični onima u primarnom hiperparatiroidizmu. Najteže su pogođeni bubrezi, u

kojih dolazi do pojave nefrolitijaze i oštećene bubrežne funkcije, te kosti, gdje se osim čestih patoloških fraktura, javljaju i osteitis fibrosacystica, subperiostalna resorpcija i difuzna osteopenija. Ostali simptomi uključuju slabost, umor, anoreksiju, mučninu, povraćanje, gubitak težine, dispepsiju, zatvor, glavobolju, polidipsiju i poliuriju. U iznimnim slučajevima uzrokuje anemiju, rekurentni teški pankreatitis i peptički ulkus.⁷ Većinu tih simptoma imala je i naša opisana bolesnica, no svi ti klinički znakovi su nespecifični i ne upućuju na malignost paratiroidne žlijezde, pa se i dijagnoza postavlja relativno kasno, čak i kod dokazane hiperkalcijemije. Manje od 10% karcinoma paratiroidne žlijezde su nefunkcionalni, te se obično dijagnosticiraju u uznapredovalom stadiju sa simptomima kompresije ili invazije susjednih struktura, kada se očituju disfagijom, dispnejom, promuklošću ili samo tvorbom na vratu.⁸ U 7 - 46% bolesnika tijekom bolesti karcinoma paratiroidne žlijezde je potpuno asimptomatski.^{9,10}

Specifični tumorski markeri za karcinom paratiroidne žlijezde još nisu otkriveni, a zbog sličnih simptoma s benignim uzrocima hiperparatiroidoze otežano je preoperativno dijagnosticiranje karcinoma paratiroidne žlijezde. U bolesnika s karcinomom paratiroidne žlijezde povišene razine paratiroidnog hormona i kalcija su jače izražene. PTH je u karcinomima povišen više od četiri puta od gornje granice referentne vrijednosti. U opisane bolesnice je čak i 40 puta veći, dok je u adenomima vrijednost uglavnom između jedan i tri puta veća. Kalcij u adenomima paratiroidne žlijezde je uglavnom ispod vrijednosti od 13 mmol/L, za razliku od vrijednosti u karcinomu koja je redovito iznad 14 mmol/L. Simptomi bolesti u karcinomima redovito zahvaćaju više organskih sustava, češće su i hiperkalcijemijske krize, a bolesnici su mlađi, uglavnom u petom desetljeću života.^{11,12,13} U postavljanju dijagnoze važan je i fizički pregled, jer se palpabilna masa na vratu nalazi u 30-76% bolesnika s karcinomom paratiroidne žlijezde, za razliku od bolesnika s benignom bolešću, gdje je taj simptom prisutan u manje od 5% bolesnika.^{12,14} Slikovne metode mogu pomoći u lokalizaciji tumora, ali pouzdano razlikovanje benigne od maligne bolesti nije uvijek moguće. Tumori koji su ultrazvučno hipoeogeni, nehomogeni, s lobuliranim ili neograničenim rubovima, te u kojih je izražena intranodularna kalcifikacija, degenerativne promjene, s debelom kapsulom, sumnjivom vaskularnošću i lokalnom invazijom, moraju pobuditi sumnju na zloćudnost.^{15,16,17} U lokaliziranju tumora i praćenju rekurentne bolesti pomaže scintigrafija s Tc-99m MIBI, a kompjuterizirana tomografija (MSCT) i

nuklearna magnetska rezonancija (NMR) mogu pružiti informacije o eventualnoj invaziji u limfne čvorove, okolne strukture ili udaljene metastaze.^{18,19} U slučaju postojanja preoperativne sumnje na karcinom paratiroidne žlijezde ne preporučuje se citopunkcija zbog rupture kapsule i posljedično rizika od širenja tumora duž trakta igle, te većim rizikom od recidiva.¹⁹ Vrlo je teško razlikovati dobroćudne i zloćudne tumore paratiroidne žlijezde. Čak je 50% metastatskih karcinoma paratiroidne žlijezde u početku klasificirano kao benigni tumor.²⁰ Definitivni patognomonični markeri malignosti su kapsularna i vaskularna invazija, kao i recidivi tumora i udaljene metastaze.^{10,21}

Primarni modalitet liječenja karcinoma paratiroidne žlijezde je potpuna kirurška resekcija s mikroskopski negativnim rubovima, koja može biti ili en-block ili samo perikapsularna ekscizija zahvaćene paratiroidne žlijezde.²² Preporuka je definitivno en-block ekscizija koja se sastoji od resekcije tumora, ispilateralnog reznja štitne žlijezde i zahvaćenog okolnog mišićnog tkiva, a po potrebi i paratrahealnog limfnog tkiva i povratnog laringealnog živca, ukoliko je zahvaćen tumorom.²³ To podupire i podatak od 8% lokalnog recidiva nakon en-block resekcije, za razliku od 51% nakon standardne paratiroidektomije.²⁴ U opisane bolesnice autori su prvo pristupili lokalnoj perikapsularnoj eksciziji, a potom je u reoperaciji učinjena *en-block* resekcija, kao i disekcija regije VI, što je bila dobra odluka s obzirom na postojanje metastatskog limfnog čvora. S druge strane, retrospektivni podaci nisu pokazali benefit profilaktičkih disekcija limfnih čvorova središnjih regija vrata, pa se u bolesnika s klinički negativnim limfnim čvorovima mora pažljivo odvagati rizike operacije.²⁵ Čak 86% karcinoma paratiroidne žlijezde se ne prepozna u inicijalnoj obradi, te je zbog toga izričito važna preoperativna klinička sumnja ili intraoperativno prepoznavanje malignih značajki, kao npr. veličina tumora koji je uglavnom veći od 3cm, lokalna invazija tkiva i prisutnost suspektnih metastatskih limfnih čvorova.²⁶ U prvoj operaciji opisane bolesnice tumor paratiroidne žlijezde bio je veličine 2×1,5cm, te nije bilo drugih malignih značajki, što se uklapa u podatak da je neočekivana postoperativna dijagnoza karcinoma najčešći scenarij i objašnjava samo 12% *en block* resekcija u prvotnoj operaciji.²⁷ Intraoperativno mjerenje PTH je korisna praksa u dokazivanju uklanjanja hiperfunkcionalnog paratiroidnog tkiva, dok intraoperativnim smrznutim presjecima tkiva nije moguće diferencirati adenom od karcinoma.²⁷ Autori su mjerili intraoperativne vrijednosti PTH koje su se u reoperaciji uistinu snizile za značajan udio. Iako postoje izolirani slučajevi, u kojima je bilo uspjeha,

u liječenju karcinoma paratiroidne žlijezde adjuvantnom kemoterapijom ili radioterapijom ne postoje standardizirani protokoli za takve pristupe liječenju.^{10,28,29} Opisana bolesnica trenutno je četiri mjeseca nakon operacije bez znakova recidiva i redovno kontrolira vrijednosti kalcija i PTH, uz kontrolne preglede od strane onkologa i otorinolaringologa. U više od 50% bolesnika dolazi do razvoja recidiva bolesti koji se može pojaviti nakon dvije, pa sve do 23 godine nakon resekcije. Većinom su to regionalne metastaze koje u vrijeme postavljanja dijagnoze nisu uobičajene, kao ni udaljene metastaze koje se u postoperativnom praćenju javljaju u 25% bolesnika.^{26,30} Najčešća sjela udaljenih metastaza su pluća, kosti i jetra, a kirurška resekcija recidiva i udaljenih metastaza, koliko je to moguće, najbolji je izbor liječenja. Time se povećava dugoročno preživljenje i do 30%, ali je rijetko kurativno.^{20,31} Glavni uzrok morbiditeta i letaliteta su metabolički poremećaji i komplikacije hiperkalcijemije, koji se pokušavaju kontrolirati infuzijama fiziološke otopine i diureticima, zatim bisfosfonatima, mitramicinom, kalcitoninom i galijevim nitratom koji sprječavaju resorpciju kosti, te kalcimimeticima, WR2721 i oktreetidom koji sprječavaju lučenje PTH.¹²

Proгноza nefunkcionalnog karcinoma paratiroidne žlijezde je lošija jer se često dijagnosticira u uznapredovalim stadijima, a smrt je primarno posljedica regionalne bolesti i udaljenih metastaza. U funkcionalnih karcinoma obično je posljedica zatajenje bubrega, pankreatitisa ili srčanih aritmija koje su posljedica nekontrolirane hiperkalcijemije.^{30,32} Rano prepoznavanje i potpuna resekcija u inicijalnoj operaciji ključni su za najbolju moguću prognozu. Petogodišnje stope preživljenja variraju od 40-86%, dok je desetogodišnje preživljenje 49-77%.^{1,21,26,30,31} Po završenom kirurškom liječenju karcinoma, periodične kontrole s određivanjem kalcija u serumu su izričito važne. Ukoliko dođe do porasta vrijednosti serumskog kalcija i povišenja razine PTH, mora se posumnjati na recidiv. U dijagnosticiranju točnog mjesta recidiva pomaže scintigrafija s Tc99m MIBI, UZV, NMR ili MSCT vrata, ali i prsnog koša, radi otkrivanja plućnih metastaza. U slučaju dijagnoze nasljednog oblika karcinoma paratiroidne žlijezde, u obzir dolazi i genetsko testiranje bližih srodnika. U bolesnika s poznatim mutacijama HRPT2, osim rutinskog, laboratorijskog nadziranja razine kalcija, PTH i vitamina D, preporučuje se i povremeni UZV vrata radi otkrivanja nefunkcionalnog karcinoma paratiroidne žlijezde, kao i ortopantomogram svakih pet godina, radi otkrivanja tumora čeljusti.³¹ Autori smatraju da je genetsko testiranje bolesnice, a po

potrebi i bližih srodnika, korak koji još uvijek nije poduzet, ali se može uzeti u razmatranje u daljnjem liječenju opisane bolesnice.

Karcinom paratiroidne žlijezde izrazito je rijedak entitet na koji treba posumnjati u hiperparatiroidizmu s teškom hiperkalcijemijom, velikom cervikalnom masom, te popratnom bubrežnom i koštanom bolesti. Takva dijagnoza zahtijeva operativnu intervenciju i cjeloživotno praćenje vrijednosti serumskog kalcija i PTH. Osim postavljanja sumnje preoperativno, bitna je i edukacija operatera da intraoperativno prepozna karcinom paratiroidne žlijezde. To će mu omogućiti izvođenje odgovarajuće *en block* resekcije ključne za bolesnika s malignom bolešću. S obzirom na rijetkost bolesti, potrebne su daljnje multicentrične studije, kako bi se unaprijedilo i standardiziralo liječenje bolesnika s karcinomom paratiroidne žlijezde.

Literatura

1. Lee PK, Jarosek SL, Virnig BA, et al: Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer* 2007;109:1736-1741
2. Givi B, Shah JP: Parathyroid carcinoma. *Clin Oncol (R Coll Radiol)* 2010;22:498-507
3. Sharretts JM, Simonds WF: Clinical and molecular genetics of parathyroid neoplasms. *Best Pract Res Clin Endocrinol Metab* 2010;24:491-502
4. Shattuck TM, Välimäki S, Obara T, et al: Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. *N Engl J Med* 2003;349:1722-1729
5. Gao WC, Ruan CP, Zhang JC, et al: Nonfunctional parathyroid carcinoma. *J Cancer Res Clin Oncol* 2010;136:969-974
6. Fingeret AL: Contemporary Evaluation and Management of Parathyroid Carcinoma. *JCO Oncology Practice* 2021;17:1, 17-21
7. Marcocci C, et al. Parathyroid carcinoma. *J Bone Miner Res.* 2008;23(12):1869-80.
8. Fernandez-Ranvier GG, Jensen K, Khanafshar E, Quivey JM, Glastonbury C, Kebebew E, Duh QY, Clark OH. Nonfunctioning parathyroid carcinoma: Case report and review of literature. *Endocr Pract.* 2007;13:750-757.
9. Sharretts JM, Kebebew E, Simonds WF. Parathyroid cancer. *Semin Oncol.* 2010;37(6):580-90.
10. Busaidy NL, Jimenez C, Habra MA, et al: Parathyroid carcinoma: A 22-year experience. *Head Neck* 2004;26:716-726
11. Levin KE, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. *Surgery* 1987;101:649-660
12. Shane E. Clinica lreview 122: Parathyroid carcinoma. *J Clin Endocrinol Metab* 2001;86:485-493
13. Kebebew E. Parathyroid carcinoma. *Curr Treat Options Oncol* 2001;2:347-354

14. Mittendorf EA, McHenry CR. Parathyroid carcinoma. *Journal of Surgical Oncology*. 2005;89:136-142
15. Kwon JH, et al. Neck ultrasonography as preoperative localization of primary hyperparathyroidism with an additional role of detecting thyroid malignancy. *Eur J Radiol*. 2013;82(1):e17–21.
16. Hara H, et al. Ultrasonographic features of parathyroid carcinoma. *Endocr J*. 2001;48(2):213–7.
17. Nam M, Jeong HS, Shin JH. Differentiation of parathyroid carcinoma and adenoma by preoperative ultrasonography. *Acta Radiol*. 2017;58(6):670–5.
18. Duan K, Mete O, Carcinoma P. Diagnosis and clinical implications. *Turk Patoloji Derg*. 2015;31(Suppl 1):80–97.
19. Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. *Curr Treat Options in Oncol*. 2012;13(1):11–23.
20. Sandelin K, Tullgren O, Farnebo LO. Clinical course of metastatic parathyroid cancer. *World J Surg*. 1994;18(4):594–8; discussion 599.
21. Bondenson L, Grimelius L, DeLellis RA, Lloyd R, Akerstrom G, Larsson C, Arnold A, Eng C, Shane E, Bilezikian JP. Parathyroid carcinoma. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. *Pathology and genetics of tumours of endocrine organs*. WHO Classification of Tumours. Lyon, France: IARC Press; 2004. p. 124–127.
22. Schulte KM, et al. Classification of parathyroid cancer. *Ann Surg Oncol*. 2012;19(8):2620–8.
23. Clayman GL, et al. Parathyroid carcinoma: evaluation and interdisciplinary management. *Cancer*. 2004;100(5):900–5.
24. Koea JB, Shaw JH. Parathyroid cancer: biology and management. *Surg Oncol*. 1999;8(3):155–65.
25. Hsu KT, Sippel RS, Chen H, Schneider DF. Is central lymph node dissection necessary for parathyroid carcinoma? *Surgery* 2014;156(6), 1336–1341
26. Hundahl SA, Fleming ID, Fremgen AM, et al. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*. 1999;86(3):378-80
27. Adam MA, Untch BR, Olson JA. Parathyroid carcinoma: current understanding and new insights into gene expression and intraoperative parathyroid hormone kinetics. *Oncologist* 2010;15(1), 61–72
28. Bukowski RM, Sheeler L, Cunningham J, et al. Successful combination chemotherapy for metastatic parathyroid carcinoma. *Arch Intern Med* 1984;144:399-400
29. Munson ND, Foote RL, Northcutt RC, et al. Parathyroid carcinoma: Is there a role for adjuvant radiation therapy? *Cancer* 2003;98:2378-2384
30. Harari A, Waring A, Fernandez-Ranvier G, et al. Parathyroid carcinoma: A 43-year outcome and survival analysis. *J Clin Endocrinol Metab* 2011;96:3679-3686
31. Sandelin K, Auer G, Bondeson L, et al: Prognostic factors in parathyroid cancer: A review of 95 cases. *World J Surg* 1992;16:724-731
32. Aldinger KA, et al. Parathyroid carcinoma: a clinical study of seven cases of functioning and two cases of nonfunctioning parathyroid cancer. *Cancer*. 1982;49(2):388–97.

Locally aggressive giant basal cell carcinoma of the head with focus on surgical treatment– a case report

Lokalnoagresivni gigantski bazocelularni karcinom vlasišta s posebnim osvrtom na kirurško liječenje – prikaz slučaja

Fatima Juković-Bihorac, Hakija Bečulić, Emir Begagić, Rasim Skomorac*

Summary

Introduction: Basal cell carcinoma is the most common non melanoma skin cancer. It accounts for approximately 80% of all skin cancers.

Case report: We presented a 62-year-old patient with a giant, deeply infiltrative, destructive lesion of the head which lasted for 15 years. Microbiological analysis showed contamination, computed tomography (CT) scan showed deep infiltration and bone destruction. The risks of operative treatment were numerous. The treatment was more complicated by infection, infiltrative spreading and the patient's comorbidity. Regardless, we decided on a wide surgical resection with pathohistological evaluation of the resection margins. The patient denied oncological treatment. After 10 years, there were no recurrent tumours.

Conclusion: Aggressive surgical treatment is the treatment of choice for giant basal cell carcinoma. In the case of giant locally aggressive and advanced neoplasms, when surgery is not appropriate or not possible, medical treatment becomes oncological.

Key words: non melanoma skin cancer, basal cell carcinoma, giant skin carcinoma

Sažetak

Uvod: Bazalno-stanični karcinom je najčešći nemelanomski maligni tumor kože. U prosjeku čini 80% svih malignih kožnih tumora.

Prikaz slučaja: Predstavljamo bolesnika u dobi od 62 godine, s gigantskom, dubokoinfiltrativnom, destruktivnom lezijom glave, koja je trajala 15 godina. Mikrobiološke analize pokazale su infekciju, a CT nalaz duboku infiltraciju i destrukciju kosti. Rizici operativnog tretmana bili su brojni. Tretman je dodatno bio kompliciran infekcijom, dubokom infiltracijom i komorbiditetima bolesnika. Odlučili smo se na široku kiruršku resekciju s patohistološkom evaluacijom resekcionih margina. Bolesnik je odbio onkološko liječenje. Nakon 10 godina recidiva tumora nije bilo.

Zaključak: Kirurški tretman je tretman izbora gigantskih, bazalno-staničnih karcinoma. U slučaju neoperabilnih gigantskih, lokalnoagresivnih i uznapredovalih bazalno-staničnih karcinoma, tretman izbora je onkološka terapija.

Ključne riječi: nemelanomski maligni tumor kože, bazocelularni karcinom, gigantski karcinom kože

Med Jad 2023;53(3):219-224

* **Cantonal Hospital Zenica, Department of Pathology, Zenica, Bosnia and Herzegovina** (Fatima Juković-Bihorac, MD); **Cantonal Hospital Zenica, Department of Neurosurgery, Zenica, Bosnia and Herzegovina** (PhD Hakija Bečulić, MD; PhD Rasim Skomorac, MD);

University of Zenica, Medical Faculty, Department of General Medicine (Emir Begagić)

Correspondence address/ *Adresa za dopisivanje:* Fatima Juković-Bihorac, MD, Cantonal hospital Zenica, Department of pathology, Crkvice 67, 72000 Zenica, Bosnia and Herzegovina E-mail: fatima.bihorac@live.com

Received/*Prilježeno* 2022-10-29; Revised/*Ispravljeno* 2023-06-21; Accepted/*Prihvaćeno* 2023-08-17

Introduction

There are 2 main types of skin malignancies: melanoma and nonmelanoma skin cancer. Non melanoma skin cancer includes basal cell skin cancer, squamous cell skin cancer and other rare types.¹ Basal cell carcinoma (BCC) is the most common nonmelanoma skin cancer. The incidence of basal cell carcinoma is increasing. It is accounting approximately 80% of all skin cancers.¹ This tumor is most associated with UV radiation. Solar UVB radiation generally is considered to be the most important risk factor for the development of BCC. The other risk factors are light skin color, red or blonde hair color, and a family history of melanoma or sunburn reactions.²

The tumor is slow growing but invasive and locally aggressive. Its metastases are very rare and have been reported in between 0.0028 and 0.55 of all BCC cases.^{1,3} BCC is classified into several basic types of which it is the most common nodular, superficial, nodulocystic, morpheic, metatypical, pigmented, and ulcerative.⁴

Nodular and superficial type of BCC have a low risk for local recurrences, but morpheic, infiltrating and metatypical type are very destructive and with higher recurrence rate. That division of BCC is of big clinical importance.⁵

Giant basal cell carcinoma (GBCC) is a BCC which is larger than 5cm in diameter. The occurrence rate of GBCC is approximately 0.5–1% out of all BCC types.⁶ Most often BCC are small tumors, mostly localized in the head and neck region.⁷

In the treatment of giant locally aggressive and advanced neoplasms, metastatic or recurrent, when surgery is not appropriate or not possible, medical treatment becomes oncological. The most common treatment is oral hedgehog pathway and check point inhibitors.⁸

There are two ways of hedgehog pathway treatment, which are approved by FDA.^{8,9} Vismodegib is the first hedgehog inhibitor approved by the FDA in 2012. An objective response rate (ORR) was 47.6% for locally advanced BCC and 30% for metastatic BCC at 12 months.^{9,10} Sonidegib is the second oral HHI for the treatment of BCC, approved by the FDA in 2015. It is indicated for the treatment of locally advanced BCC that has recurred after surgery or radiation treatment or for the patients who are not candidates for surgery or radiation therapy. The research revealed an ORR of 56.1% with a median duration of response of 26.1 months and in 93.2% a 2-year survival rate for locally advanced BCC. An ORR of 7.7% was reported for metastatic BCC.¹¹

Immunotherapy of the advanced, non-melanoma skin cancer is gaining importance, because their high mutational burden index is high (MBI). Two anti-PD-1 antibodies, cemiplimab and pembrolizumab are approved.¹²

PD-1 inhibitors produce persistent effects, with improved survival. Patients are capable to stop with therapy while they have benefits from treatment. PD-1 inhibitor therapy is well tolerated and safe among patients specifically with comorbidity.¹³

Several case reports with anti-PD-1 agents¹⁴⁻¹⁶ and anti-CTLA-4 therapy¹⁶ revealed good responses in advanced disease. Seven patients received pembrolizumab plus vismodegib and nine patients received only pembrolizumab.¹⁷ The ORRs were 44% and 29% at 18 weeks, respectively. The authors concluded that combination therapy is not much better than monotherapy. The usage of pembrolizumab has been registered in 5 case reports more with complete or partial responses.¹⁴⁻¹⁷

We present the case of locally aggressive and deep penetrating, extremely big basal cell carcinoma, located in the hairy part of head. The treatment options of such highly risked tumors must be carefully considered.

Case report

The Ethics Committee of the Zenica Cantonal Hospital allowed the data used in this case report and the patient gave us informed consent for the data and figures we used in this article also.

A 62-year-old patient arrived by car of the Emergency Medical Service to the Department of Emergency Medical Assistance (UB). On admission to UB he was somnolent, disoriented in time, space and towards persons, gave no answers to questions, could not perform more complicated requests, without pronounced lateralization in neurological findings, febrile (TT 39° C), eupnoic, normotensive, tachycardic (f 100/min). We obtained heteroanamnestic data that the patient had had a "head wound" for 15 years, which was bleeding occasionally. He bandaged the wound and hid it with a scarf. He had not consulted a doctor about this problem earlier.

He has been a diabetic on insulin therapy for many years. In the local finding we found a large ulcerated, deeply infiltrated tumor of the head, about 11cm in diameter, with purulent contents at the bottom, necrotic and gangrenous edges (Figure 1).

At the UB, we cleaned and bandaged the tumor, took wound swabs and made a computed tomography (CT) scan of the head. CT showed extensive and deeply infiltrative lesion that destroys the bone

(Figure 2).



Figure 1 Preoperative image of the extensive and ulcerative BCC of the scalp (Department of Neurosurgery Zenica Cantonal Hospital)

Slika 1. Preoperativna slika ekstenzivnog i ulcerativnog BCC vlasišta (Odjel Neurokirurgije Kantonalne bolnice Zenica)

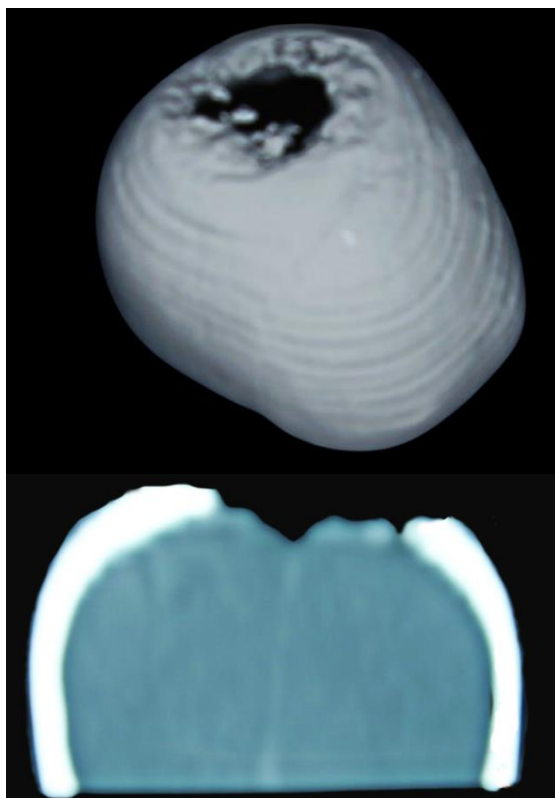


Figure 2 CT scan of the head (bone window) (Department of Neurosurgery Zenica Cantonal Hospital)

Slika 2. CT snimak glave (prozorakost) (Odjel Neurokirurgije Kantonalne bolnice Zenica)

After receiving adequate primary care and diagnostic processing at the UB, we transferred the patient to the Intensive Care Unit (ICU).

At the ICU, we connected the patient to vital functions monitoring and observed him intensively. In the laboratory findings, we found hypocalcemia, hypochromic anemia, metabolic ketoacidosis, and the level of glucose in the blood was from 8.5 to 12.5. Microbiological analysis of the wound swab showed contamination with *Staphylococcus aureus*. During the stay at the ICU, we prescribed appropriate antibiotic therapy, according to the antibiogram, and appropriate symptomatic therapy.

After the patient was stabilized, we started the surgery procedure. Following an appropriate positioning of the head, washing and limiting the operative field, we excised the tumor-infiltrated part of the skin. Then we osteoclastically removed the tumor-affected and severely softened bone down to the healthy tissue. We gradually removed the upper layer of the dura mater, which was also thickened and infiltrated by the tumor. After that, we opened the dura mater parasagittally on the left and allowed the spontaneous release of copious purulent content from the subdural space. We additionally washed it with saline and antibiotic solution. After establishing adequate hemostasis, we closed the defect with local transpositional flaps taken from the frontal and occipital regions. We covered the donor defect in that area with epidermal grafts according to Tirsch, which we took from the back of the left upper leg and lower leg. We did not reconstruct the calvaria and dura.

Postoperatively, we referred the patient to the ICU for postoperative treatment. In the further course, the flaps were without local signs of necrosis, as well as the epidermal graft. The patient was vitally stable, subjectively felt well. On the second day postoperatively, he was conscious, oriented, communicative, afebrile, eupnoic and the wounds were properly healed.

On the pathohistological examination we got the diagnosis of a giant basal cell carcinoma – metatypical type, with keratin pearls and infiltrative peripheral border. Locally aggressive, deeply infiltrated, ulcerated mass, resected in its entirety with clear resection margin at the end (Figure 3A-C). Separately delivered dura and bone were tumor-infiltrated with free resection margins at a distance of 5 mm at least.

After 15 days, the patient was discharged from the hospital to home treatment and care. About 30 days after the operation, the patient was ordered for a follow-up examination. During the control examination, the patient was in a normal state of consciousness and neurological findings. In the local findings there were no signs of infection and necrosis (Figure 4).

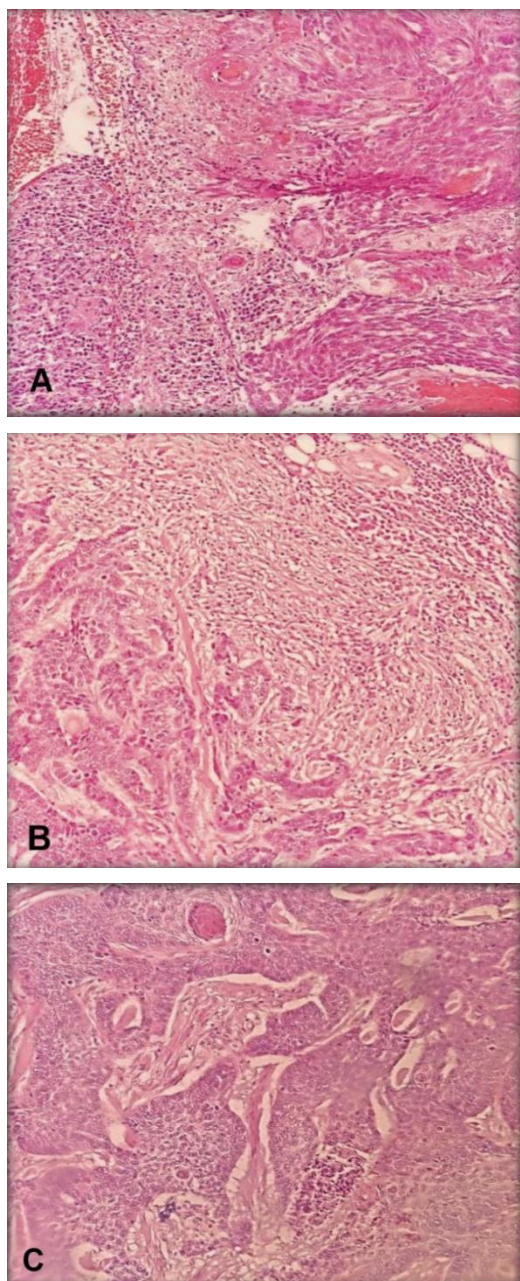


Figure 3 This picture of a giant basal cell carcinoma demonstrating A) ulcerated surface, B) invasion of the fat by highly infiltrated trabeculae of basaloid cells, with the absence of peripheral palisading (C) and the area of squamous differentiation. Note the formation of keratin pearls (C) (H&E, original magnification $\times 20$)

(Department of Pathology Zenica Cantonal Hospital)
 Slika 3. Slika gigantskog bazocelularnog carcinoma koji pokazuje: A) ulceriranu površinu, B) invaziju masnog tkiva visoko infiltrativnim tračcima bazaloidnih stanica, bez izražene neperiferne palisadizacije C) aree skvamozne diferencijacije i keratinske perle (HE, $\times 20$) (Odjel patologije Kantonalne bolnice Zenica)

The patient was recommended further treatment. But, due to his good physical condition, the patient refused oncological treatment. The locoregional status was satisfactory. Ten years after discovering

the BCC lesion, the patient died due to a heart attack.



Figure 4 Appearance of the patient 30 days after the operation (Department of Neurosurgery Zenica Cantonal Hospital)

Slika 4. Izgled pacijenta 30 dana nakon operacije (Odjel Neurokirurgije Kantonalne bolnice Zenica)

Discussion

Typical BCC lesions are small tumors with indolent behavior, located mostly at the skin which is exposed to the sun and UV light.²

The treatment of the BCC depends on the tumor characteristics which are based on their prognostic factors. The most important prognostic factors are size, site, tumor subtype, status of resection margins and prior treatment. In that regard, BCC are categorized in low and high risk tumor.¹⁸

The worst impact on tumor prognosis has large, long-standing lesions, infiltrating, morpheic or metatypical pathohistological subtype with an aggressive way of growth in the deeper lesion layers. Also, on the choice of treatments, a great influence is the medical condition of the patient, coexisting disease, and current medication. In addition, experience and the ability of the physician are undoubtedly significant.¹⁸

The treatment of these large-dimensional tumors could be surgical and non-surgical. Surgical treatments are surgical resection, Mohs micrographic resection, radiotherapy and chemotherapy in unresectable tumors.^{18,19}

Tumors located in the head area, especially large tumors, are in themselves classified as high-risk tumors²⁰. High risk tumors require a more careful approach, primarily due to the volume and severity of the resection, but also the completeness of the excision. An aggressive surgical resection with tumor-free resection margins offers the best results and healing. The cure rates are averaging from 90% to 91%.²⁰

In one study, the age of the patient, duration of the lesion and duration of the treatment were not significantly connected with the increased risk of relapse.²¹

Our patient arrived in our hospital's intensive care unit in a serious condition, with deep, infiltrative lesion on the head which had lasted for the last 15 years. The case was complicated by staphylococcal infection of the tumor surface in subdural space, and tumor infiltration of the dura of the upper sagittal sinus.

The risks of operative treatment were reflected in the possibility of intraoperative damage and thrombosis of the upper sagittal sinus, sepsis, damage of intracranial structures, liquefaction and postoperative necrosis of transplanted skin flaps. The case was more difficult due to the insulin-dependent diabetes.

There was a risk of closing the resulting defect with a skin flap due to the possibility of its infection and necrosis. Usually, the flaps are not applied to the infected substrate immediately but after a few days, when there is certainty that the infection has been cured.²² Wide excision of GBCC of the head and neck can consequently have large complex of soft tissue and bone defects and even in brain exposure. How the defect will be reconstructed depends on the extent of the defect. The large and complex defect in the head and neck area can be properly covered by the selection of free, regional, or local flaps.²³ Nevertheless, after extensive removal of the tumor mass, removal of necrotic tissue and washing of the subdural space with an antibiotic solution, we decided to close the defect. The reason for such a decision was the general poor condition of the patient, the possibility of superinfection in an open wound with a more resistant strain, its spread towards the intracranial space, cerebrospinal fluid (CSF) and good blood circulation in the head. Our procedure, considering the postoperative course and rapid recovery of the patient, proved to be justified. After

10 years, there were no recurrent tumors and patient died due to a heart attack.

Metastatic BCC is very rare. It has been described in bone, lungs and axillary lymph nodes.^{24,25} In the case of BCC with pulmonary metastasis, after surgery, sonidegib, a hedgehog signaling inhibitor, was used as a first-line treatment and cemiplimab in the second act.²⁴

In the treatment of giant locally aggressive and advanced neoplasms, metastatic or recurrent after surgery treatment and radiotherapy, then in case surgery is not appropriate or not possible, medical treatment becomes just oncological. The most common treatment is oral hedgehog pathway and check point inhibitors.⁸

Further investigation of immunotherapy, especially of PD-1inhibitors is needed to define its optimal role for patients with this disease.

References

1. Mehta KS, Mahajan VK, Chauhan PS, et al. Metastatic Basal cell carcinoma: a biological continuum of Basal cell carcinoma?. *Case Rep Dermatol Med*. 2012;2012:157187.
2. Mott SE, Hunter WJ, Silva E, Huerter CJ. Approach to management of giant basal cell carcinomas. *Cutis*. 2017;99:356-362.
3. Seo SH, Shim WH, Shin DH, Kim YS, Sung HW. Pulmonary metastasis of Basal cell carcinoma. *Ann Dermatol*. 2011;23:213-216.
4. McKee PH, Calonje J, Lazar A, et al, eds. *Pathology of the Skin with Clinical Correlations*. 4th ed. Vol 2. Philadelphia, PA: Elsevier Mosby; 2011.
5. Elder DE. Basal cell carcinoma. In: Elder DE, Elenitsas R, Johnson Jr BL, et al, eds. *Lever's Histopathology of the Skin*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009;826-832.
6. Cantisani C., Rossi R., Nisticò SP. et al. Management of patients with giant basal cell carcinoma during SARS COV2 outbreak in Italy. *Transl Biophotonics* 2022;\$.e20200009.
7. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353:2262-2269.
8. Ahmed M, Muradashvili T, Soliman S, Ghaly M. Metastatic insidious super giant basal cell carcinoma. *BMJ Case Reports CP* 2022;15:e249873.
9. Sekulic A, Migden MR, Basset-Seguín N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer*. 2017;17:332.
10. Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol* 2015;72:1021-1026.
11. Lear JT, Migden MR, Lewis KD, et al. Long-term

- efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol* 2018;32:372–81
12. Ascierto PA, Schadendorf D. Update in the treatment of non-melanoma skin cancers: the use of PD-1 inhibitors in basal cell carcinoma and cutaneous squamous-cell carcinoma. *J Immunother Cancer* 2022;10:e005082.
 13. In GK, Nallagangula A, Choi JS, et al. Clinical activity of PD-1 inhibition in the treatment of locally advanced or metastatic basal cell carcinoma. *J Immunother Cancer* 2022;10:e004839.
 14. Ikeda S, Goodman AM, Cohen PR. Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy. *NPJ Genom Med* 2016;1:16037.
 15. Lipson EJ, Lilo MT, Ogurtsova A. et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. *J Immunother Cancer* 2017;5:23.
 16. Cannon JGD, Russell JS, Kim J, Chang ALS. A case of metastatic basal cell carcinoma treated with continuous PD-1 inhibitor exposure even after subsequent initiation of radiotherapy and surgery. *JAAD Case Rep* 2018;4:248–50.
 17. Chang ALS, Tran DC, Cannon JGD, et al. Pembrolizumab for advanced basal cell carcinoma: an investigator-initiated, proof of-concept study. *J Am Acad Dermatol* 2019;80:564–6.
 18. Telfer NR, Colver GB, Morton CA; British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008;159:35-48.
 19. Peris K, Fargnoli MC, Garbe C. et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. *Eur J Cancer* 2019;118:10-34.
 20. Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. *Arch Dermatol* 1983;119:373-377.
 21. Silverman MK, Kopf AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol* 1992;18:471-476.
 22. Faruk Konjihodžić: Udžbenik hirurgije, Sarajevo: NIR, 2001; 335-6.
 23. Arslan H, Güzel MZ, Cnar C. Treatment of giant basal cell carcinomas of the head and neck with aggressive resection and complex reconstruction. *J Caniofac Surg* 2012;23: 1634–1637.
 24. Fordham SA, Shao EX, Banney L, Azer M, Dettrick A. Management of basal cell carcinoma with pulmonary metastasis. *BMJ Case Rep* 2023;16:e251700.
 25. Li R, Lee G, Huang M, El-Sherief A. Rare basal cell metastasis of a basal-squamous skin collision tumour to the lung and axillary lymph node. *BMJ Case Rep* 2019;12:e231487.

Management of fetal supraventricular tachyarrhythmia – case report

Postupak kod dijagnosticirane fetalne supraventrikularne tahiaritmije – prikaz slučaja

Zdeslav Benzon, Jasminka Rešić, Zoran Meštrović, Indira Kosović, Sandra Benzon¹

Summary

The conduction system of the fetal heart is defined by the 16th week of gestation when it matures and normally produces a regular rhythm and rate between 110 and 160 beats per minute (bpm) for the remainder of the pregnancy. Deviations from these parameters are fetal arrhythmias. They are diagnosed in 2% of unselected pregnancies. They are mostly benign and transient but some of them are persistent and associated with structural defects or can cause heart failure, fetal hydrops and intrauterine death. Routine prenatal care includes screening for fetal arrhythmias in the second and third trimester with fetal ultrasound examinations which include a view of the four cardiac chambers and both ventricular outflow tracts. The fetal outcomes are improved upon appropriate antepartum diagnosis and care. Here we present a pregnancy and multidisciplinary management, prenatal evaluation and intervention with maternal transplacental treatment of a 28-year-old female, gravida II, para II, in 28+5 weeks of gestation with fetal arrhythmia, in tertiary university hospital. She had a history of previous caesarean section, in the 40th week of gestation due to an infection of the sinus pylonidalis. We confirmed suspected fetal arrhythmia as supraventricular tachyarrhythmia without fetal hydrops, based on the ultrasound doppler M mode imaging, and started transplacental administration of antiarrhythmic agent, digoxin. It has been considered the first line agent for treatment of fetal supraventricular tachycardia but higher maternal doses are required to maintain a therapeutic serum level. We converted fetal heartbeat into normal sinus rhythm after three days of administration of digoxin. We continued to monitor the fetus once a week with controlling levels of digoxin and electrolytes in maternal blood until the end of the pregnancy at 38+6 weeks of gestation.

Key words: fetal arrhythmia, prenatal diagnosis, transplacental therapy

Sažetak

Provodni sistem fetalnog srca definiran je do 16. tjedna trudnoće, kada producira regularan ritam i frekvenciju od 110 do 160 otkucaja u minuti, do završetka trudnoće. Fetalne aritmije definiraju se kao odstupanja od ovih parametara. Dijagnosticiraju se u 2% svih trudnoća. Uglavnom su benigne i prolazne, ali neke od njih povezane su sa strukturalnim defektima, mogu izazvati dekompenzaciju srca, fetalni hidrops ili intrauterinu smrt. Rutinska prenatalna skrbb uključuje ultrazvučni skrining za fetalne aritmije u drugom i trećem tromjesečju. Uključuje pregled četiri srčane komore, kao i izlazišta velikih krvnih žila. Ishod trudnoće je bolji što se prije postavi dijagnoza i započne s liječenjem. Ovdje predstavljamo trudnoću i multidisciplinarni pristup u liječenju 28-godišnje trudnice, u njezinoj drugoj trudnoći u 28+5 tjednu gestacije s dijagnosticiranom fetalnom aritmijom, u tercijarnom centru. Prethodna trudnoća dovršena je carskim rezom u 40. tjednu trudnoće zbog infekcije sinus pilonidalisa. Po primitku u bolnicu, ultrazvučno doplerom u M modu je postavljena dijagnoza supraventrikularne tahiaritmije bez fetalnog hidropsa, te je nakon toga započeta transplacentarna terapija antiaritmikom digoxinom. Smatra se prvom linijom liječenja fetalnih supraventrikularnih tahikardija, uz neophodno davanje većih doza majci, kako bi se postigao

¹ **University Hospital of Split, Department of Obstetrics and Gynecology, University of Split, School of Medicine** (Zdeslav Benzon, MD, PhD; Jasminka Rešić, MD, PhD; Zoran Meštrović, MD, PhD; Indira Kosović, MD, PhD; Sandra Benzon, MD, PhD); **University of Split, University Department of Health Studies** (Jasminka Rešić, MD, PhD; Sandra Benzon, MD, PhD)

Correspondence address/*Adresa za dopisivanje*: Sandra Benzon, University Hospital of Split, Department of Obstetrics and Gynecology, Spinčićeva 1, 21000 Split, Croatia E-mail: sbenzon68@gmail.com

Received/*Primljeno* 2022-11-24; Revised/*Ispravljeno* 2023-06-29; Accepted/*Prihvaćeno*/ 2023-09-06

terapijski učinak. Normalan sinus ritam je postignut nakon trećeg dana primjene digoksina. Nakon toga nastavilo se praćenje fetusa jednom tjedno, uz kontrolu serumske koncentracije digoksina i elektrolita u majčinoj krvi, sve do kraja trudnoće u 38+6 tjedana.

Ključne riječi: fetalna aritmija, prenatalna dijagnoza, transplacentalna terapija

Med Jad 2023;53(3):225-228

Introduction

Fetal arrhythmias are phenomena with rather complicated etiologies. There are debates regarding prenatal diagnosis and treatment of fetal arrhythmias. Understanding the human cardiogenesis is necessary to understand pathophysiology of fetal arrhythmia and congenital heart disease. The embryological development of the cardiovascular system begins with cardiac progenitor cells migration in the epiblast just lateral to the primitive streak. The cardiac loop is finished by approximately 22-28 days after the heart tube elongates.¹ At five weeks of gestation, there is a first sign of sinus node development.² The AV node is recognizable morphologically when the looping heart divides into atrial and ventricular components. At 16 weeks of gestation the conduction system is functionally developed.³ The cardiac electrical conduction system consists of: Sinoatrial Node, Atrioventricular Node, His-Purkinje System which propagates electrical impulse through the myocardium to produce each heartbeat. Automaticity is a characteristic of the cardiac conduction system. Cardiac electrophysiology is extremely important since arrhythmias result from abnormalities in the generation and/or conduction of electrical impulses.⁴ Clinically, fetal arrhythmias can be categorized into 3 types: premature contractions, tachyarrhythmias and bradyarrhythmias.⁵ Premature contractions are most common. They can be divided by their origin: premature atrial contractions and premature ventricular contraction. It is difficult to distinguish premature atrial contraction from premature ventricular contractions. Prognosis is good in the near and long terms, and fetal growth and development are not affected. In general, isolated premature contractions do not require therapy and they resolve spontaneously before delivery.⁶ Fetal tachycardia is defined as HR >180 bpm. It can be classified as sustained when the arrhythmia and present for more than 50% of the examination time or intermittent when periods of tachycardia alternate with predominately normal heart rate, and subdivided into sinus tachycardia, supraventricular tachycardia and ventricular tachycardia. The most common fetal tachycardias are paroxysmal supraventricular tachycardia either with 1:1 atrioventricular conduction or atrial flutter with variable, mostly 2:1

AV conduction.⁴ Bradyarrhythmia is defined as persistent fetal HR of less than 110 bpm, and may be secondary to sinus bradycardia, blocked atrial bigeminy or high-grade atrioventricular block. Persistent sinus bradycardia below 100 bpm is rare and can be seen in fetal distress, hypoxia and acidosis. Another important cause of fetal bradycardia is also altered conduction of atrial impulses to the ventricles resulting in complete dissociation of the atria and ventricle.⁷ Isolated complete atrioventricular block in the fetus in the absence of congenital heart disease is usually immune mediated in association with transplacental transfer of circulating antibodies to Ro (SSA), and La (SSB) antigens from the mother. The risk is 2-3% with recurrence risk of 14-17%.⁸ Currently, fetal echocardiography in combination of M mode and Doppler tissue imaging is the most common used tool for diagnosis and follow up of fetal arrhythmias in clinical practice. In the presence of a suspected arrhythmia, the important features to be evaluated are: fetal heart rate, rhythm regularity and the relation, and time intervals of the atrial and ventricular contractions. In case of arrhythmia, M-mode cursor is usually placed across an atrium and ventricle, so that the relationship of atrial to ventricular contractions is recorded, while pulsed Doppler echography AV time interval assesses. Fetal magnetocardiography is also used, which is ECG analogous and a noninvasive technique for recording the electrical activity of the fetal heart, but it is still a very expensive method and has limited clinical applicability.⁴ The prognosis of fetal arrhythmias depends on the type and severity of arrhythmia and the associated fetal conditions. Life threatening fetal arrhythmias include atrial flutter (AF), ventricular tachycardias and bradyarrhythmia.⁵ Fetal demise occurs in cases of fetal congestive heart failure, hydrops fetalis or congenital heart disease. Benign fetal arrhythmias do not need any treatment before or after birth. Individualized and clinical treatment should be determined according to specific types.⁹

Case report

The patient has provided informed consent for publication of the case. A previously healthy pregnant 28-year-old woman (gravida two para two) was presented to our hospital at 29 weeks of gestation with

fetal arrhythmia. She had a history of previous caesarean section due to sinus pylonidalis. We confirmed fetal arrhythmia as supraventricular tachyarrhythmia, based on the ultrasound doppler M mode imaging. Fetal echocardiogram revealed structurally normal heart with no evidence of hydrops or ventricular dysfunction. Maternal serum electrolyte levels were normal. We prescribed oral metildigoxin loading dose for rapid loading of 1 to 2 mg, which had been given in three doses: 0,5 mg; 0,3 mg; 0,2 mg over 24 hours, followed by a metildigoxin blood level. Our target level was 1 to 2 ng/ml. After this target was achieved, we waited for a 48 to 72 hours period of observation to assess the fetal response to maximum maternal dose. We monitored daily the maternal electrocardiographic changes and other potential symptoms looking for low grade metildigoxin toxicity. Fetal ultrasound after 72 hours of administration of metildigoxin with levels of 1 ng/ml revealed the termination of tachycardia. She continued to take metildigoxin at a dose of 0.2 mg, 0.2 mg; 0.1 mg with a correction of the dose depending on the concentration in the blood. We controlled the levels of metildigoxin once a week together with the maternal echocardiography and electrolyte serum level. Follow up assessment at 32, 34 and 36 weeks showed normal heart rate and rhythm. The baby was delivered at 38+6 weeks of gestation by elective cesarean section at our perinatology center. It was male, 3490 g in weight and 51 cm long. Apgar was ten at the first minute. The transthoracic echocardiogram was performed and showed normal cardiac function and the absence of structural heart defects. The electrocardiogram showed no signs of arrhythmia in the next seven days, so the baby was discharged with mandatory cardiological control after one month. Periodic assessment during the follow-up showed sinus rhythm. Referring such patients to the tertiary centers with expertise in diagnosis and management is of essential importance.

Discussion

Supraventricular tachycardia is the most common form of fetal tachycardia.⁹ It can be seen in maternal hyperpyrexia, use of stimulants, maternal thyrotoxicosis or fetal systemic disease such as anemia, fetal distress and rare infections. Factors which are included in the decision to treat tachycardia or not are: mechanism of tachycardia, fetal gestational age and the well-being, presence or absence of congenital heart disease. In general, three options are available: no treatment with close monitoring, transplacental drug therapy and finally

delivery of fetus. Sustained fetal arrhythmias that predispose the occurrence of hydrops fetalis, cardiac dysfunction, or even fetal demise require early treatments and the effect of therapy depends on the type and etiology of fetal arrhythmia and fetal condition.¹⁰ The conversion rate is high with the use of the first line antiarrhythmic agents via transplacental route. Individualized and clinical treatment should be determined according to the specific type. In general, the transplacental administration of antiarrhythmic agents includes digoxin which is widely accepted as the first line treatment. Sotalol, amiodaron and flecainide are second line drugs when digoxin fails to achieve conversion to sinus rhythm. Combined therapy is reserved for refractory fetal tachycardias.¹¹ Digoxin is prized for its safety and efficacy, but higher doses are required to maintain a therapeutic serum level, especially in the presence of hydrops fetalis.¹² Sotalol and flecainide should be used as a first line treatment for hydropic fetal tachyarrhythmias. Concerning the treatment of fetal tachycardias, digoxin monotherapy showed a lower rate of effectiveness than combined digoxin and sotalol/flecainide.¹³ In conclusion, fetal arrhythmias have to be diagnosed on time and treated using the right antiarrhythmic drugs. Delayed treatment might result in permanent damage. Awareness and knowledge of proper management and treatment of fetal tachyarrhythmias should be kept in mind so prematurity and other complications could be avoided.

References

1. Mathew P, Bordoni B. Embryology, Heart. 2022 Aug 8. Treasure Island (FL): StatPearls Publishing; 2023; Jan-PMID: 30725998
2. Moorman AF, de Jong F, Denyn MM, Lamers WH. Development of the cardiac conduction system. *Circ Res* 1998;82:629-44.
3. van Weerd JH, Christoffels VM. The formation and function of the cardiac conduction system. *Development* 2016;143:197-210.
4. Bravo-Valenzuela NJ, Rocha LA, Machado Nardoza LM, Junior EA. Fetal cardiac arrhythmias. *Current evidence. Ann Pediatr Card* 2018;11:148-63.
5. Strasburger JF, Cheulkar B, Wichman HJ. Perinatal arrhythmias: diagnosis and management. *Clin Perinatol* 2007;34:627-52.
6. Chang HT, Li H. Short and long term clinical prognoses of various types of fetal arrhythmia. *J Pract Obstet Gynecol* 2012;28:950-953.
7. Srinivasan S, Strasburger J. Overview of fetal arrhythmias. *Curr Opin Pediatr* 2008;20:522-31.
8. Buyon JP, Clancy RM. Neonatal lupus: basic research and clinical perspectives. *Rheum Dis Clin North Am* 2005;31:299-313.
9. Yuan SM, Xu ZY. Fetal arrhythmias: prenatal

- evaluation and intrauterine therapeutics. *Ital J of Pediatrics* 2020;46:21.
10. Chang HT, Li H. Short and long-term clinical prognoses of various types of fetal arrhythmia. *J Pract Obstet gynecol* 2012;28:950-3.
 11. Ueda K, Maeno Y, Miyoshi T, Inamura N, Kawataki M, Takeatazu M, et al. The impact of intrauterine treatment on fetal tachycardia: a nationwide survey in Japan. *J Matern fetal Neonatal Med.* 2018;31:2605-10.
 12. AlSoufi M. Successful treatment of fetal tachycardia by sotalol. *J Cardiol Curr Res* 2017;9:00322.
 13. Karmegeraj B, Namdeo S, Sudhakar A, Krishnan V, Kunjukutty R, Vaidyanathan B. Clinical presentation, management and postnatal outcomes of fetal tachyarrhythmias: a 10 year single center experience. *Ann Pediatr Cardiol* 2018;11:34-9.

Dissociative amnesia with fugue features in a patient with Huntington's disease

Disocijativna amnezija s obilježjima fuge kod bolesnika s Huntingtonovom bolešću

Ante Štefić, Vanja Đuričić, Valentin Kordić, Sara Đuričić, Maristela Šakić, Melita Jukić*

Summary

Huntington's disease is a severe, incurable neurological disease characterised by motor, cognitive, and psychological symptoms. This paper presents the case of a Huntington's disease patient with dissociative symptoms. Clinical characteristics, genetic background, diagnostics, and guidelines for treating Huntington's disease are shown in the paper. We emphasised the importance of knowing the genetic basis and testing the descendants of the patients. We highlighted the difference between behavioural perseveration as a common psychomotor disorder in these patients and symptoms of obsessive-compulsive disorders.

Dissociative disorders may occur under extreme mental stress and exhaustion, such as when dealing with a severe incurable illness. These disorders are not typical psychopathological phenomena for Huntington's disease, but conditions of hopelessness and despair after facing a severe diagnosis may lead to dissociative symptoms. Dissociative disorders as indicators of exhaustion of mental functioning require caution, especially given their high frequency of occurrence with suicidality as extreme exhaustion of mental functioning.

So far, treatment of Huntington's disease is only symptomatic, emphasising the relaxation of motor choreatic movements and heterogeneous mental disorders. Antipsychotics that reduce choreatic movements but also affect psychotic symptoms, behavioural perseverations and mood stabilisation are used primarily to relieve symptoms.

As it is a progressive disease that ends in severe motor deficit, dementia and death, treating these patients with a multidisciplinary team that includes neurological, psychiatric and palliative care, physical therapy, nursing, and social care is necessary. Psychotherapeutic and sociotherapeutic approaches make it easier for patients and their families to cope with this severe disease. Genetic testing of the offspring is desirable to determine the potential carrying of the mutated gene and its transmission to subsequent generations in which the disease appears earlier.

Key words: Huntington's disease, dissociative amnesia, chorea, antipsychotics, behavioural perseverations

Sažetak

Huntingtonova bolest je teška, neizlječiva, neurološka bolest, karakterizirana motoričkim, kognitivnim i psihičkim simptomima. Ovaj rad je prikaz slučaja bolesnika s Huntingtonovom bolešću kod kojega su se razvili disocijativni simptomi. U radu su prikazane kliničke značajke, genetska podloga, dijagnostika i smjernice za liječenje Huntingtonove bolesti. Naglasili smo važnost poznavanja genetske osnove tetestiranja potomaka oboljelih. Istakli smo razliku između bihevioralnih perseveracija kao čestog poremećaja psihomotorike kod ovih bolesnika i simptoma opsesivno-kompulzivnih poremećaja.

* Nacionalna memorijalna bolnica „Dr. Juraj Njavro“, Vukovar, Hrvatska (Ante Štefić, dr.med.; Vanja Đuričić, dr.med.; doc.dr.sc. Melita Jukić, dr.med.); Klinički bolnički centar Osijek, Osijek, Hrvatska (Valentin Kordić, dr.med.); Medicinski fakultet Osijek, Osijek, Hrvatska (Sara Đuričić, studentica medicine); Specijalna bolnica za psihijatriju i palijativnu skrb „Sveti Rafael“, Šumetlica, Hrvatska (Maristela Šakić, dr.med.)

Correspondence address/Adresa za dopisivanje: Ante Štefić, dr.med., Nacionalna memorijalna bolnica „Dr. Juraj Njavro“, Županijska 35, 32 000 Vukovar, Hrvatska E-mail: ante.stefic@gmail.com

Received/Primljeno 2023-05-28; Revised/Ispravljeno 2023-07-20; Accepted/Prihvaćeno 2023-10-05

U stanjima izraženog psihičkog stresa i iscrpljenosti, kao što je suočavanje s teškom neizlječivom bolešću, mogu se javiti disocijativni poremećaji. Ovi poremećaji nisu tipični psihopatološki fenomeni za Huntingtonovu bolest, ali stanja beznađa i očaja nakon suočavanja s teškom dijagnozom, mogu dovesti do pojave disocijativnih simptoma. Disocijativni poremećaji kao pokazatelji iscrpljenosti mentalnog funkcioniranja zahtijevaju oprez, posebice s obzirom na njihovu visoku učestalost javljanja sa suicidalnošću kao krajnjim iscrpljenjem psihičkog funkcioniranja.

Liječenje Huntingtonove bolesti za sada je samo simptomatsko s naglaskom na ublažavanje motoričkih koreatskih pokreta, te heterogenih psihičkih smetnji. Za ublažavanje simptoma koriste se u prvom redu antipsihotici koji reduciraju koreatske pokrete, ali imaju djelovanje i na psihotične simptome, bihevioralne perseveracije, te stabilizaciju raspoloženja.

Kako se radi o progresivnoj bolesti koja završava teškim motoričkim deficitom, demencijom i smrtnim ishodom, kod ovih bolesnika liječenju je nužno pristupiti s multidisciplinarnim timom koji uključuje neurološku, psihijatrijsku i palijativnu skrb, te fizikalnu terapiju, adekvatnu njegu i socijalnu skrb. Psihoterapijski i socioterapijski pristupi olakšavaju nošenje oboljelih i njihovih obitelji s ovom teškom bolešću. Poželjno je genetsko testiranje potomaka, kako bi se utvrdilo potencijalno nošenje mutiranog gena i prijenos na sljedeće generacije kod kojih se bolest javlja u sve ranijoj dobi.

Ključne riječi: Huntingtonova bolest, disocijativna amnezija, korea, antipsihotici, bihevioralne perseveracije

Med Jad 2023;53(3):229-234

Introduction

Huntington's disease (HD), also called Huntington's chorea, is a neurological and mental disorder inherited in an autosomal dominant manner. It is characterised by a range of motor, psychological, and cognitive impairments.¹ The motor abnormalities are a loss of coordination and disorganised, uncontrollable motions called chorea that become more obvious as the disease progresses.² HD patients often have mental problems that differ across individuals and can be very upsetting.³ HD is characterised by the degradation of neurons in the striatum and, as the disease advances, in the cerebral cortex, which results with dementia. Cortical atrophy progresses from the posterior to the anterior regions. This spatially selective degeneration may explain the clinical heterogeneity of neurological and mental symptoms of HD.⁴

Patients with HD often have heart failure, muscular atrophy, and weight loss as additional symptoms. Symptoms usually appear between the ages of 30 and 50. However, they may occur at any age. Life expectancy is lowered due to complications such as pneumonia, cardiovascular diseases, and injury from falls. The disease lasts about 20 years from the diagnosis and ends with death.⁵

In populations of European origin, the prevalence of HD ranges from 10 to 14 per 100,000 people.⁶ Croatia has a lower prevalence, at 4.46 per 100 000 residents.⁵ It is a very rare disease in Asia with a prevalence of less than 1 per 100 000 people and most commonly sporadic as a new mutation without a family history.⁷ Men and women around the world are equally affected.⁵

The huntingtin gene (HTT) is located on

chromosome 4 and contains the genetic information for the transcription of the protein huntingtin. Huntingtin is widely expressed in the cytoplasm of neurons and their vesicle membranes, especially in large striatal and cortical neurons.⁸

The disease is typically inherited from a parent whose HTT has been changed. The new mutation is to blame in up to 10% of cases.⁹ Wild-type alleles have up to 35 cytosine-adenine-guanine (CAG) repeats, while HD patients have 36 and more repeats.¹⁰ HD can be inherited through the maternal and paternal germlines, but it manifests more often and earlier when inherited through the paternal germline. As the disease passes through generations, symptoms may manifest at younger ages as the number of CAG repeats increases. The amplification of the CAG repeats in the gene responsible for encoding the huntingtin protein produces an aberrant mutant protein that damages brain cells through various mechanisms. In these patients, CAG repeats are unstable and expand when transmitted along the germline, resulting in a decrease in the age of onset with each generation. This phenomenon is known as anticipation.¹¹

Meiotic division in males and females differs. During spermatogenesis, the number of CAG repeats increases, while during oogenesis, there are almost equal increases and decreases. It is a reason why the earlier onset of HD is frequently inherited through the male germline.¹²

Variations of symptoms can be seen in HD patients' motor, cognitive, and mental characteristics.¹³ Chorea, characterised by short, uncontrollable, exaggerated, and semi-purposeful movements, is one of the most conspicuous symptoms.¹⁴ It progresses from sporadic, low-

amplitude facial and extremity twitches to continuous, large-amplitude body movements. Dystonia can affect writing, eating, and balancing. It often causes persistent muscular contractions that induce unusual postures such as torticollis and opisthotonos. Intercurrent diseases, stress, and worry can rapidly worsen motor symptoms.¹⁵

HD deteriorates cognitive, perceptive, and emotional functions. A wide range of mental symptoms in HD includes anxiety, depression, apathy, obsessive-compulsive disorders (OCD), suicidality, disinhibition, irritability, psychosis, and cognitive, behavioural, and sexual disorders. Cognitive and behavioural problems can manifest up to 15 years before motor abnormalities and significantly diminish life quality.⁶

Impaired emotional functions often include anxiety, depression and apathy, whose prevalence ranges from 38% to 73%.¹⁶ Less regular is OCD, ranging from 10% to 52%.¹⁷ Behavioural perseverations, however, might be mistakenly identified as OCD and can affect up to 75% of patients with HD.¹⁸ The difference between OCD and behavioural perseveration is that the will does not control behavioural perseveration. In contrast, the patient can control actions in OCD despite internal tension.¹⁷ Psychotic symptoms are less common, with prevalence ranging from 3% to 11%.¹⁹ Sexual dysfunctions in HD are prevalent, 85% of men and up to 75% of women report having significant sexual problems²⁰, with the majority exhibiting symptoms of a hypoactive sexual condition, but paraphilia and increased sexual desire were also observed.²¹ The suicide risk is highest when premanifest patients develop disease and lose independence. 20–30% of HD patients report having suicidal thoughts at some point, and 7–10% commit suicide.²²

Dissociative disorders are not usual in patients with Huntington's disease, but various forms of dissociative disorders may occur. A transient or permanent interruption of the continuity of standard integration of consciousness and other mental functions such as perception, attention, memory, movement and behaviour control characterises these disorders. Although dissociative conditions are recorded in brain damage and under the influence of anaesthetics, they are thought to arise due to several biological and psychosocial factors. These disorders usually do not have an organic cause but occur in mental exhaustion due to psychological trauma as a primary etiological factor. The psychological explanation says that their purpose is to defend the conscious mind against an unacceptable idea, considering that more than 70% of patients with dissociative disorder attempt suicide and often self-

harm behaviour.²³

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), dissociative disorders include depersonalisation/derealisation disorder, dissociative fugue, dissociative amnesia, and dissociative identity disorder. The tenth revision of the International Classification of Diseases (ICD-10) classifies dissociative disorders with conversion disorders and distinguishes amnesia from fugue. Dissociative amnesia is the inability to recall the event immediately before and after the traumatic event, and dissociative fugue contains all forms of dissociative amnesia but also includes leaving home or the workplace, during which the patient maintains self-care and makes simple social contacts. Such a journey does not fit the schedule and the patient's plans. A clear line between dissociative amnesia and fugue cannot be established. These two entities are probably part of the continuum. Conditions of severe stress, hopelessness, and despair in serious and incurable diseases can trigger dissociative reactions.²⁴

Despite the limited data available, several published studies have estimated that 0.2% of the general population experiences dissociative amnesia and a fugue state during life.²⁵ This phenomenon is most prevalent in the third and fourth decades of life, with an identical frequency among both genders.²³

HD is a severe, neurodegenerative disease, and no specific disease-modifying medications are currently available. The only cure is symptomatic. The goal of treatment for chorea is to lower its severity to make it more tolerable. First-line therapies for motor difficulties include approved tetrabenazine and antipsychotics. The specific mechanism of action of tetrabenazine needs to be clarified. It is thought that inhibiting the vesicular monoamine transporter by tetrabenazine leads to a reduction of the uptake of monoamines into synaptic vesicles and a consequent lack of monoamines in presynaptic nerve terminals, including dopamine, which might cause the anti-chorea effect.²⁶

Antipsychotics used in treating psychotic conditions have the unwanted property of blocking the nigrostriatal pathway, consequently causing the development of extrapyramidal movements. To treat choreatic movements, the unwanted property of antipsychotics in treating psychotic symptoms is used to reduce the activity of dopaminergic D2 receptors in the nigrostriatal pathway.²⁷ Antipsychotics with strong D2 antagonistic properties, like the first-generation antipsychotic haloperidol, effectively stop choreatic movements. However, it has unwanted adverse side effects on muscarine, histamine, and adrenergic receptors, resulting in hyposalivation,

obstipation, sedation, hypotension, and neurotoxicity.²⁸ Nowadays, the first-choice antipsychotics for HD patients are newer second-generation antipsychotics with strong D2 antagonistic properties, like risperidone and olanzapine. They effectively reduce chorea and psychotic symptoms while having fewer unwanted side effects.²⁹

Various agents have been studied for treating different symptoms, but the benefit of some of them remains unclear. Compared to motor HD symptoms, mental symptoms are more susceptible to treatment.⁶ Psychiatric symptoms, frequently distressing for patients, are commonly addressed with conventional pharmacological therapies for patients without HD. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are commonly prescribed for treating depression, anxiety, and OCD. In addition to controlling unwanted choreatic movements, antipsychotics are used for psychotic symptoms like delusions and hallucinations. However, they can help with psychotic-depressive symptoms, expressed OCD and behavioural perseverations. Trials of memantine and cholinesterase inhibitors used to treat cognitive difficulties in Alzheimer's disease have been unsatisfactory in HD.^{3,30} The loss of cognitive ability is progressive, and dementia is unavoidable. The modern HD patient's treatment team often includes allied health professionals from neurology, psychiatry, palliative care, physiotherapy, nursing, and social care.⁴

Case Report

The emergency psychiatric clinic received a patient from police officers. The patient was found alone in a car in a cornfield, where he had been for two days. The mother with whom he lives reported him missing after he said he would have a cup of coffee in town but failed to return as promised for lunchtime. The patient sat in the car for two days and did not eat or drink anything during that time. He said it was chilly, but he ignored it. He did not know why he had not gotten out of the car or sought help.

The patient was a 41-year-old man, divorced for two years, and the father of two daughters. The daughters lived with his ex-wife. He had recently been diagnosed with Huntington's disease and had been living with his mother since then. The mother took care of his therapy (haloperidol of 2mg in the morning and evening, mirtazapine of 15 mg in the evening, and alprazolam of 0.25 mg as needed in cases of tension). She said that he did not take a more significant amount than usual. The patient

denied the consumption of alcohol and other illicit psychoactive substances. He said that he was upset and saddened before leaving home after having gotten a call from his daughters, saying they would not visit him.

The patient was partially time-oriented when arriving at the emergency psychiatric clinic; he thought the date was two days earlier. He was in a lowered mood and congruent affective state. His thought flow was slowed down, punctuated with occasional blocks of thought but without delusions or hallucinations. There were not any destructive or suicidal ideas or urges. During the examination, he was repeatedly sitting on the floor, even though he could not explain why he was doing it, and it was not under his control. He had expressed involuntary choreatic movements of both hands.

From the medical record, he was known to have received treatment for anxiety and depressive disorders for the previous three years, had a decreased libido, and was under pressure due to frustrating circumstances related to divorce for the last two years. He had occasional involuntary hand twitches, and a neurologist performed magnetic resonance of the brain, which showed basal ganglion atrophy. After that, a genome analysis confirmed that the reason for brain damage was the Huntington's disease. In addition to mental disorders and proven Huntington's disease with 48 CAG repeats, he had no other diseases.

The family had no psychiatric history. He had a mother of 72 years, his father had died at the age of 65 from colon cancer, and his older sister was healthy at age 45.

A laboratory examination of red and differential blood counts and basic biochemical parameters revealed that all required parameters were within the reference interval.

Mirtazapine was replaced with fluvoxamine (100 mg in the evening), resulting in fewer behavioural perseverations. Haloperidol was replaced with risperidone (1 mg in the morning and evening), to which he responded favourably by reducing involuntary movements; alprazolam 0.5 mg was continued as needed. He got psychotherapeutic and socio-therapeutic support in accordance with his capacities. Despite the treatment, the amnesia for the time of two days when he had been alone in the car was persistent.

Discussion

We decided to show a rare occurrence of dissociative amnesia with features of dissociative fugue in a patient with a rare disease such as HD.

Dissociative disorders are not characteristic of HD, but the despair in which this patient found himself may cause this reaction. Even minor frustrations in patients with these severe illnesses who face feelings of hopelessness can also lead to the development of suicidal behaviour. In this case, although the patient denied suicidal ideation and urges upon arrival. We cannot safely rule out their occasional existence, especially considering the high suicidal rate in HD patients.²²

In the European Union, a prevalence of 1 per 2000 inhabitants is used to define rare diseases³¹, so HD in Croatia, with a prevalence of 4.6 per 100 000 inhabitants, meets the criteria of rare diseases.⁵

Due to the rare occurrence of this disease, we wanted to gather information about its aetiology, clinical picture, diagnostics, and treatment. The aetiology of this disease is quite clear. The underlying cause of the disease is a genetic mutation in the number of CAG repeats, whose number in each subsequent generation increases and thus manifests the disease at an earlier age. Since this patient has a living mother who is elderly and does not have this disease, it is not possible that he inherited HTT from his mother. It is unlikely but possible that he inherited it from his father due to the phenomenon of anticipation in this disease, who never had symptoms of HD and died of cancer at a relatively older age than the patient was at the time of getting the diagnosis of HD. This patient is most likely to have a rare occurrence of a new mutation that causes HD in less than 10% of cases.⁹ More than 40 CAG repeats result in the complete penetration of the disease by age 65, so the occurrence of a manifest disease at approximately 40 years of age, which is also the most common age at which this disease manifests, is not surprising with 48 repeats.¹ Testing patients' daughters for the possible expectation of disease symptoms and transmission to subsequent generations is crucial.³²

Since there is not any specific treatment that would change the course of the disease, we relied on symptomatic treatment. To treat motor symptoms, we opted for risperidone as a second-generation antipsychotic because it has fewer side effects than first-generation antipsychotics.²⁷ Considering that fluvoxamine also blocks enzymes involved in the elimination of risperidone, which leads to a rise in its concentration, lower doses of risperidone were sufficient, even though higher doses of antipsychotics are usually needed to stop chorea than to treat psychotic disorders.³³ The combined activity of risperidone and fluvoxamine also reduced disease-specific behavioural perseverations, occasionally misclassified as OCD.²⁹ It is necessary to consider the

presence of depressive and anxious symptoms in these patients because they may have a biological basis in brain damage. Additionally, the extended period of unrecognised prodromal symptoms can lead to impaired social functioning, cognitive difficulties, and sexual disorders, increasing the burden on these patients.⁶

Conclusion

HD is a genetic neurodegenerative disease of unusual occurrence at an earlier age as it passes through generations of offspring and requires good knowledge of the genetic basis, biological characteristics, and course of the disease.

Motor symptoms characterise this disease, but since it is a degenerative disease, various psychological symptoms and comorbidities of mental disorders often develop depending on the affected brain structures and gene penetration. Among common symptoms such as behavioural perseverations, psychotic symptoms, mood disorders, and impaired sexual and cognitive functions, dissociative disorders may occur based on psychological grounds of exhaustion and hopelessness. Dissociative disorders as indicators of exhaustion of mental functioning during severe stressful conditions require caution, especially considering the high frequency of suicidality in patients with HD, which might result from the fatigue of these patients to cope with the difficulties and despair that this disease brings.

It is essential to distinguish the symptoms of HD into different categories and to approach each symptom with a characteristic treatment. The choice drugs for motor symptoms without the availability of tetrabenazine, with which we have no experience, are newer antipsychotics with expressed D2 effects, such as risperidone and olanzapine. These antipsychotics also treat other less common mental disorders in these patients, such as psychotic symptoms, psychotic depressive disorders, and very common behavioural perseverations. Various antidepressants are also helpful in treating depressive and anxiety symptoms, OCD, and behavioural perseveration. It is essential to comprehend the relationship between different psychiatric drugs and their synergistic effects in treating the various symptoms of HD.

The psychotherapeutic and socio-therapeutic approaches make it easier to carry patients and their families with this severe disease, where genetic testing of descendants is desirable to identify the potential carrying of a mutated gene.

References

1. Tabrizi SJ, Flower MD, Ross CA, Wild EJ. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. *Nat Rev Neurol* 2020; 16:529–46.
2. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin Lowering Strategies for Disease Modification in Huntington's Disease. *Neuron* 2019;101:801–19.
3. Eddy CM, Parkinson EG, Rickards HE. Changes in mental state and behaviour in Huntington's disease. *Lancet Psychiatry* 2016;3:1079–86.
4. Pan L, Feigin A. Huntington's Disease: New Frontiers in Therapeutics. *Curr Neurol Neurosci Rep* 2021;21:10.
5. Pogledić I, Relja M. Huntington's disease. *Lijec Vjesn* 2012;134:346–50.
6. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *Eur J Neurol* 2018;25:24–34.
7. Xu M, Wu ZY. Huntington Disease in Asia. *Chin Med J (Engl)* 2015;128:1815–19.
8. Savolainen M, Emerich D, Kordower JH. Disease Modification Through Trophic Factor Delivery. *Methods Mol Biol* 2018;1780:525–47.
9. Myers RH. Huntington's disease genetics. *NeuroRx*. 2004;1:255–62.
10. Monteys AM, Ebanks SA, Keiser MS, Davidson BL. CRISPR/Cas9 Editing of the Mutant Huntingtin Allele In Vitro and In Vivo. *Mol Ther* 2017;25:12–23.
11. Ridley RM, Frith CD, Crow TJ, Conneally PM. Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *J Med Genet* 1988 ;25:589–95.
12. Khampang S, Parnpai R, Mahikul W, Easley CA, Cho IK, Chan AWS. CAG repeat instability in embryonic stem cells and derivative spermatogenic cells of transgenic Huntington's disease monkey. *J Assist Reprod Genet* 2021;38:1215–29.
13. Schultz JL, Langbehn DR, Al-Kaylani HM et al. Longitudinal Clinical and Biological Characteristics in Juvenile-Onset Huntington's Disease. *Mov Disord* 2023;38:113-122
14. Radanović-Grgurić L, Petek A, Laufer D, Koić O, Radanović B, Filaković P. Pharmacologic side effects and/or neurologic disorder: case report. *Psychiatr Danub*. 2009;21:575–8.
15. Paoli RA, Botturi A, Ciammola A. et al. Neuropsychiatric Burden in Huntington's Disease. *Brain Sci* 2017;7:67.
16. Karagas NE, Rocha NP, Stimming EF. Irritability in Huntington's Disease. *J Huntingtons Dis* 2020;9:107–13.
17. Hoffmann R, Schröder N, Brüne M, von Hein S, Saft C. Obsessive-Compulsive Symptoms are Less Common in Huntington's Disease than Reported Earlier. *J Huntingtons Dis* 2019;8:493–500.
18. Oosterloo M, Craufurd D, Nijsten H, van Duijn E. Obsessive-Compulsive and Perseverative Behaviors in Huntington's Disease. *J Huntingtons Dis* 2019;8:1–7.
19. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. *J Neuropsychiatry Clin Neurosci* 2007;19:441–8.
20. Schmidt EZ, Bonelli RM. Sexuality in Huntington's disease. *Wien Med Wochenschr* 2008;158:78–83.
21. Jhanjee A, Anand KS, Bajaj BK. Hypersexual features in Huntington's disease. *Singapore Med J* 2011;52:e131-3.
22. Kachian ZR, Cohen-Zimmerman S, Bega D, Gordon B, Grafman J. Suicidal ideation and behavior in Huntington's disease: Systematic review and recommendations. *J Affect Disord* 2019;250:319–29.
23. Foote B, Smolin Y, Neft DI, Lipschitz D. Dissociative disorders and suicidality in psychiatric outpatients. *J Nerv Ment Dis* 2008 196:29–36.
24. Kocijan Hercigonja D, Hercigonja Novkovic V, Koren D, Jurac S. Specificity of Diagnosing Dissociative Disorders in Children and Adolescents. *Soc Psihijatr* 2019;46:406–12.
25. Gill G, Dumlao N, Singh G, Susaimanickam B, Korenis P. Dissociative Amnesia With Fugue in a Middle-Aged Man. *Prim care companion CNS Disord* 2023;25:22cr03306..
26. Fasano A, Bentivoglio AR. Tetrabenazine. *Expert Opin Pharmacother* 2009;10:2883–96.
27. Unti E, Mazzucchi S, Palermo G, Bonuccelli U, Ceravolo R. Antipsychotic drugs in Huntington's disease. *Expert Rev Neurother* 2017;1:227–37.
28. Nasrallah HA, Chen AT. Multiple neurotoxic effects of haloperidol resulting in neuronal death. *Ann Clin Psychiatry* 2017;29:195–202.
29. Copen EM, Roos RAC. Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. *Drugs* 2017;77:29–46.
30. Perković R, Tomić S, Jurić S, Gudelj E, Hrvoić L. Nove terapije u liječenju Alzheimerove bolesti. *Med Flum* 2023;59:4–15.
31. Maiella S, Rath A, Angin C, Mousson F, Kremp O. Orphanet and its consortium: where to find expert-validated information on rare diseases. *Rev Neurol (Paris)*. 2013;169 Suppl:S3-8.
32. Quaid KA. Genetic testing for Huntington disease. *Handb Clin Neurol* 2017;144:113–26.
33. D'Arrigo C, Migliardi G, Santoro V. et al. Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia. *Pharmacol Res* 2005 Dec;52:497–501.

Recenziji podliježu članci koji se prema općim standardima dijele u četiri kategorije:

- izvorni znanstveni članak (Sadrži dotada neobjavljene rezultate znanstvenog istraživanja. Članak mora sadržavati sve detalje nužne radi ponovljivosti opisanog rada.)
- prethodno priopćenje (Sadrži dotad neobjavljene preliminarne rezultate znanstvenog istraživanja koje je poželjno brzo objaviti.)
- pregledni članak (Sažet i kritičan pregled specifičnog istraživačkog područja sa svježim informacijama o trenutačnom stanju razvoja i usmjerenja.)
- stručni članak (Sažet i kritičan pregled odabrane teme, s usmjerenjima i kontroverzama u njoj. Mora biti razumljiv i nespecijalistima tog područja. Od znanstvenoga se razlikuje prvenstveno u tomu što ne donosi originalne rezultate autora istraživanja nego rabi već objavljene rezultate i koje usustavljuje i objašnjava.)

Kategoriju članka predlaže autor, a konačan sud donosi urednik na prijedlog recenzenata rada. Nekategorizirani radovi (recenzije, prikazi i slično) ne podliježu recenzentskom postupku, uredništvo ih prihvaća na temelju vlastitih uvida.

Recenzent je odgovoran za kritičku procjenu kvalitete rada koji je dobio na ocjenu.

Dužnost mu je iznijeti detaljne primjedbe i savjete o istraživanju i formulaciji rezultata kako bi autoru/ima pomogao pri poboljšanju njihova rada. Procjena rada uključuje ocjenu njegove izvornosti i važnosti, njegova metodološkog ustroja te valjanosti zaključaka izvedenih na temelju dobivenih rezultata.

Recenzent je dužan upozoriti uredništvo o mogućim poteškoćama koje bi ga spriječile u objektivnosti pri postupku recenziranja. Također je dužan s dobivenim člankom postupati kao s povjerljivim spisom, tj. ne pokazivati rad bilo kome drugom bez pristanka uredništva, ne koristiti rezultate iz rada koji im je poslan na recenziju za vlastita istraživanja prije objave rada.

Recenzent je dužan recenziju obaviti na vrijeme i zadržati akademsku razinu komunikacije pri pisanju recenzije.

Nakon pročitano rada, recenzent je dužan dati svoj sud o tome treba li rad objaviti, predložiti kategorizaciju ukoliko je recenzija pozitivna te iznijeti sud o tome treba li se u radu išta popraviti ili doraditi. Ocjena se treba kretati unutar sljedećih smjernica:

- DA – („Prihvaća se“) Bezuvjetno odobrenje za objavu rada.
- DA, POD UVJETOM DA – („Prihvaća se uz doradu“) Odobrenje predviđa izvjesne modifikacije/poboljšanja koja se trebaju izvršiti na radu
- NE, OSIM U SLUČAJU – („Ne prihvaća se“) Nužna temeljita revizija i rekonstrukcija rada.
- NE – („Ne prihvaća se“) Ne postoji niti minimum elemenata koji se mogu iskoristiti.

Recenzije su dvostruko slijepe, tj. recenzent neće znati ime autora niti će autor znati ime recenzenta.

Articles divided into four categories according to general standards are subject to reviews such as:

- Original scientific article (It contains previously unpublished results of scientific research. The article must contain all the details necessary for the reproducibility of the described work.)
- Previous announcement (It contains previously unpublished preliminary results of scientific research, desired to be published quickly)
- Review article (A concise and critical overview of a specific research area with fresh information on the current state of development and direction)
- Expert article (A concise and critical overview with guidelines and controversies in it. It must be understandable to non-specialists of the field. It differs from the scientific article primarily in that it does not bring the original results of the authors of the research, but uses already published results it systematizes and explains.)

The author suggests the article category, while the final judgement is made by the editor at the suggestion of the reviewer of the work. Non-categorized works (reviews, displays and similar) are not subject to review procedure, the editorial board accepts these based on their own insights.

The reviewer is responsible for critically evaluating the quality of the work received for evaluation. It is his duty to provide detailed remarks and advice on research and formulation of results in order to help the author/s in improving his/their work. The evaluation of the paper includes an assessment of its originality and importance, its methodological structure and the validity of the conclusions drawn based on the obtained results.

The reviewer is obliged to warn the editorial board on the possible difficulties that may prevent him in being objective in the review procedure. He is also obliged to treat the received article as a confidential file, i.e. not show the work to anyone without the approval of the editorial board, not use for his own research the work results sent for review prior to the work being published.

The reviewer is obliged to perform the review on time and retain the academic level of communication in writing his review.

Having read the paper, the reviewer is obliged to give his judgment on whether the paper should be published, suggest the categorization if the review is positive, and make a judgment on whether anything in the paper should be corrected or amended.

The evaluation should be within the following guidelines:

- YES – (“Accepted“) Unconditional approval for the publication of the paper.
- YES, UNDER THE CONDITION THAT – (“Accepted with amendments“) The approval foresees certain amendments/improvements that are to be performed in the work
- NO, EXCEPT IN THE CASE THAT – (“Not accepted“) A thorough revision and reconstruction of the work is necessary.
- NO – (“Not accepted“) There is not even a minimum of elements that can be used.

Reviews are double blind, i.e. the reviewer shall not know the name of the author nor shall the author know the name of the reviewer.

Časopis MEDICA JADERTINA objavljuje uvodnike, izvorne znanstvene i stručne radove, prethodna priopćenja, pregledne radove, izlaganja sa znanstvenih skupova i druge priloge iz područja temeljnih i kliničkih medicinskih znanosti. Rukopisi mogu biti napisani na hrvatskom ili na engleskom jeziku.

Uredništvo primljene radove upućuje na obveznu recenziju dvama recenzentima. Izneseni stavovi u radovima predstavljaju mišljenje autora, stoga je svaki autor odgovoran za etičku prihvatljivost svojega rada. Radovi objavljeni u časopisu zaštićeni su autorskim pravom. Tekst i slike iz ovog časopisa mogu se koristiti za osobnu i edukacijsku svrhu uz poštivanje autorskih prava autora i izdavača. Svaka druga uporaba zabranjena je bez izričitog pisanog dopuštenja izdavača, Opće bolnice Zadar. Svi radovi vlasništvo su izdavača časopisa.

Uredništvo radove ne mora objavljivati slijedom kojim pristižu. Tiskani radovi u časopisu, dostupni su u cijelosti na Portalu hrvatskih znanstvenih radova – HRČAK. Radove poslati naslovu na elektroničku adresu: opca-bolnica-zadar@zd.t-com.hr ili poštom na adresu: Uredništvo časopisa MEDICA JADERTINA, Opća bolnica Zadar, Bože Peričića 5, 23000 Zadar, Hrvatska.

Priprema rada

Izvorni znanstveni i pregledni radovi ne smiju biti dulji od 3000 riječi (iznimno 4000 riječi). Preduge radove, osim onih naručenih, Uredništvo neće prihvatiti i vratiti će ih autorima.

Radove treba pisati na računalu u programu MS Word ili sličnom programu s proredom (1,5) u fontu Times New Roman, veličina slova 12. Format stranice mora biti A4, a margine 2,5 cm sa svih strana. Svako poglavlje rada treba započeti na novoj stranici. Svi dijelovi rada uključujući tablice, slike i popis literature moraju biti u jednom elektronskom dokumentu. Uz rukopis je potrebno priložiti izjave o nepostojanju sukoba interesa, financijskog ili bilo kakvog drugog interesa, autorstvu i prijenosu autorskih prava, te izjavu da rad nije već objavljen ili prihvaćen za objavu u nekom drugom časopisu. Obrazac izjave nalazi se na kraju ovog dokumenta.

Naslovna stranica

Naslovna stranica treba sadržavati naslov rada na hrvatskom i engleskom jeziku, puna imena i prezimena svih autora, s njihovim akademskim stupnjevima te specijalnostima, kao i službenim nazivima organizacija u kojima rade. U naslovu rada ne smiju se koristiti kratice. Pri dnu stranice treba navesti ime, prezime, adresu i elektronsku adresu autora za dopisivanje.

Sažetak (Summary)

Sažetak s najviše 300 riječi na hrvatskom i engleskom jeziku treba biti strukturiran, na zasebnoj stranici. Preporučuje se pisati u prvom licu množine, izbjegavati pasivne glagolske oblike i ne koristiti kratice.

Ključne riječi

Na stranici s hrvatskim, odnosno engleskim sažetkom ispod teksta valja napisati tri do šest ključnih riječi karakterističnih za glavnu temu rada i prikladnih za uvrštenje u bibliografska kazala. Ključne riječi moraju biti u skladu s naslovima u Index Medicusu.

Rad

Kada je moguće, rad podijeliti na: uvod, bolesnici (materijal) i metode, rezultati, rasprava, zaključak i literatura. U uvodu se navodi svrha rada i razlog provođenja ispitivanja. Poglavlje bolesnici i metode obuhvaća sve važne karakteristike ispitivanja. Nužno je navesti koje je etičko povjerenstvo dalo pristanak za provođenje ispitivanja, te da je ono provedeno u skladu s etičkim načelima Helsinške deklaracije. Treba naznačiti da su ispitanici dali svoj informirani pristanak za sudjelovanje u ispitivanju, kao i priložiti pismeni pristanak pacijenta za objavljivanje njegovih podataka u "Prikazu slučaja". Potrebno je opisati korištene statističke metode kao i statistički program koji je korišten za obradu podataka. Značajnost rezultata potrebno je statistički potkrijepiti. Mjerne jedinice moraju biti izražene prema SI sustavu. Rasprava treba naglasiti nove i važne spoznaje koje proizlaze iz ispitivanja te ih usporediti s rezultatima iz literature. Kratice u tekstu mogu se koristiti tek nakon drugog spominjanja potpune riječi u tekstu. Iznimno je moguće koristiti istaknute riječi u tekstu italic fontom. Potrebno je označiti mjesta na kojima će se tiskati tablice i slike, navodeći u tekstu zagradu – npr. (Tablica 1.). Sve priloge uz tekst rada treba svesti na razuman broj (najviše šest tablica, odnosno slika).

Tablice i slike

Tablice treba izraditi na zasebnoj stranici s rednim brojem i naslovom. Riječi u tablicama ne smiju se kratiti. Naslovi i tekstualni sadržaj tablice moraju biti dvojezični, na hrvatskom i engleskom jeziku. Svaka tablica mora imati redni broj. Naslov i redni broj pišu se iznad tablice. Izbjegavati korištenje vertikalnih linija u tablici. Legende tablica pisati ispod tablice.

Iznimno, na zahtjev recenzenata ili Uredništva časopisa, autori će dostaviti podatke na temelju kojih su izrađeni grafikoni (u formatu .xls). Naslovi slika (crteža, ilustracija, fotografija) moraju biti navedeni dvojezično, na hrvatskom i engleskom jeziku i

označeni rednim brojem. Naslov i redni broj pišu se ispod slike, a umetnuti su na posebnoj stranici na kraju dokumenta. Slike je potrebno dostaviti posebno u .jpeg, .png ili .tiff formatu (min. razlučivosti 300 dpi). Potrebno je označiti gornji dio slike te po potrebi bitna mjesta na slikama označiti strelicom. Za reprodukcije slika i tablica iz drugih izvora treba priložiti dozvolu njihovih izdavača/autora. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji. U protivnom osoba na fotografiji mora biti neprepoznatljiva (prekrivene oči). Uredništvo pridržava pravo odbiti slike koje kvalitetom ne zadovoljavaju.

Literatura

Popis literature sadržava radove koji su navedeni u tekstu i to slijedom kako se pojavljuju u tekstu. Popis je potrebno navesti na posebnoj stranici. Pojedine citate na popisu navesti rednim brojem pod kojim se nalaze u tekstu, gdje su označeni superskriptom. Za nazive časopisa koristiti kratice iz Index Medicusa.

Literatura se citira:

a) Periodične publikacije

Članak u časopisu

Navesti sve autore ako ih je šest ili manje, ako ih je sedam ili više, navesti prva tri i dodati: i sur., a u literaturi na engleskom jeziku: et al.

Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemostatic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976; 194:687-90.

Čupić V, Čupić N, Dražančić A i sur. Neuro-psihološki razvoj nedonoščadi. *Liječ Vjesn* 1983;105:343-6.

Članak na webu

Liang T, ur. Priručnik za prevenciju i liječenje COVID-19 2020 Dostupno na adresi: <https://www.bolnica-zadar.hr/wp-content/uploads/2020/03/Manual-for-Covid19-Patients-from-First-Zhejiang-University4986927707241581013.pdf> Datum pristupa: 20.3.2020.

Zajednički autor

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma glutamyl transferase in blood. *Scand J Clin Lab Invest* 1967;36:119-25.

Nepoznati autor

Anonymous. Fetal nicotine poisoning. *J Amer Med Ass* 1938;110:143-45.

Bez autora

Coffee drinking and cancer of the pancreas (editorial). *Br Med J* 1981;283:628.

Suplement časopisa

Poje G, Kovač Bilić L. Computer assisted endoscopic sinus and skull base surgery. *Med Jad* 2020;50 (Suppl 1):41.

Novinski članak

Matić-Glažar Đ. Etičke dileme. *Novi list* 1985. Prosinac 13;11.

b) Knjige, monografije, zbornici, doktorski ili diplomski radovi

Iza navedenog citata navesti godinu tiska i brojeve stranica poglavlja u knjizi ili zborniku na kojima je naveden citat. Kod doktorskog, diplomskog ili sličnog rada, osim godine tiska treba napisati stranicu na kojoj je naveden citat.

Jedan autor knjige

Richter B. *Medicinska parazitologija*. 3. izd. Zagreb: Liber, 1982;112-3.

Urednik

Zergollern-Čupak Lj, ur. *Humana genetika*. Zagreb: Jumena, 1983;17-60.

Poglavlje u knjizi

Sunter V, Yigit O, Skitarelić N. Combined Open and Endoscopic Approach to the Paranasal Sinus. In: Cingi C, Bayar Muluk N. Ed. *All Around the Nose*. Berlin: Springer, 2019;629-633.

Zbornik radova

Alter M. The epidemiology of multiple sclerosis. An overview. In: Hartog Jager WA, Bruyn GM, Heijstee APJ, Ed. *Proceedings of the 11th World Congress of Neurology*. Amsterdam: Excerpta medica, 1978;330- 50.

Doktorski rad

Šimurina T. Model predviđanja povraćanja nakon opće anestezije pri laparoskopskim ginekološkim zahvatima [doktorski rad]. *Medicinski fakultet Sveučilišta u Zagrebu*, 2011;98.

MEDICA JADERTINA journal releases editorials, original scientific and professional articles, earlier announcements, review articles, presentations from scientific meetings and other supplements from basic and clinical medical fields. The manuscripts can be written in the Croatian or English language. The Editorial Board of the paper submits a mandatory review to two reviewers. The stated articles in the papers represent the opinion of the author, therefore, each author is responsible for the ethical approval of his paper. The papers released in the journal are copyrighted. The text and illustrations from the journal can be used for personal and training purposes respecting the copyright of the author and publisher. Any other use is prohibited without the expressed written permission of the publisher, Zadar General Hospital. All papers are the property of the journal publisher.

The Editorial Board does not have to release the papers in the order of their arrival. The printed papers in the journal are available in full on the Portal of Croatian scientific papers – HRČAK. Papers are to be sent to the above at the electronic address: opca-bolnica-zadar@zd.t-com.hr or by post at the address: MEDICA JADERTINA Editorial Board, Zadar General Hospital, Bože Peričića 5, 23000 Zadar, Croatia.

Preparation of works

Original scientific and review papers may not exceed 3000 words (exceptionally 4000 words). The Editorial Board will not accept too long articles other than those ordered and will return them to the authors.

Papers should be written on a MS Word program or similar line spacing programs (1.5) in Times New Roman font, size 12. The page size should be A4, with 2.5 cm margins on all sides.

Every paper chapter is to start on a new page. All parts of the paper, including tables, illustrations and bibliography list must be in one electronic document. The manuscript must include statements of no conflict of interest, no financial or any other conflict of interest, authorship or transfer of copyright, and a statement that publication has not been published or accepted in another journal. The statement form can be found at the end of this document.

Cover page

The cover page must consist of the paper title in the Croatian and English language, full name and surname of the authors with their academic title and specializations, as well as the official titles of their working organization. The paper title must not consist of abbreviations. The name, surname, address and electronic address for correspondence is to be stated at the bottom of the page.

Summary

A summary of at most 300 words in the Croatian and English language must be structured on a separate page. It is recommended to be written in the first person plural, avoiding the passive voice and the use of abbreviations.

Key words

Three to six key words are to be written on a page in the Croatian language, the English language summary under the text respectively, characteristic of the main theme of the paper and suitable for inclusion in the Bibliographical Index. The key words must be in accordance with the Index Medicus titles.

Articles

When possible, the paper should be divided as follows: introduction, patients (material) and methods, results, discussion, conclusion, summary and the bibliography. The introduction is to state the purpose of the paper and reason for carrying out the research. The patients and methods chapter covers all the important research characteristics. It is necessary to state that the Ethics Committee has given its approval for the examination which has been performed in line with the ethical principles of the Helsinki Declaration. It is to be emphasized that the examinees gave their consent to participate in the examination as well as the submission of their patient's consent to publishing their data in the "Case Presentation". It is necessary to describe the used statistical methods as well as statistical program used for data processing. The significance of the results needs to be statistically substantiated. The measurement units must be expressed according to the SI system. The discussion should emphasize new and important knowledge arising from the research and compare theses with the results from the bibliography. The abbreviations can be used in the text only after the second mention of the entire word in the text. It is possible to use prominent words in italic font in exceptional cases. It is necessary to mark the places where the tables or illustrations are to be placed citing the parenthesis in the text – i.e. (Table 1). All supplements to the paper text are to be reduced to a reasonable number (six tables at most, illustrations/figures respectively).

Tables and figures

The tables should be prepared on a separate page in ordinal number and titles. The words in the tables must not be abbreviated. The titles and text contents of the tables must be in bilingual, in the Croatian and English language. Each table must have its ordinal number. The title and ordinal number are to be written above the table. Avoid the use of vertical lines in the table. Write the table legend under the table. Exceptionally, and at the request of the reviewer of the journal Editorial

Board, the authors will provide the data on which the graphs were made (.xls format). The titles of the figures (drawings, illustrations, figures) must be bilingual, in Croatian and English and marked in ordinal number. The titles and ordinal numbers are to be written under the figures, and placed on a separate page at the end of the document. The figures need to be sent separately in .jpeg, .png or .tiff format (min. resolution 300 dpi). The upper part of the figures needs to be marked, and, if necessary, the essential parts of the figure marked with an arrow. Permission from publishers/authors should be attached to the reproduced figures and tables from other sources. Photos of persons may only be published with the written permission of the person in the photograph. Otherwise, the person in the photo must be unrecognizable (eyes covered). The Editorial Board reserves the right to reject figures that do not meet the quality requirements.

Bibliography index

The bibliography consists only of papers mentioned in the text and in the order in which they appear in the text. The bibliography index must be written on a separate page. Separate quotes on the list are to be mentioned in the ordinal number under which they are found in the text, where they are marked in superscript. Use Index Medicus for journal titles.

The bibliography is quoted:

a) Periodical publications

Article in journal

Mention all the authors, if there are six or less, if seven or more, then mention the first three and add et al. in the English bibliography.

Soter Na Wasserman SJ, Austebn KF. Cold urticarial: release into the circulation of histamine and eosinophil chemostatic factor of anaphylaxis during cold challenge.

N Engl J Med. 1976;194:687-90.

Čupić V, Čupić N, Dražančić A et al. Neuro-psihološki razvoj nedonoščadi. Liječ Vjesn 1983; 105:343-6.

Web article

Daszak P, Olival KJ, Li H. A strategy to prevent future epidemics similar to the 2019-n CoV outbreak. Bioasafety Health 2020 Accessible at the address: <http://dx.doi.org/10.1016/j.bsheal.2020.01.003> Date accessed: March 22, 2020

Mutual author

The Committee of Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the

determination of gamma glutamyl transferase in blood. Scand J Clin Lab Invest 1967;36:119-25.

Unknown author

Anonymous. Fetal nicotine poisoning. J Amer Med Ass 1938;110:143-45.

Without author

Coffee drinking and cancer of the pancreas (editorial) Br Med J 1981;283:628.

Journal Supplement

Poje G, Kovač Bilić L. Computer assisted endoscopic sinus and skull base surgery. Med Jad 2020;50 (Suppl 1):41.

News article

Matić-Glažar Đ. Etičke dileme. Novi list 1985. Dec 13;11.

b) books, monographs, proceedings, doctoral or graduate thesis

State the year of the print and the page numbers of the chapter in the book or proceedings citing the quote after the mentioned quote. In case of a doctoral, diploma or similar thesis, except for the year of printing, the page on which the citation is quoted should be written.

One book author

Richeter B. Medicinska parazitologija. 3. izd. Zagreb: Liber, 1982;112-3.

Editor

Zergollen-Čupak Lj, ed. Humanica genetica. Zagreb: Jumena, 1983;17-60.

Chapter in the book

Sunter V, Yigit O, Skitarelić N. Combined Open and Endoscopic Approach to the Paranasal Sinus. In: Cingi C, Bayar Muluk N. Ed. All Around the Nose. Berlin: Springer, 2019;629-633.

Proceedings

Alter M. Epidemiology of multiple sclerosis. An overview. In: Hartog Jager Wa, Bruyn GM, Heijstee APJ, Ed. Proceedings of the 11th World Congress of Neurology. Amsterdam: Excerpta medica, 1978;330-50.

Doctoral thesis

Šimurina T. Model predviđanja povraćanja nakon anestezije pri laparoskopskim ginekološkim zahvatima [dinarski rad]. Medicinski fakultet Sveučilišta u Zagrebu, 2011;98.

Medica Jadertina
Priznanje autorstva, Izjava o publikaciji,
Izjava o sukobu interesa i Ugovor o prijenosu autorskih
prava
Medica Jadertina objavit će Vaš rad ("Rad") pod naslovom:

Svi autori moraju značajno doprinijeti izradi rada. Svaki autor preuzima odgovornost za sadržaj rada. Urednici mogu tražiti od autora da obrazlože svoj doprinos radu, što može biti i objavljeno.

Autor za dopisivanje u ime svih autora prenosi na *Medicu Jadertinu* vlasništvo nad autorskim pravima rada i pravima vezanima uz rad, u svim oblicima i svim medijima. Navedeni autor jamči da je rad izvoran, da nije u razmatranju za objavljivanje u drugom časopisu i da nije prethodno objavljen. Također, autor za dopisivanje potvrđuje da su svi navedeni autori rada upoznati sa sadržajem rada, te su suglasni s objavljivanjem rada u obliku u kojem je upućen Uredništvu časopisa.

Autori su dužni navesti eventualni financijski ili bilo koji drugi sukob interesa, vezan uz navedeni rad, kao i eventualnu financijsku potporu radu.

Ovu izjavu potpisuje autor za dopisivanje.

Ime i prezime autora za dopisivanje

Potpis

Datum

Medica Jadertina
Acknowledgement of Authorship, Publication Statement,
Conflict of Interest Statement, and Transfer of Copyright Agreement

The Medica Jadertina will publish your article (“the Work”) entitled:

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content. Editors may ask authors to describe what each one contributed; this information may be published.

The undersigned corresponding author, on behalf of all authors, transfers all copyright ownership in and relating to the Work, in all forms and media, to Medica Jadertina. The corresponding author warrants that the Work is original, that it is not under consideration by another journal, and has not been previously published. Also, the undersigned corresponding author confirms that all designated authors are familiar with the content of the work, and agree to publish the paper in the form in which it has been sent to the Editorial Board.

When authors submit the Work, whether an article or a letter, they are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work. They should acknowledge in the manuscript all financial support for the Work and other financial or personal connections to the Work.

This agreement must be signed by the corresponding author.

Corresponding author’s name & signature

Date

